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REVIEW

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Harnessing the nutriceutics in early-stage breast cancer: mechanisms, combinational therapy, and drug delivery

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Abstract

Background Breast cancer (BC) is a significant health challenge, ranking as the second leading cause of cancer-related death and the primary cause of mortality among women aged 45 to 55. Early detection is crucial for optimal prognosis. Among various treatment options available for cancer, chemotherapy remains the predominant approach. However, its patient-friendliness is hindered by cytotoxicity, adverse effects, multi-drug resistance, potential for recurrence, and high costs. This review explores extensively studied phytomolecules, elucidating their molecular mechanisms. It also emphasizes the importance of combination therapy, highlighting recent advancements in the exploration of diverse drug delivery systems and novel routes of administration. The regulatory considerations are crucial in translating these approaches into clinical practices.

Results Consequently, there is growing interest in exploring the relationship between diet, cancer, and complementary and alternative medicine (CAM) in cancer chemotherapy. Phytochemicals like berberine, curcumin, quercetin, lycopene, sulforaphane, resveratrol, epigallocatechin gallate, apigenin, genistein, thymoquinone have emerged as promising candidates due to their pleiotropic actions on target cells through multiple mechanisms with minimal toxicity effects. This review focuses on extensively studied phytomolecules, elucidating their molecular mechanisms. It also emphasizes the importance of combination therapy, highlighting recent advancements in the exploration of diverse drug delivery systems and novel routes of administration. The regulatory considerations are crucial in translating these approaches into clinical practices.

Conclusion The present review provides a comprehensive understanding of the molecular mechanisms, coupled with well-designed clinical trials and adherence to regulatory guidelines, which pave the way for nutrition-based combination therapies to become a frontline approach in early-stage BC treatment.

Keywords Breast cancer, Chemotherapy, Dietary phytomolecules, Nutrition-based combination therapy, Complementary and alternative system of medicine, Novel drug delivery systems

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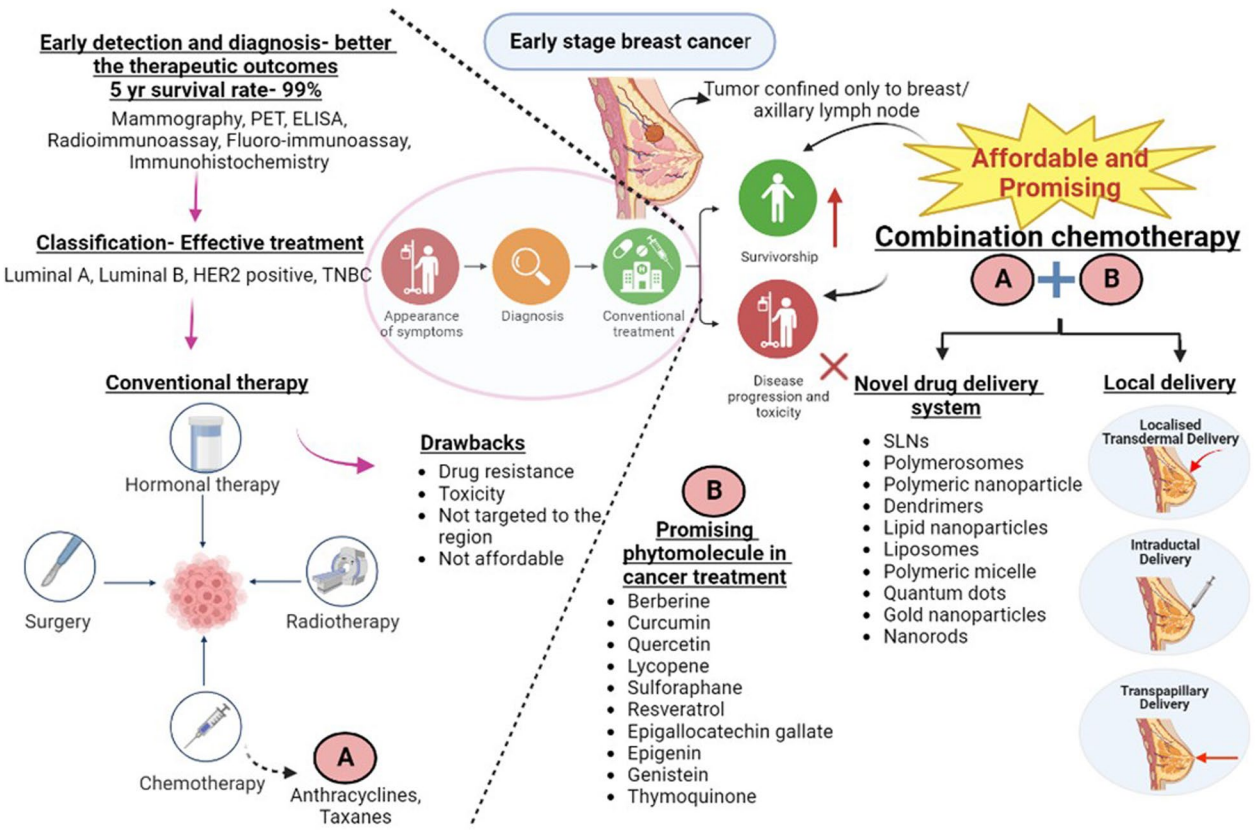
Graphical Abstract



Introduction

Breast cancer is characterized by the aberrant growth of breast cells, typically originating in the lobules (lobular carcinoma) or the milk ducts (ductal carcinoma). As evidenced by various epidemiological data, numerous risk factors play a role in this carcinogenesis, including hormonal, physiological, viral, nutritional, and lifestyle factors. Among these factors, genetic factors are considered the primary underlying cause of carcinogenesis in affected individuals. However, breast cancer has also been associated with disruptions in enzymes involved in metabolic processes such as glucose metabolism, amino acid metabolism, and lipid metabolism. The activity of these enzymes, which promotes tumorigenesis, is directly or indirectly influenced by tumor-related genes. Mutations in tumor suppressor protein 53 (Tp53) have been well-documented in various types of breast cancer. Normally, Tp53 functions to inhibit the tumorigenesis process by regulating glycolytic pathway enzymes, cellular mitochondrial respiration, and the simultaneous production of reactive oxygen species. Another influential factor is c-Myc, whose conditional amplification is associated with high metastatic behavior in tumorigenesis. Upregulation of c-Myc has been specifically observed in various breast cancers, contributing positively to increased amino acid uptake. Similarly, mutations in the PI3K/AKT/mTOR pathway enhance glucose uptake and glycolysis, serving as the primary energy source for cancer cell growth. However, various phytochemicals can target these critical pathways at different stages, as elaborated in this review paper.

According to a 2021 global report by World Health Organization (WHO), Breast Cancer (BC) accounts for more disability-adjusted years of life in women than any other type of cancer. Approximately 8 million active BC cases were reported in the same year. The global annual statistics of the International Agency for Research on Cancer (IARC) for 2020 also reported BC as the leading cause of death, overtaking lung cancer, wherein approximately 2.26 million BC cases were reported, with 685000 deaths. Furthermore, the statistics indicate an increasing trend in BC cases. The situation in India reflects a similar

scenario, as BC is the most prevalent cancer in the Indian population. According to the National Cancer Registry Programme Report 2020, released by the Indian Council of Medical Research (ICMR) and the National Centre for Disease Informatics & Research (NCDIR), Bengaluru, BC, contributed to 2.0 lakhs (14.8%) of the total cancer burden. In specific databases of certain states (like New Delhi, Dibrugarh, Bhopal, Chennai, Mumbai, and Bangalore), BC was at the top from 2012 to 2014. According to WHO, in 2022, there were 2.3 million women diagnosed with breast cancer globally and 670,000 deaths from the disease. In 2024, an estimated 310,720 women and 2,800 men in the U.S. will be diagnosed with invasive breast cancer. It is estimated that in 2024, approximately 30% of all new female cancer diagnoses will be breast cancer. The 5-year relative survival rate for breast cancer diagnosed at the localized stage is 99%.

Consequently, no country is an exception to the snowballing burden of BC. The cases of BC (8,85,000 cases) in developing countries have been reported to be higher than in developed countries (7,94,000 cases). Early detection and timely intervention are the most useful strategies for BC management, according to the World Cancer Report 2020. The cost of BC therapy increases with the stage of the disease, further emphasizing the importance of early diagnosis in terms of affordable treatment.

The therapies available in the modern system of medicine to treat cancer are like a hiltless double-edged sword, i.e., one is bound to be wounded either one attacks or defends. Among various therapies employed for the treatment of cancer, it is chemotherapy that is associated with numerous adverse effects. Complementary and Alternative systems of medicine, including the use of bioactive, are hence becoming increasingly popular worldwide. Many cancer patients start consuming conventional medications upon being diagnosed with a non-communicable disease like cancer. A universal belief that phytoconstituents from natural sources are safe is also embedded in the minds of people; hence, people even opt for self-medication with phytomolecules -based formulations. However, the safety and efficacy of the bioactives used without rationale is a question to ponder! Providing alternative treatments alongside conventional ones was rarely practiced in the past but there has been a rise in interest to provide a rational approach for combining phytomolecules with standard anticancer drugs in recent days. This approach originated with the concept of nutraceuticals initiated by Stephen DeFelice in 1989. Studies even demonstrate positive outcomes from such an approach.

Unlike other reviews, this review comprehensively discusses the various attempts being made to develop a rational approach for complementary medicine approach ie., using dietary phytomolecules with approved anticancer molecules for early-stage BC. We explored and critically discussed the molecular mechanisms underlying this combination, as well as *in-vitro* and *in-vivo* studies evaluating its effectiveness. Additionally, the review focuses on the development of combination-based formulations and highlights novel routes of administration. Finally, we emphasize the regulatory considerations that need to be addressed for the successful commercialization of such combination-based formulations. The current review is unique in providing a distinctive perspective about bringing to practice combination therapy treating early-stage BC. The literature from various disciplines has been comprehensively analyzed, seamlessly integrated, and forward-looking novel avenues that contribute to improved management of early-stage BC are presented in the current review.

Classification of breast cancer

BC is a clinically and genetically heterogenous condition further classified into subtypes. A comprehensive understanding of the heterogeneity of BC is crucial to achieving effective therapy. Immunohistochemical classification is one of the widely accepted classifications and is based on the expression of various hormone receptors like progesterone (PR), estrogen (ER), and human epidermal growth factor (HER2). Although this review primarily focuses on early BC, it is important to recognize that even within the early stages, different subtypes exist based on receptor expression, namely Luminal A, Luminal B, HER2-positive, and triple-negative BC. ER receptors are highly expressed in about 70–75% of BC, and progesterone receptors are expressed in more than 50% of ER receptor-positive conditions. The abundant expression of ER and PR receptors makes them prognostic and diagnostic markers for BC. HER2 is overexpressed in the early stage of BC and is a promising real-time marker for the presence of tumors. Luminal A tumors exhibit the ER and PR receptors but without HER2. They are also characterized by a low (< 20%) cell proliferation marker Ki-67. They are low-grade, grow slowly, have a high survival rate, and respond very well to hormonal therapy with Tamoxifen. They do not respond much to chemotherapy. Luminal B tumors exhibit ER receptors but can be PR receptor-negative. They are also characterized by a high (> 20%) expression of Ki-67, which is the reason for their fast growth. They are of higher grade and hence, require hormonal therapy and chemotherapy. The HER2-positive tumors account for about 10–15% of BCs and are characterized by high expression of HER2 with the presence/absence of ER and PR receptors. They are aggressive and grow faster than luminal tumors. They respond well to HER2- targeted therapies. Subgroups include: luminal

HER2 (HER2+, E+, PR+, Ki-67:15–30%) and HER2-enriched (HER2+, E-, PR-, Ki-67 > 30%). They respond well to chemotherapy with Trastuzumab, Pertuzumab, and Lapatinib. Triple-negative BC (TNBC), constituting about 20% of BC, does not express ER or PR receptors and is HER2-negative. They are commonly seen in women below 40 years of age, mainly in African-American women. Subgroups include- claudin-low, basal-like (BL1 and BL2), luminal androgen receptor (LAR), mesenchymal (MES), and immunomodulatory (IM). It is aggressive, has a high proliferation rate, and has an early relapse. TNBC is sensitive to chemotherapy with anthracycline, doxorubicin, cyclophosphamide, taxanes, and fluorouracil (5-FU). However, treating it is very challenging, especially in advanced stages.

Early-stage breast cancer

Carcinogenesis can happen in every cell, tissue, and organ, resulting in degenerative changes that cause a large proportion of malignancies. Apoptosis avoidance, adoption of an infinite capacity for division, increased angiogenesis, resistance to anti-growth signals, activation of own growth signals, and metastasis are the main processes resulting in cancerous growth in the breast, termed BC, identified by a lump or mass. BC begins in the milk glands (lobules) or the ducts, which connect the lobules to the nipple. It is heterogeneous at the molecular level, which is the basic principle behind many modern-day therapies, but the ultimate decision of therapy is also influenced by its metastatic pattern. Early-stage breast cancer is characterized by tumors that are either 20 mm or smaller with involvement of up to 3 lymph nodes, or tumors sized between 20 to 50 mm without any lymph node spread. This stage encompasses breast cancer classifications such as stages 1A, 1B, and 2A [1]. BC cells are different from the normal cells as depicted in the Fig. 1.

Breast cancer predominantly affects women, with significantly higher incidence rates than in men. A first-degree relative (mother, sister, daughter) with breast cancer increases an individual's risk by 1.75-fold, rising to 2.5-fold with two or more affected relatives. Inherited BRCA1 and BRCA2 gene mutations markedly elevate breast cancer risk[2]. Factors such as early menstruation (before age 12), late menopause (after age 55), nulliparity, and having a first child after age 30 further heighten the risk. Each year delay in menopause increases risk by 3%, while each additional childbirth reduces it by 10%[2]. Postmenopausal overweight or obesity is associated with increased risk, as is alcohol consumption, with risk escalating with higher intake. Childhood or young adult chest

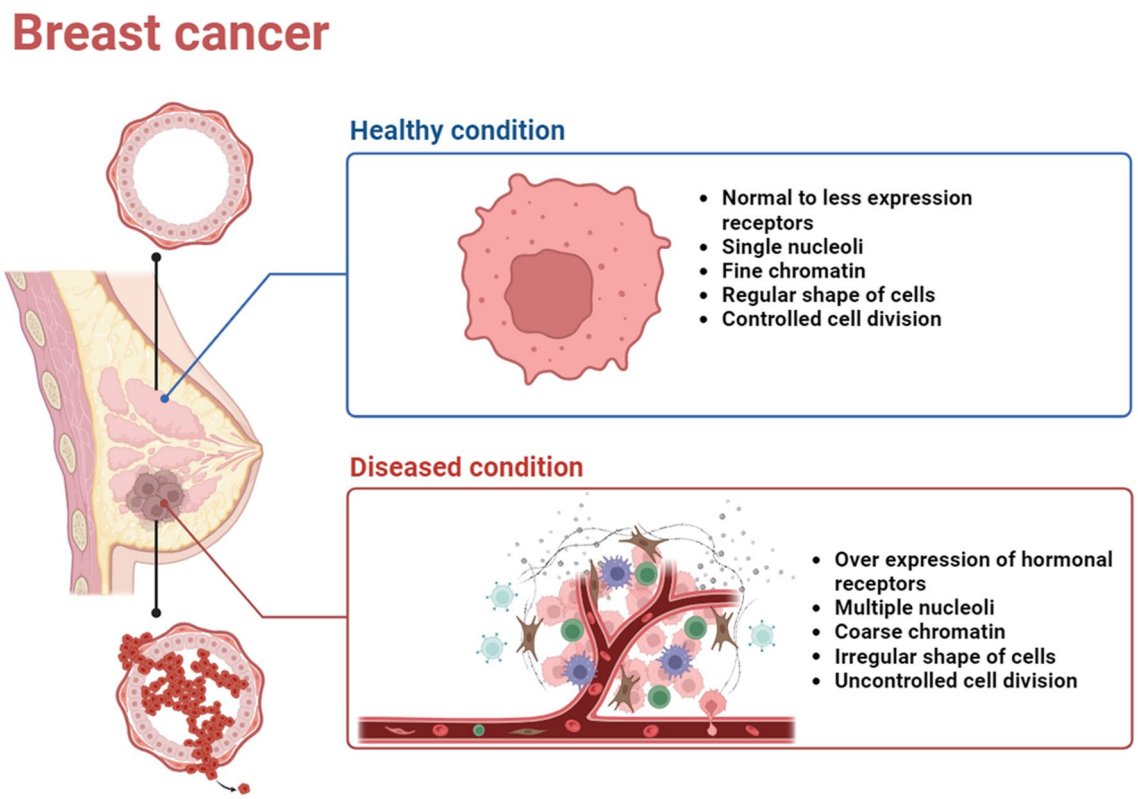


Fig. 1 The morphological difference between breast cancer and normal cells. (Created with BioRender.com)

radiation exposure significantly raises risk, and combination hormone therapy for menopausal symptoms also increases risk, although this risk diminishes upon cessation of the therapy.

Detection of early breast cancer

According to the American Cancer Society, 65% of BC cases are detected early, and 99% of these patients have a survival rate of 5 years. The World Health Organization (WHO) has identified several symptoms of BC, including a lump in the breast, skin retraction, asymmetry, blood-stained nipple discharge, recent nipple retraction, and eczematous changes in the areola. However, these symptoms may not be significant indicators in the early stages of the disease. Therefore, screening plays a crucial role in the early detection of BC. Currently, mammography is the gold standard screening technique for BC. However, mammography has certain limitations. It is less effective for individuals under 40 and those with dense breasts. It is also less sensitive in detecting small tumors and does not provide information about the potential progression of the disease. An alternative to mammography is magnetic resonance imaging (MRI), which can detect small lesions that mammography may miss. However, MRI is a costly method with a low specificity, which can lead to overdiagnosis. Positron emission tomography (PET) is another technique used in BC detection. It is highly precise and can predict the tumor response to the treatment and metastasis. Breast biopsies are often conducted alongside screening methods to differentiate between malignant and benign tissues. In addition to these methods, BC diagnosis can be performed using biomarker-based molecular techniques such as enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, fluoro-immunoassay, and immunohistochemistry.

Mammography is the primary breast cancer screening method, using low-dose X-rays to produce breast images. It is the only screening tool proven to reduce breast cancer mortality, detecting cancers up to 10 years earlier than physical exams. Clinical Breast Exams (CBEs) involve a physical examination by a healthcare professional, but their benefit is unclear when combined with regular mammography. Similarly, Breast Self-Exams (BSEs) show little evidence of efficacy alongside mammograms. Breast ultrasound uses sound waves to create breast tissue images, distinguishing between solid masses and fluid-filled cysts, and is useful in guiding biopsies and providing additional lesion information. Breast MRI uses magnetic fields and radio waves for detailed breast images, often enhanced by dye injections. It is particularly recommended for high-risk women. In diagnostics, Full-Field Digital Mammography (FFDM) detects tumors and ductal carcinoma in situ (DCIS) using X-rays. Digital Breast Tomosynthesis (DBT) captures multiple X-ray images from different angles to create 3D breast images for better tissue visualization. Contrast-enhanced mammography involves dye injection to highlight breast tissue and detect cancerous lesions[3]. Needle biopsy, guided by imaging techniques such as X-rays, ultrasound, or MRI, involves extracting tissue samples for analysis, often marking the biopsy site for monitoring. Thermography uses a special camera to record skin temperature over the breasts, potentially detecting tumors through temperature changes, although its effectiveness is limited. Emerging technologies include shear wave elastography, an ultrasound technique measuring breast tissue stiffness to differentiate between benign and malignant lesions, and functional MRI (fMRI), which assesses breast tissue metabolic activity to identify cancerous areas. These advanced methods aim to improve early detection and diagnostic accuracy in breast cancer.

Early breast cancer management in practice

In the preceding section, the therapy options for different classes of BC, considering receptor expression, are described. Nonetheless, treatment decisions are not solely dependent on receptor expression due to the associated costs of diagnosis. Consequently, presented below are several available treatment options.

Surgery

Breast conservation surgery and mastectomy are two significant surgical procedures available for early BC. Breast conservation therapy is generally offered in case of small, localized tumors confined to one area of the breast. On the other hand, mastectomy is recommended when a tumor is large, involves multiple foci, or affects two or more breast quadrants. Additionally, it is worth noting that an increasing number of women opt for surgery on their contralateral (opposite) breasts to achieve improved symmetry and prevent cancer recurrence.

Chemotherapy

Chemotherapy for BC can be administered either before surgery (neoadjuvant) or after surgery (adjuvant)[4]. Neoadjuvant chemotherapy was traditionally used for inoperable and locally advanced BC but is now employed for operable BC as well, as it has prognostic significance. Achieving a complete pathological response (pCR), indicating no detectable residual cancer during subsequent surgery is a desirable outcome of neoadjuvant chemotherapy. Patients who achieve pCR have significantly improved survival rates. If pCR is not achieved, additional chemotherapy is given after surgery. Combination therapy involving multiple drugs, rather than a single drug, is commonly used for early BC chemotherapy.

Anthracyclines and taxanes typically used sequentially, are included in the chemotherapy regimen of early BC unless contraindicated[5]. The effectiveness of chemotherapy depends on the individual's risk level.

Anthracyclines such as Doxorubicin and Daunorubicin, primarily recognized as antibiotics, are important antineoplastic agents in early BC[5]. Although the exact mechanism of action is still under investigation, DNA is considered a primary target. Anthracyclines exert their effect by damaging DNA through various mechanisms, including free radical formation, topoisomerase-II poisoning, and formation of DNA-anthracycline adducts[6]. Anthracyclines also induce the production of free radicals within cells, which are responsible for the cytotoxic effect of these drugs. While they are potent drugs used in BC treatment, cumulative doses of anthracyclines have been associated with an increased risk of cardiotoxicity[5, 7, 8].

Taxanes are another widely used class of chemotherapy agents for early BC. Paclitaxel and Docetaxel are important and widely used anti-cancer drugs in this class[9]. Paclitaxel, the first natural drug and the prototype of this family, acts by stabilizing microtubules. Microtubules are dynamic polymers in cells composed of tubulin and other associated proteins. They play a crucial role in mitosis, including spindle organization and functioning, ensuring the integrity of segregated DNA. Taxanes stabilize these microtubules, blocking cell cycle progression and acting as anti-tumour agents. Based on the evidence, using taxanes in early-stage BC improves the survival rate and reduces the likelihood of cancer recurrence. However, using taxanes is also associated with side effects such as febrile neutropenia and neuropathy. Therefore, the decision to include taxanes in the treatment regimen along with anthracyclines should be based on a well-considered risk-reward ratio.

Radiotherapy

Another treatment option is radiotherapy, primarily recommended to reduce the risk of cancer recurrence in the breast. In patients with a low-risk profile, radiotherapy is usually omitted.

Is chemotherapy a hiltless double-edged sword?

As discussed, chemotherapy is one of the primary treatments for cancer. It aims to destroy rapidly growing cancer cells by using cytotoxic compounds. However, the outcomes do not meet the expectations, and toxicity becomes a concern. During the early stages of diagnosis, conversations mainly revolve around short-term chemotherapy toxicities such as myelosuppression, anaemia, alopecia, and nausea. Chemotherapeutic agents, while intended to target only rapidly dividing cancer cells, also harm healthy cells that divide quickly, leading to inevitable side effects like hair loss in the skin, nausea and vomiting in the gastrointestinal tract, anemia causing fatigue, infections due to leukopenia, and bleeding resulting from thrombocytopenia in the bone marrow.

Many BC survivors also experience long-term and post-chemotherapy effects, some of which can be chronic and devastating. Thus, chemotherapy significantly impacts the patient's well-being both during and post-chemotherapy. Often overlooked aspects that can impair the quality of life for women undergoing therapy for BC are concerns related to body image, changes in sexual functioning, and premature menopause. All of these factors can have a tremendous psychological impact!

As mentioned, cardiotoxicity is a significant adverse effect that can occur with higher cumulative doses of Anthracyclines. Studies have shown that the risk of cardiotoxicity increases with anthracycline therapy as the cumulative doses reach certain thresholds. Specifically, at cumulative doses of 150 mg/m^2, 350 mg/m^2, and 550 mg/m^2, the associated risks of cardiotoxicity are approximately 7%, 18%, and 65%, respectively [10]. Anthracycline drugs inhibit Topoisomerase 2β, an active enzyme in non-proliferating cells like cardiomyocytes. This inhibition leads to a disruption of mitochondrial biogenesis and the activation of cell death pathways, ultimately resulting in cardiotoxicity. However, studies have shown that Doxorubicin liposomes can help reduce the risk of cardiotoxicity[11].

Approximately 60% to 70% of patients undergoing chemotherapy with Taxanes are reported to experience Chemotherapy-Induced Peripheral Neuropathy (CIPN) within the first 2 months of therapy. CIPN has become a leading cause for early termination of treatment. However, discontinuing the therapy can worsen the condition. Unfortunately, there are limited treatment options available for managing CIPN. Additionally, in premenopausal women, there is a risk of cessation of menses (menstruation) due to the chemotherapy treatment.

Chemotherapy becomes further complicated when drug resistance is seen. Inactivation of the drug, decreased drug uptake, increased drug efflux, apoptosis suppression, changes in the drug target, alteration in drug metabolism, changes in tumor microenvironment etc., are some of the plausible reasons for it.

Undoubtedly, the number of individuals with a history of early-stage BC has increased each year due to advancements in detection and therapy. According to the BC Facts & Figs. 2019–2020 provided by the American Cancer Society, more than 3.8 million women in the United States with a history of BC were alive as of January 1, 2019, a substantial statistic demonstrating the progress being made. The report also emphasizes that some

women were cancer-free, highlighting the importance of focusing on the five-year survival rates, which indicate no cancer recurrence within five years of diagnosis. However, it is crucial to consider what happens after the initial five years. Can cancer still recur? Research confirms that estrogen receptor-positive BC can recur after five years of diagnosis, which seems short when recurrences have been observed up to 32 years after the primary diagnosis!

Certainly, there are ongoing efforts to address the drawbacks and challenges associated with chemotherapy which are explained below.

Herbal medicine alongside conventional standard therapy as a novel solution

According to World Health Organization (WHO), 80% of cancer patients use Complementary and Alternative Medicine (CAM) in one or the other form. CAM refers to a wide array of practices, including acupuncture, Traditional Chinese medicine (TCM), herbal preparations, vitamin supplementation, Ayurvedic system of medicine, homoeopathic remedies, spiritual practices, physiological and psychological practices, music therapy and other spiritual techniques. The use of CAM by cancer patients is not a part of the treatment regimen in many countries, but various attempts and studies are being made in this direction as it plays a crucial role in improving the patient's Quality of Life. Li et al., 2020 conducted a systematic review and meta-analysis to investigate the effectiveness of Chinese Herbal Medicine (CHM) in reducing chemotherapy-related side effects in breast cancer patients. CHM was administered in various forms, including decoctions, herbal preparations or extracts, patented herbal formulas, and herbal compounds. Some of the formulations studied included ginger powder, Jinlong capsule, Danggui Buxie decoction, Sugan Jianpi Sanjie compound, Yiqi Jianpi Hewei Therapy, Fuzheng Kangai compound, Fuzheng Jiedu formula, Aidi injection, and Guilu Erxian Decoction. Based on the obtained data, they concluded the above practice to be beneficial [12]. CAM is integrated into national health, insurance policies, and education in the countries like Japan, China, Taiwan, and the Republic of Korea. On the other hand, though not integrated into oncological practice, 16% to 63% of cancer patients in North America commonly use Spiritualism, Botanicals, acupuncture, vitamin therapies, and hypnosis. BC patients more frequently use CAM, with approximately 45% of patients across different treatment stages [13]. One of the randomized control trials (RCTs) demonstrated that using herbal medicines like Danggui (*Angelica sinensis-radix*) and Ren Shen (*Panax ginseng-radix*),in combination with chemotherapeutic agents can sensitize the cancer cells to treatment and minimize the side effects of conventional therapy, thus increasing patient survival rate and QOL[14]. Such extensive use and support for CAM use in cancer patients worldwide indicate the need to explore the direction further. The use of herbs/ herbal products by cancer patients, specifically women, is widespread even in India. Such increasing demand for herbs and other traditional systems of medicine like Ayurveda has resulted in considerable research and developments in this direction. In 2016, a premier national cancer institute under the Indian Council of Integrative Medicine joined hands with the All-India Institute of Ayurveda (AIIA) to set up a Center of Integrative Oncology to develop traditional medicine as adjuvant therapy to reduce the ADRs of chemotherapy.

Chemoprevention is a related aspect that is gaining tremendous interest. It involves chronic use of natural dietary substances or related synthetic molecules to quash the process of carcinogenesis and prevent further complication. Three types of chemoprevention include-primary, secondary, and tertiary. Chemoprevention is termed 'primary' when it is for the general 'healthy' population or those with no disease but has the risk factors for example, using Oltipraz, a synthetic derivative of the cruciferous vegetable product 1,2-dithiole-3-thione[15]. It acts as a chemo protectant by inducing Phase I or II enzymes and modifying the carcinogen metabolism. Chemoprevention is termed 'secondary' when the population with premalignant lesions are administrated with agents that prevent progression to invasive cancer. The 'Tertiary chemoprevention' is the administration of agents to prevent recurrence. Thus, the following topics discuss the positive outcome of using various dietary phytomolecules alongside standard anticancer agents that can benefit patients with early-stage BC.

Global perspective

A group of researchers from University of Western Sydney, Macarthur explored the experiences of patients with respect to using Chinese Herbal Medicine alongside standard therapy for the treatment of Breas Cancer and obtained a positive response. The experiences documented hold a significance importance in this context as it establishes a demand for herbal medicine in managing Breast Cancer. The study shows that use of multiple herbs is a common practise and in certain cases practitioners alter the classical formulation by adding those components proven to show anticancer property. Bai hua she she cao (*Oldenlandia diffusia*) is one such component commonly added herb. This herb is proven to inhibit the growth of growth of Ras oncogene transformed R6 cells. They are also proven to possess the ability to inhibit cancer cells without affecting surrounding health cells[16, 17]. Another interesting study carried out by researchers

form University of Bologna, Italy proved the efficacy of Tibetan medicine in decreasing psychological stress in women with Breast Cancer. The study also proved that this Tibetan system of medicine can effectively improve somatic dimension like fatigue. The contributions of African medicinal plants too are notable. *Colocasia esculenta* is a tropical plant found in most regions of Africa, and its aqueous extract is studied to inhibit the growth of breast cancer cells. Dicoma anomala Sond roots are effective against MCF-7 breast cancer cells and aqueous extracts of *Dicoma capensis* against MCF-12A, MDA-MB-231 and MCF-7.

[18]. Ayurveda, the traditional Indian medical system, incorporates numerous potential treatments for breast cancer. Currently, ayurvedic formulations are integrated as complementary therapies alongside conventional treatments to overcome toxicity and improve the therapeutic efficacy. The formulations commonly used contains mixture of herbs in metallic preparation, called "Bhasma"[19]. Herbs like *Gmeliana arborea*, *Commiphora mukul*, *Foeniculum vulgare*, *Brassica juncea*, *Vitis vinifera, Withania somnifera* etc. are studied to exhibit anti- cancer potential by supressing nuclear factor-kappa B (NFκB), *Curcuma longa, Zingiber officinale* etc., are found to inhibit Bcl 2, Aloe vera is studied to possess a potential in supressing HER 2 receptors. These are just few of the many such Ayurvedic plants being used in supportive therapy of management of Breast cancer.

Phytochemicals in the treatment of cancer

Records of using plants for medicinal purposes date back 5,000 years to the Sumerians, showcasing humanity's early understanding of the healing properties of the natural world. However, recent archaeological studies have pushed the origins of herbal medicine even further back in time, providing evidence of medicinal plant use dating as far back as 60,000 years ago in the region now known as Iraq. This remarkable historical backdrop underscores the deep-rooted relationship between humans and the plant kingdom when it comes to seeking remedies for various ailments.

Despite its longstanding tradition and numerous instances of proven effectiveness, the popularity of herbal medicine gradually waned with the progress of modern Western medicine. The primary reason for this shift was the lack of scientific validation and rigorous verification that characterized the conventional medical practices of the time. However, recent research has rekindled interest in the therapeutic potential of phytochemicals, reigniting the discussion about their role in human health. In the contemporary context, individuals are increasingly taking a proactive approach to their well-being, exploring the benefits of natural compounds found in plants. These include their role as potent antioxidants, immunomodulators, antimicrobial agents, anti-inflammatory compounds, and even anticancer properties that show promise in cancer prevention and treatment[20, 21]. In vitro and in vivo experimental results prove the diverse and wide-ranging effects of these phytochemicals on the suppression of cancer development. Mechanism of action of selected few secondary metabolites are illustrated in the current review. These secondary metabolites are non- nutrient chemicals that plants produce for their defence mechanisms, and humans have utilized as food and medicines. Alkaloids, glycosides, polyphenols, carotenoids, organosulfur compounds are few such secondary metabolites.

Some of these secondary metabolites from nutraceuticals have also demonstrated potential in treating early BC **(**Fig. 2**).** Figure 2 provides a detailed overview of various molecular pathways involved in apoptosis, inflammation, cell cycle arrest, and angiogenesis, with a central focus on how certain compounds (like 9-cis RA, DHA, EPA, etc.) can influence these processes. Here's a breakdown of the pathways depicted: TRAIL Receptor Pathway: this triggers a cascade involving the activation of caspase-8, leading to the cleavage of BID protein. Cleaved BID interacts with BAK/BAX proteins in the mitochondrial membrane, leading to the release of cytochrome c. Execution Phase: Cytochrome c release activates caspase-9, which subsequently activates caspases 3, 6, and 7, leading to apoptosis (cell death). miR-122-5p: This microRNA is associated with the regulation of apoptosis, possibly promoting cell death in this context. NF-κB Pathway: Activation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) can lead to the production of inflammatory cytokines like TNF-α (Tumor Necrosis Factor-alpha). PGE-2 and COX-2 Pathway: Inflammatory signals can also lead to the production of prostaglandin E2 (PGE-2) via the cyclooxygenase-2 (COX-2) enzyme, further promoting inflammation. IL-6: Interleukin-6 (IL-6) is another pro-inflammatory cytokine depicted, which can be involved in the chronic inflammatory response. The p53 protein, a tumor suppressor, can induce cell cycle arrest in response to DNA damage or stress. p21 Activation: p53 activates p21, which inhibits cyclin-dependent kinases (Cdks) like Cdk2 and Cdk4/6. Cyclin-Cdk Complexes: Cyclin D-Cdk4/6: This complex is involved in the G1 phase of the cell cycle, and its inhibition by p21 leads to cell cycle arrest. Cyclin E-Cdk2: This complex is involved in the transition from the G1 phase to the S phase of the cell cycle. Inhibition by p21 results in cell cycle arrest. miR-21 and miR-221: These microRNAs are known to promote angiogenesis (the formation of new blood vessels). VEGF, HIF-1, PDECGF: VEGF

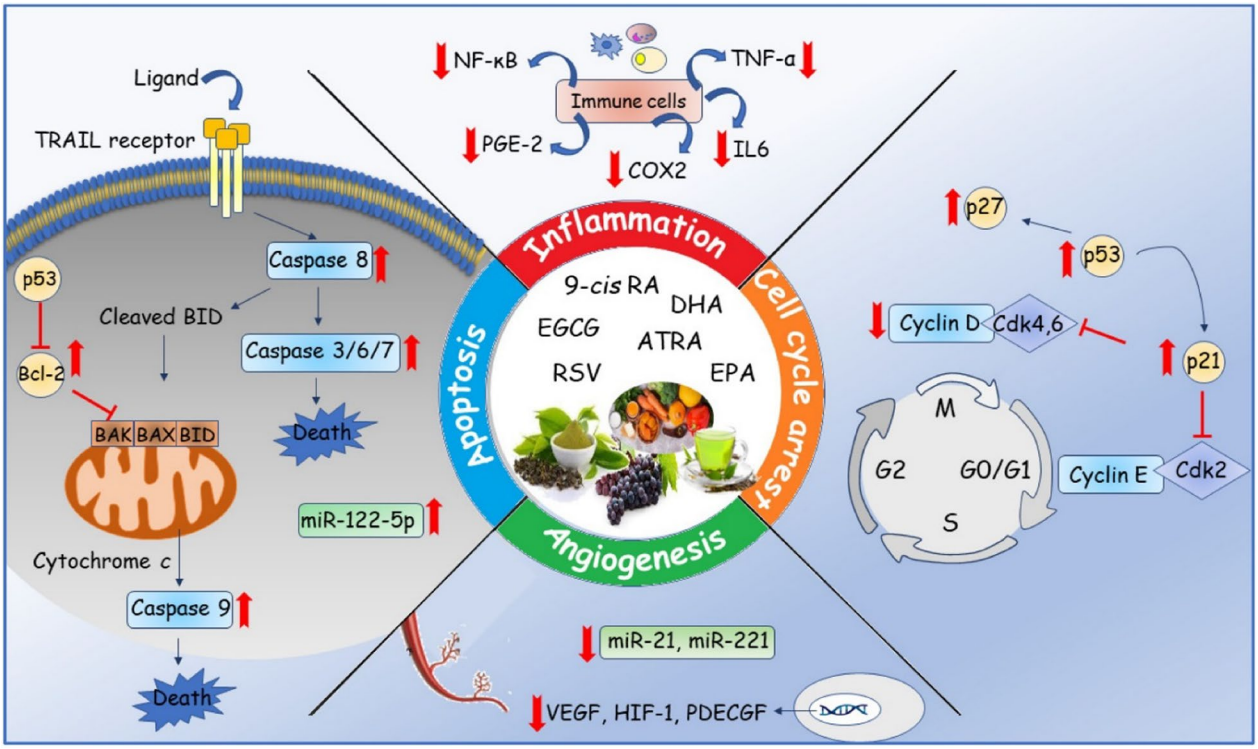


Fig. 2 A schematic illustration showing the potential anti-tumoral effects exerted by the nutraceuticals of the MD in the breast cancer progression. Bcl-2: B- cell lymphoma 2; CDK: cyclin-dependent kinase; COX-2: cyclooxygenase 2; HIF-1: hypoxia-inducible factor; IL 6: interleukin 6; miR: microRNA; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; TNF-α: tumor necrosis factor alpha; PDECGF: platelet-derived endothelial cell growth factor; PGE-2: prostaglandin E2; TRAIL: TNF- related apoptosis-inducing ligand; VEGF: vascular endothelial growth factor. This figure was reprinted with permission from Ref [80], Copyright @2021

(Vascular Endothelial Growth Factor): Promotes blood vessel formation. HIF-1 (Hypoxia-Inducible Factor 1): Regulates the response to low oxygen levels, including promoting VEGF expression. PDECGF: Another factor promoting angiogenesis. Central Regulatory Compounds: 9-cis RA, DHA, ATRA, EPA, EGCG, RSV: These are bioactive compounds, including retinoic acid (RA), docosahexaenoic acid (DHA), all-trans retinoic acid (ATRA), eicosapentaenoic acid (EPA), epigallocatechin gallate (EGCG), and resveratrol (RSV). These compounds are indicated as having roles in regulating apoptosis, inflammation, cell cycle arrest, and angiogenesis. Immune Cells: The central image also indicates that immune cells are involved in these processes, particularly in inflammation. Overall, the image illustrates how these different pathways interact with one another, and how certain bioactive compounds might modulate these processes in a way that could be beneficial, such as in cancer prevention or therapy [22–25]. The source of various phytochemicals discussed in this review is depicted in Table 1. Table 2 depicts the various phytomolecules in clinical trials.

Mechanism of action of some potential phytomolecules

Undoubtedly, humans have been utilizing herbs for various purposes for countless generations. However, with advancements in scientific understanding, studying the various phytochemicals at the molecular level has become possible. To harness the full potential of traditional knowledge, it is crucial to explore and comprehend the molecular mechanisms underlying their effects. Therefore, the molecular mechanisms of selected phytochemicals demonstrating anticancer activity have been elucidated in Fig. 3.

Berberine

Berberine (BBR) is an isoquinoline alkaloid obtained from goldenseal, European barberry, phellodendron, goldthread, tree turmeric, Oregon grape, etc. It is widely marketed as highly water-soluble berberine chloride. Other salt forms with bromide, sulphate, and phosphate are also available. It is extremely bitter and hence, administered by coating it with sugar.

Table 1 The major source of phytomolecules discussed

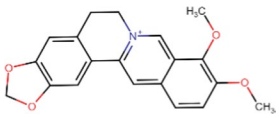
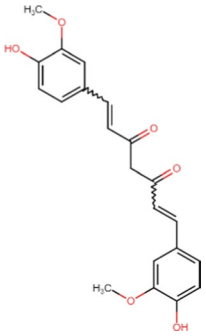
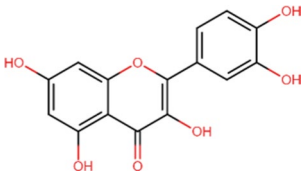
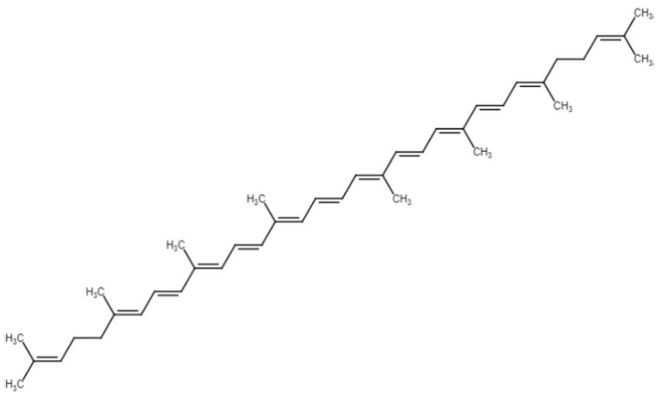
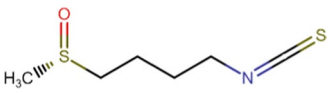
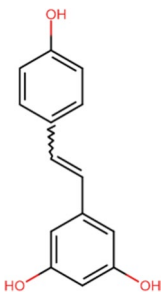
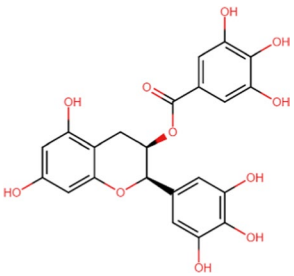
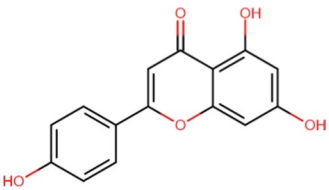
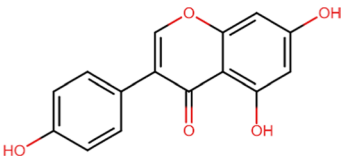
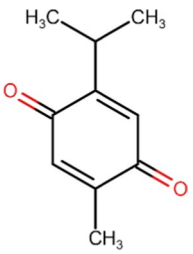
Sl. no	Phytomolecule/ Group	Structure	Major source of phytomolecules	Reference
1	Berberine (Alkaloid)		Common name: Barbearry Biological source- Fruits, bark, root, and stem of *Berberis vulgaris* belonging to the family Berberidaceae	[82]
2	Curcumin (Flavonoid- Isolflavones)		Common name: Turmeric Bioloigcal source: Rhizomes of *Curcuma longa* belonging to the family Zingiberaceae	[83]
3	Quercetin (Flavonoid- Flavonols)		Common name: Onion Biological source: Edible bulb of *Alium cepa* belonging to the family Amaryllidaceae	[84]
4	Lycopene (Terpene)		Common name: Tomato Biological source: Fruits of *Solanum lycopersicum* belonging to the family Solanceae	[85]
5	Sulforaphane (Organosulfur compound)		Common name: Brocolli Biological source: Clusters of unopened flower buds and tender flower stalks of *Brassica oleracea* belonging to the family Brassicaceae	[86]
6	Resveratrol (Stilbenes)		Common name: Grapes Biological source: Fruits of *Vitis vinifera* belonging to the family Vitaceae	[87]

Table 1 (continued)

Sl. no	Phytomolecule/ Group	Structure	Major source of phytomolecules	Reference
7	Epigallocatechin gallate (Flavonoid- Flavanols)		Common name: Tea leaves Bioligcal source: Leaves of *Camellia sinensis* belonging to the family Theaceae	[88]
8	Apigenin (Flavonoid-Flavones)		Common name: Antichoke Biological source: Flower heads of *Cynara cardunculus* belonging to the family Solanaceae	[89]
9	Genistein (Flavonoid- Isoflavones)		Common name: Dyer's greenweed Biological source: Twigs, leaves, and flowering stems of *Genista tinctoria* belonging to the family Fabaceae	[90]
10	Thymoquinone (Terpenes)		Common name: Black cumin Biological source: Seeds of *Nigella sativa* belonging to the family Ranunculaceae	[91]

Co- crystallization with sweeteners like Acesulfame, Saccharin etc., has been demonstrated to reduce its bitterness.

BBR has been extensively studied and demonstrated to exert significant in vivo and *in-vitro* anticancer activities. Its anticancer activity is attributed to multiple mechanisms such as inhibition and reproduction of viruses (like *Helicobacter pylori*, Hepatitis B Virus) and other such microorganisms that are responsible for the formation of tumor, inhibition of the proliferation of human cells by regulating the cell cycle and promoting apoptosis, supporting cell autophagy, interacting with microRNAs, and inhibiting the activity of telomerase thus also preventing cell proliferation. Transcriptional regulation of certain oncogenes is also a well-studied mechanism. In addition, berberine is a broad-spectrum enzyme inhibitor exhibiting its action on cyclooxygenase-2, N-acetyltransferase, topoisomerase, and protein expression. The above mechanism of action is exhibited along with its antioxidant, and anti-inflammatory properties [26].

Additionally, the suppression of tumor growth and improvement in multidrug resistance both *in-vivo* and *in-vitro* is one of the most useful applications of berberine when combined with therapy, clearly indicating its immense potential as a combination therapy molecule. Explained above is its general mechanism of action in treating Cancer, as a specific mechanism of action in treating BC is unclear. However, few BC-specific molecular targets studied include Salt-inducible kinases 3 (SIK3), Ephrin-B2, Histone lysine demethylase 1 (LSD 1), MiR-23a, etc. SIK3 is that oncogene, overexpression promoting proliferation and growth of BC cells. Berberine acts as SIK3 inhibitor by binding to its ATP-binding pocket via hydrogen bonding. This binding results in cell cycle arrest at G1/S and apoptosis in BC cells[27]. Ephrin-B2 is a membrane-bound ligand belonging to the family of eph

Table 2 Combinational therapies studied for the treatment of breast cancer

Combinations studied	Dose	Model	Mechanism of action	References
Berberine + Doxorubicin	Berberine 200 mg/ kg/ day (i.g.) + Doxorubicin 4 mg/ kg (intravenous injection (i.v.) 2 mL, every other day) for 2 weeks	Adult male Sprague–Dawley rat	Ameliorated cardiac dysfunction caused by doxorubicin	[92]
	Berberine 20 mg/Kg (i.g) once a day for 10 consecutive days + Doxorubcin 20 mg/Kg (i.p) single dose on 8th day	Rat	Berberine provided protection against hepatorenal toxicity caused by doxorubicin	[93]
Berberine + Cisplatin	Cisplatin 13 mg/Kg(i.p.) + Berberine 3 mg/Kg (p.o.) for 2 successive days 48 h after Cisplatin injection	Male Sprague–Dawley Mouse	Ameliorated kidney damage caused by cisplatin	[94]
	13 µM + 13.3 µM Berberine 52.178 µM + Cisplatin 49.541 µM for 48 h	MCF-7	Berberine can sensitize cisplatin to BC cells through caspase-3-dependent apoptotic pathway	[95]
Curcumin + Paclitaxel	Curcumin 30 µM + Paclitaxel 10 nM for 48 h	MCF-10F, MCF7 and MDA-MB-231 cell lines	Higher apoptosis	[96]
Curcumin + Docetaxel	Docetaxel (100 mg/m^2) was administered as a one-hour intravenous infusion every three weeks on day 1 for six cycles. Concurrently, curcumin was given orally, starting at 500 mg per day for seven consecutive days per cycle (from day -4 to day + 2), with the dosage increased until dose-limiting toxicity was observed	Clinical trials- Phase I	Improvement in clinical responses. The maximum tolerated dose of curcumin was determined to be 8,000 mg per day	[97]
Quercetin + Docetaxel	Quercetin 95 nM + Docetaxel 7 µM for 48 h	MDA-MB-231	Synergistic effects were seen due to increased apoptotic response. It also restored sensitivity of docetaxel in TNBC	[98]
Lycopene + Tamoxifen	Lycopene 40 mg/Kg (i.p) for 7 days + Tamoxifen 45 mg/Kg (i.p.) for 7 days	Adult female Albino Rat	Lycopene showed protective effect against hepatotoxicity caused by Tamoxifen	[99]
Sulforaphane + Docetaxel	Sulforaphane 50 mg/Kg daily (i.p.) + Docetaxel 10 mg/Kg once every 7 days (i.p.)	Orthotopic mouse xenograft model	Could reduce the secretion of inflammatory-related genes IL-6 and IL-8	[100]
Sulforaphane + Doxorubicin	Doxorubicin (5 mg/kg, *i.v.* injection) every three days for four times, Sulforaphane (4 mg/kg, *i.p.* injection) every two days for six times, and a combination (Sulforaphane/ Doxorubicin) of Doxorubicin (5 g/kg) and Sulforaphane (4 mg/kg)	wild-type BALB/c mice	SFN blocked Myeloid-derived suppressor cells (MDSC) accumulation and the improved therapeutic effects of DOX	[101]
Resveratrol + Doxorubicin	Resveratrol 15 µg/ml 24 h before Doxorubicin + Doxorubicin 0.035 µg/ml Treatment continued for further 48 h	MCF-7 cell lines	Resveratrol acted as a chemosensitizer and increased the cytotoxicity of doxorubicin	[102]
Resveratrol + Doxorubicin	Resvertrol 11.39 µM for 48 h	Doxorubicin resistant MCF-7	Effectively suppressed doxorubicin chemoresistance by downregulating MRP-1 and p-glycoprotein	[103]
EGCG + Paclitaxel	EGCG 30 mg/Kg (i.p.) everyday + Paclitaxel 10 mg/Kg (i.p.) once in every 2 days for 24 days	BALB/c mice	EGCG in combination with Paclitaxel showed synergistic effect	[88]
EGCG + Tamoxifen	EGCG 25 mg/kg (i.p) + Tamoxifen 75 µg/Kg (p.o.) once daily for 70 days	Female CD1 athymic nude mice	Tamoxifen alone could effectively suppress ER-negative tumour growth, and EGCG showed a modest effect. But the combination showed marked tumour suppression	[104]
Apigenin + Doxorubicin	Apigenin 10 µM + Doxorubicin 0.1 µM for 6 days	MDA-MB-231	Apigenin by targeting hnRNPA2 Sensitizes human TNBC spheroids to Doxorubicin	[105]

Table 2 (continued)

Combinations studied	Dose	Model	Mechanism of action	References
Genistein + Doxorubicin	Genistein 73.89 µM + Doxorubicin 70 µM for 48 h	MCF-7/Adr	A synergistic effect was observed. Increased intracellular accumulation of doxorubicin and suppression of HER2/neu expression was studied as the possible mechanism	[106]
Genistein + Doxorubicin	Genistein 50 µM + Doxorubicin 10 µM for 72 h	4T1	Enhanced cytotoxic and antimigratory activities of doxorubicin	[107]
Thymoquinone role was studied in doxorubicin-resistant cell lines	Thymoquinone 50 µM for 48 h	MCF-7/DOX	Up-regulation of signalling factor, PTEN (Phosphatase and tensin homolog) expression and induced apoptosis in doxorubicin-resistant human BC cells was observed	[108]
Thymoquinone + Tamoxifen	Tamoxifen 2 µM + 50 µM Thymoquinone for 48 h Tamoxifen 2 µM + 75 µM Thymoquinone for 48 h	MCF-7 MDA-MB-231	The Presence of thymoquinone increased the efficacy of tamoxifen-induced apoptosis after 48 h of treatment	[109]

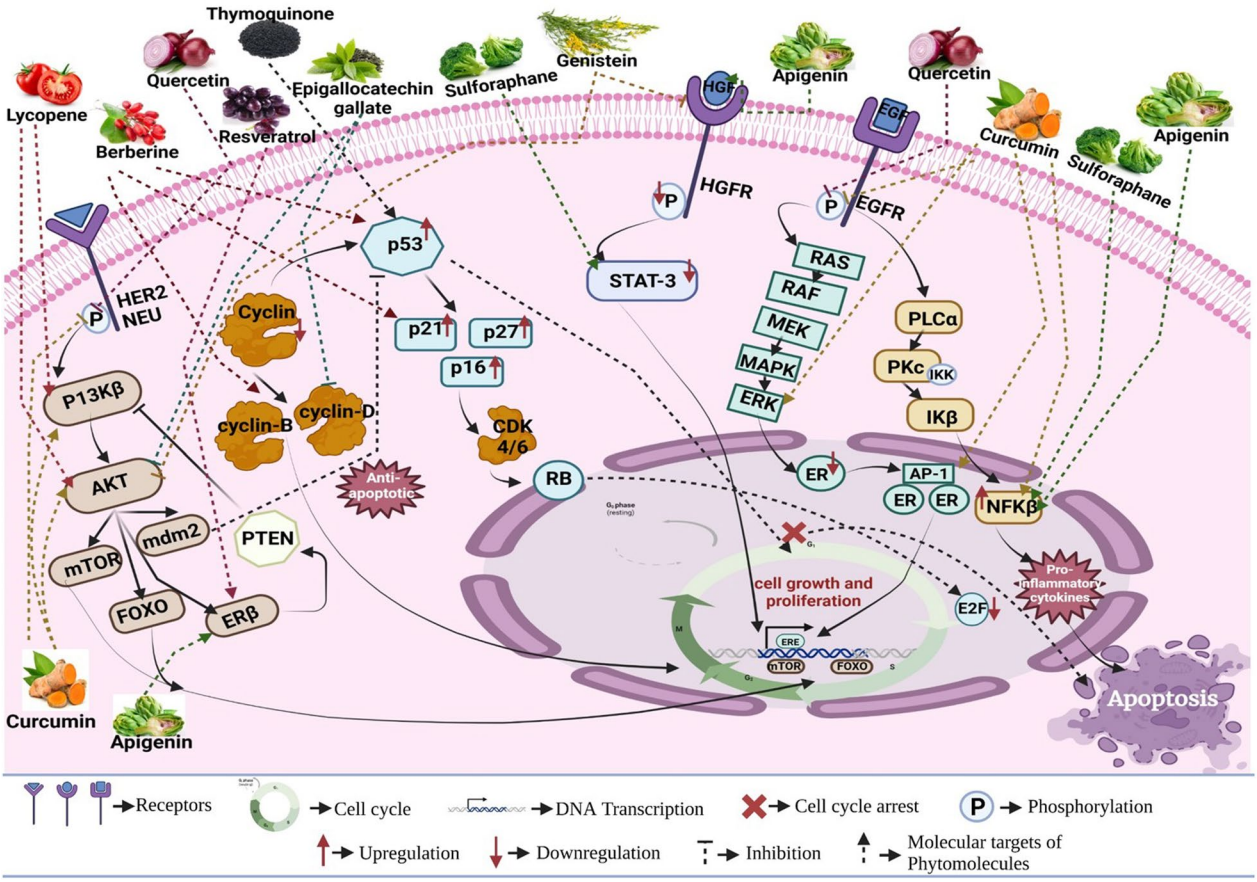


Fig. 3 Schematic representation of novel routes and formulation approaches for drug delivery in early Breast Cancer (Created with BioRender.com) (HER2, human epidermal growth factor receptor 2; HGFR, Hepatocyte Growth Factor Receptor; EGFR, Epidermal growth factor receptor; P13Kβ, Phosphoinositide 3-kinase beta; mTOR, mammalian Target of Rapamycin (Protein kinase); mdm2, Mouse Double Minute 2; FOXO, Forkhead Box O (Transcription factor); Erβ, Estrogen Receptor Beta; PTEN, Phosphatase and Tensin Homolog (tumour suppressor gene); P53, Tumour protein 53; CDK4/6, Cyclin-Dependent Kinase 4/6; RB, Retinoblastoma; STAT-3, Signal Transducer and Activator of Transcription 3; RAS, Rat Sarcoma (Oncogene); RAF, Rapidly Accelerated Fibrosarcoma (Protein kinase); MAPK, Mitogen-Activated Protein Kinase; ERK, Extracellular Signal-Regulated Kinase; ER- Estrogen receptor; AP-1, Activator Protein 1(transcription factor); PLCα, Phospholipase C Alpha; PKC, Protein kinase C; IKβ, Inhibitor of Nuclear Factor Kappa-B Kinase Beta (Protein kinase); NF-kβ, Nuclear Factor Kappa β; ERE- Estrogen Response Element)

receptor family. The binding of eph receptor and ephrin-B2 activates ephrin-B2 signalling, further promoting BC cell survival and migration. Berberine directly binds to ephrin-B2 and significantly reduces its level, thus contributing to its anticancer activity [28]. According to the literature, higher doses of BBR at 100 μM inhibits cell proliferation [29].

Although berberine's anti-cancer potential in BC via multiple mechanisms has been proven, the detailed mechanism is unclear. Before the molecule is advanced to the clinical stage, a rigorous study must be carried out to overcome certain adverse events like constipation, nausea, the allergic reaction upon intramuscular and intravenous administration etc. It is also important to work on its low water solubility and low bioavailability.

Curcumin

Curcumin is a hydrophobic bright yellow polyphenol obtained from the rhizomes of *Curcuma longa,* an herbaceous perennial plant belonging to the family of Zingiberaceae. Turmeric is a widely used spice having a reported consumption of 160–440 g/person/year in the Asian population. Curcumin has been documented as a drug to treat diverse diseases and disorders, BC being one of them (Fig. 4). Figure 4 illustrates how external signals (like ROS, growth factors, and cytokines) interact with various receptors (HER2, CXCR4, EGFR) and intracellular pathways to determine the cell's fate, whether it proceeds to proliferate, undergo apoptosis, or arrest in a specific cell cycle phase. The balance between these pathways is crucial for maintaining cellular homeostasis, and

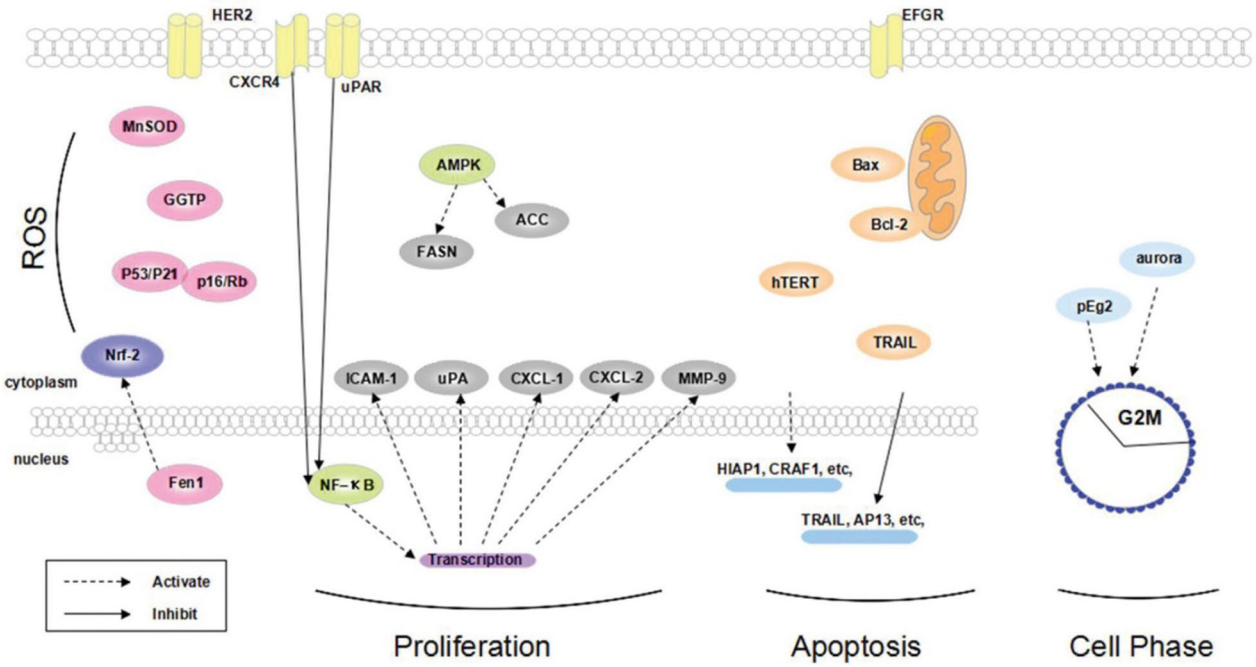


Fig. 4 Molecular targets of curcumin on ROS, proliferation, apoptosis, and cell phase arrest. HER2, human epidermal growth factor receptor 2; MnSOD, manganese-dependent superoxide dismutase; GGTP, gamma-glutamyltranspeptidase; Nrf-2, nuclear factor 2–related factor; Fen1, Flap structure-specific endonuclease 1; CXCR4, chemokine receptor 4; uPAR, urokinase plasminogen activator receptor; FASN, fatty acid synthase; ACC, acetyl-CoA carboxylase; ICAM-1, intercellular adhesion molecule 1; uPA, urokinase plasminogen activator; MMP-9, matrix metalloproteinase 9; hTERT, telomerase reverse transcriptase; TRAIL, TNF-related apoptosis-inducing ligand. This figure was reprinted with permission from Ref [32], copyright 2016, Society for Laboratory Automation and Screening

dysregulation can lead to diseases such as cancer. Mn-SOD and GGT1: Enzymes like manganese superoxide dismutase (Mn-SOD) and gamma-glutamyltransferase 1 (GGT1) help manage ROS levels. P53/p21 and p16/Rb Pathway: ROS can activate the tumor suppressor p53 and its downstream effector p21, as well as the p16/Rb pathway, leading to cell cycle arrest. Nrf2 Pathway: ROS activates Nrf2, a transcription factor that regulates antioxidant response elements (ARE), enhancing cellular antioxidant defense mechanisms. NF-κB Activation: ROS can also activate NF-κB through the inhibition of IκB (inhibitor of NF-κB), leading to the transcription of genes involved in inflammation and proliferation. HER2 and EGFR (Epidermal Growth Factor Receptor): Both receptors are involved in signaling pathways that promote cell proliferation. CXCR4 and uPAR (Urokinase-type Plasminogen Activator Receptor): These receptors are also involved in the regulation of cell migration, invasion, and proliferation. NF-κB Pathway: Once activated, NF-κB can translocate to the nucleus, promoting the expression of genes that contribute to cell proliferation, such as: ICAM-1 (Intercellular Adhesion Molecule 1), uPA (Urokinase Plasminogen Activator), CXCL-8 and CXCL-1 (Chemokines involved in recruiting immune cells), MMP-9 (Matrix Metalloproteinase 9). TRAIL (TNF-Related Apoptosis-Inducing Ligand): This ligand binds to its receptor and activates apoptotic pathways, including the activation of Bax and inhibition of Bcl-2, leading to mitochondrial outer membrane permeabilization (MOMP) and cytochrome c release, which ultimately results in apoptosis. hTERT (Human Telomerase Reverse Transcriptase): The inhibition of hTERT can lead to apoptosis by telomere shortening or other mechanisms. Inhibition of Survival Pathways: Certain molecules like HIAP1, cRAF, and others, which generally promote cell survival, are inhibited by the activation of apoptosis pathways. pEg2 (Aurora Kinase): This kinase is involved in the regulation of the G2/M phase transition in the cell cycle, promoting the progression of cells from the G2 phase to mitosis. Regulation by ROS and Other Signals: ROS and other signals can influence whether cells proceed through the cell cycle or undergo cell cycle arrest, influencing the balance between proliferation and cell death [22–25].

Both preventive and therapeutic property of curcumin in BC is well studied and documented, in addition to its anti-inflammatory and antioxidant properties. It is proven to affect the proliferation and invasion of BC cells by downregulation of Nuclear factor kappaB (*NF-κB*), a

proinflammatory transcription factor [30, 31]. It is also proven to regulate multiple intracellular signalling pathways, including transcription factors like signal transducer and activator of transcription 3 (*STAT3*), *NF-κB* and activating protein-1 (*AP-1*), kinases namely, epidermal growth factor receptor (EGFR), Janus tyrosine kinase (*JAK*) and extracellular signal-regulated kinase (ERK), receptors like HER2, interleukin 8 (IL-8), and chemokine receptor type 4 (CXCR4), cytokines like interleukin (IL), tumour necrosis factor (TNF) and macrophage inflammatory protein (MIP), enzymes like matrix metalloproteinases (MMP), inducible nitric oxide synthase (iNOS), and glutathione S-transferases (GST) and also growth factors like hepatocyte growth factor (HGF), epidermal growth factor (EGF) and nerve growth factor (NGF)[32]. Further, curcumin is an ideal chemosensitizer that inhibits P- glycoprotein (P-gp) overexpression and reverses multidrug resistance (MDR) in cancer cells.

Studies carried out to understand the combined effect of the use of curcumin with synthetic anticancer molecules in BC treatment have shown favourable outcomes. *In-vitro* study carried out by *B.S Vinod* et al. demonstrated a synergistic anticancer effect of a combination of curcumin 10 µM and 10 µM of 5-fluorouracil (5-FU) than 5-FU alone. The observation was mainly due to enhanced apoptosis, which was further understood to be due to the ability of curcumin to sensitize the BC cells to 5-FU[33]. *Tan* et al. reported in their review that combining curcumin with chemotherapy could be beneficial in cancer treatment by improving efficacy and reducing the toxic effects of drugs. Curcumin has been shown to protect biomembranes from peroxidative damage. The review demonstrates that co-treatment with curcumin and chemotherapy drugs such as docetaxel, metformin, 5-fluorouracil, doxorubicin, cisplatin, and celecoxib enhances the synergistic effect[34].

In summary, curcumin is a potent phytomolecule possessing anti-BC properties in addition to being a chemosensitizer. The combinational study of curcumin with standard anticancer molecules like 5- FU and docetaxel has improved the efficiency of the therapy and decreased associated toxic effects, indicating curcumin to be one of the phytomolecules of choice in combination chemotherapy.

Quercetin

Quercetin is a potent antioxidant belonging to the category of flavonoids and is obtained mostly from grapes, berries, broccoli, cherries, etc. Studies have shown that consuming a flavonoid-rich diet reduces the risk of BC and mechanism of action of flavonoid in triple-negative breast cancer are depicted in **(**Fig. 5**).** Studies have shown that de novo lipid synthesis stimulates the proliferation of BC cells, and therefore downregulation of de novo fatty synthesis is a novel therapeutic approach in the prevention of BC. Quercetin has reported an inhibitory effect on fatty acid synthase (*FAS*), thus acting as a potent suppressor of lipogenesis and thus resulting in apoptosis-induced cell death.

Studies by *Liu Shuo* et al. prove the multidrug resistance potential of co-treatment of 1 mg of quercetin with 3 mg of doxorubicin in MDA-MB-231/MDR1 BC cells. This combination therapy enhances the cytotoxicity of doxorubicin by increasing the intracellular accumulation of doxorubicin and facilitating apoptosis[35]. Liposome formulation containing vincristine and quercetin in the molar ratio of 1:2, developed by *Wong Man- yi* et al. showed a strong synergistic effect in addition to prolonged circulation in the hormone- and trastuzumab-insensitive JIMT-1 cells. Effective tumour growth inhibition was reported at two-thirds of the maximum tolerated dose of vincristine, indicating such combination therapy can even support the dose reduction in BC therapy [36]. According to a literature, Quercetin, administered at 50 mg/kg intraperitoneally twice daily for a month, reduced PKM2 levels in the tumor tissue of a breast cancer xenograft mouse model [37].

The research has reported a positive relationship between consuming a flavonoid-rich diet and a lower risk of BC. The studies related to the anti-BC potential of quercetin, one such flavonoid, also prove it to be a potential molecule that can be combined with standard synthetic molecules.

Lycopene

Lycopene, a tetraterpene carotenoid, is a natural antioxidant obtained mainly from tomato. Until recently, it was regarded as a common phytomolecule possessing only antioxidant properties. However, recent research has shown that, in addition to antioxidant activity, it inhibits cell proliferation, invasion, and metastasis and induces apoptosis, indicating its potential as an anticancer molecule. These activities of lycopene are mainly related to its potential to regulate several signal transduction pathways like *PI3K/Akt* pathway, suppression of sex steroid hormonal activity, modulating insulin-like growth factors system, and alteration of mitochondrial function. *Takeshima* et al. studied the anti-proliferative and apoptotic activity of lycopene against three subtypes of human bc cell lines, namely- MCF-7, SK-BR-3 and MDA-MB-468. Activation of the extracellular signal-regulated kinase ½ (ERK1 / 2), followed by suppression of cyclin D1 and upregulation of *p21* was studied to be the mechanism of action in all three cell lines. However, the study concluded that lycopene is predominantly effective in preventing TNBC. They studied that in TNBC, lycopene

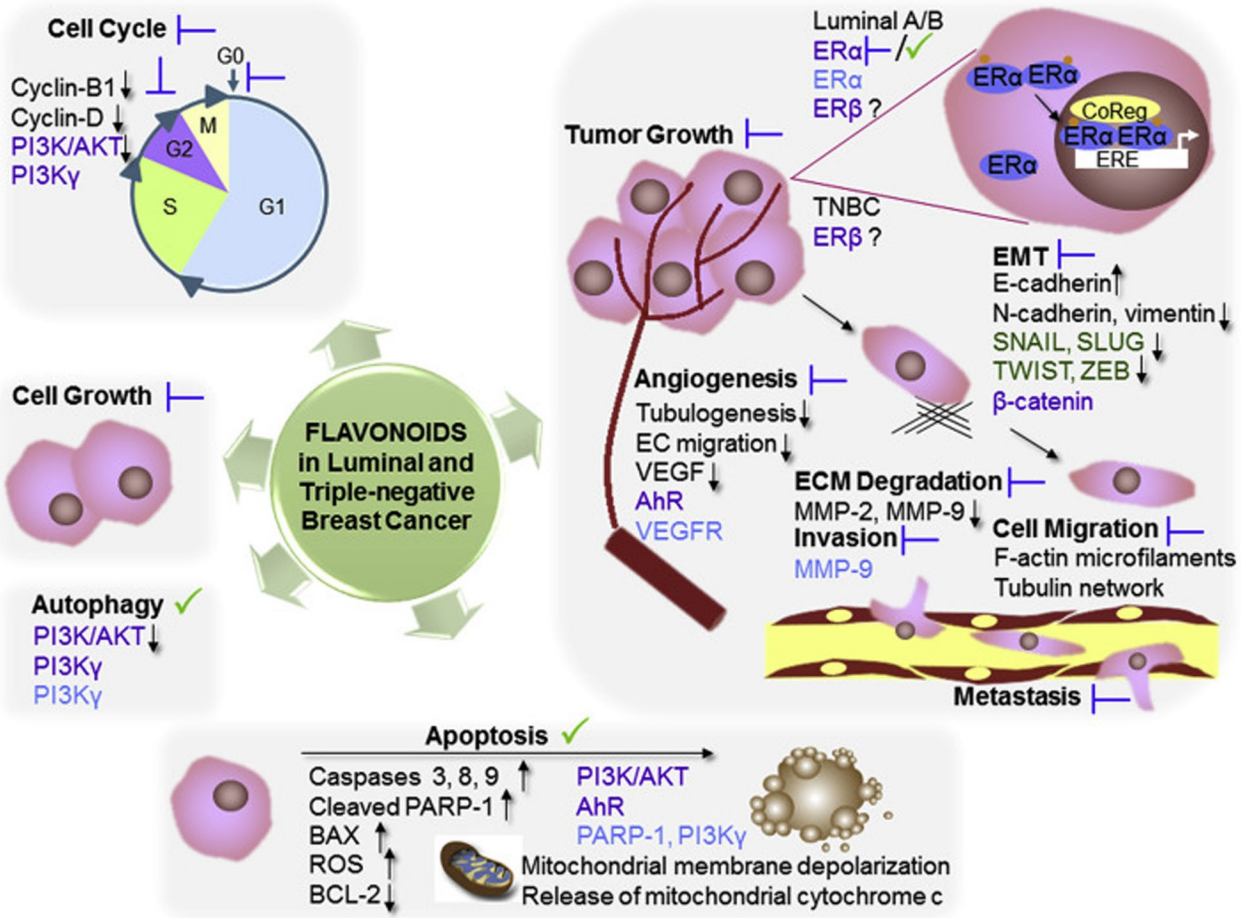


Fig. 5 Mechanisms of action frequently exerted by flavonoids in luminal and triple-negative breast cancer. Flavonoids produce numerous biological effects on breast tumor cells, modulating different signaling pathways. Certain flavonoids affect proliferation via cell cycle arrest, trigger apoptosis pathways, generate reactive oxygen species and induce autophagy modulating PI3Kγ signaling, which finally causes a reduction in tumor volume. Also, flavonoids can induce down-regulation of mesenchymal markers (and up-regulation of epithelial markers) via epithelial-mesenchymal transition-related transcription factors and the β-catenin pathway. In addition, tumor cell migration, invasion and angiogenic processes are inhibited through the modulation of metalloproteases, cytoskeletal regulation, vascular endothelial growth factor and aryl hydrocarbon receptor signaling. Some biological processes are inhibited (⊣) whereas others are induced (✓) by flavonoids. Signaling pathways involved are highlighted in violet, transcription factors are highlighted in green, and potential targets of certain flavonoids in sky blue. Some flavonoids might act as phytoestrogens and even might show biphasic effects on estrogen receptor α and β. EC: endothelial cell. This figure was reprinted from ref [81], copyright, 2022, Elsevier Masson *SAS*

inhibits the phosphorylation of protein kinase B (PKB) and its downstream molecule mammalian target of rapamycin (mTOR), followed by upregulation of proapoptotic BCL2 Associated X (Bax)[38]. Studies by *Ree et., 2010* have shown the in vitro anti-cancer and anti-metastatic potential of lycopene in MCF10A and MDA-MB-231. Inhibition of the activation of ERKs and PKB was the molecular mechanism studied by them[39].

Lycopene is a potent molecule to treat BC, TNBC in specific. Epidemiological studies have shown that consuming a lycopene-rich diet is associated with decreased cancer risk However, not many studies have been conducted to explore the exact molecular mechanism of this molecule in cancer.

Sulforaphane

Sulforaphane is another fascinating molecule from nature obtained mainly from cruciferous vegetables like cabbage, brussels, broccoli, sprouts, and kale. It exhibits anticancer properties due to the presence of glucosinolates which undergo enzymatic degradation to form isothiocyanates, and sulforaphane is one such isothiocyanate widely studied for its anticancer property. It exhibits its anticancer property by promoting cell arrest by reducing

histone deacetylases. It also reduces the activity of *NF-κB* and downregulates apoptosis inhibitors. When used in advanced stages of cancer, it has even shown to inhibit metastasis and angiogenesis. An interesting observation about the activity of sulforaphane is that it even increases the sensitivity of BC cells to chemotherapy in addition to acting as an anticancer molecule. Hence, when used with other chemotherapeutic molecules, sulforaphane might decrease the dose-dependent toxicity. However, it has limited clinical application due to hydrophobicity, poor bioavailability, and low gastrointestinal absorption.

Calcabrini cinzia et al. have described in their review that sulforaphane enhances the activity of doxorubicin and cisplatin when administered together. In their review, they have compiled various combination-based studies carried out at different doses and arrived at the above conclusion. They even opined that sulforaphane reduces the nephrotoxicity induced by cisplatin and cardiotoxicity induced by doxorubicin. However, some signs of hepatotoxicity and myelosuppression were observed when sulforaphane was administered along with Cisplatin[40]. But studies by *Xu Ying* et al. have proved that the observed side effects become negligible when this combination is delivered as polymeric nanoparticles, meaning the advantages outweigh the drawbacks. Nanoparticles significantly enhanced apoptosis mainly because of their effective internalization [41].

As explained above, its unique ability to increase the sensitivity of BC cells to therapy makes it a molecule of choice for combination therapy. Administering the combination as a nanoparticle is one of the best options for improving therapeutic outcomes.

Resveratrol

Resveratrol, a non-flavonoid polyphenol, is a phytoalexin obtained majorly from red wine and grapes. It is one such phytomolecule that exhibits both chemotherapeutic and chemo-preventive ability in BC. It mainly acts as a phytoestrogen, meaning they slow down cell growth by activating estrogen receptors β (Erβ). It behaves as both a pro-oxidant and an antioxidant. It acts as an aromatase inhibitor, lowering the estrogen levels by inhibiting the enzyme aromatase, which can convert other hormones to estrogen. Estrogen fuels the growth of BC. It can even reduce the localized estrogen production in BC cells by suppressing the transactivation of *CYP19* promoters I.3 and II.As discussed, doxorubicin used in the treatment of early BC has cardiotoxicity as a side effect due to the production of excess ROS. Researchers have proven that using Resveratrol significantly reduces the formation of ROS, making it an effective chemoprotective agent. Even though it is a potent phytomolecule, it has a very low bioavailability. Studies by *Johnson Jeremy* et al. showed that using resveratrol (100 mg/Kg; oral gavage) in combination with piperine (100 mg/Kg; oral gavage) in mice enhances its oral bioavailability, meaning piperine is a bioavailability enhancer [42].

Thus, resveratrol is a potent phytoestrogen exhibiting both chemo-preventive and chemotherapeutic properties. Its potential to reduce the cardiotoxic side effects of doxorubicin has proved its potential to be a phyto molecule of choice for combination therapy.

Epigallocatechin gallate

Epigallocatechin gallate (EGCG), a powerful antioxidant belonging to the class of flavonols, is the principal constituent of tea, *Camellia sinensis* belonging to the family Theaceae. It has been shown to exhibit anticancer activity at doses 10 and 100 μM in TNBC which does not respond to other therapies like the ones targeting HER2 protein receptors or hormonal therapies. It acts by inhibiting cell proliferation by scavenging ROS. According to researchers, this activity is shown at doses of 10 and 100 μM[43]. EGCG at the dose of 20 μM inhibits the Hs578T cell proliferation by promoting apoptosis. EGCG also acts by downregulating the expression of anti-apoptotic genes like insulin-like growth factor1 receptor (IGF1R) and myeloid cell leukaemia sequence 1 (MCL1) and arrests the breast tumor invasion in TNBC by inhibiting the expression of vascular endothelial growth factor (VEGF). Apart from this, EGCG also blocks fatty acid synthase (FASN) and inhibits the expression of β-catenin and cyclin D1.

Though the studies have proved that EGCG can control the growth of TNBC tumor, no clinical trials have been conducted to date. The main drawbacks of using this molecule are the poor bioavailability and stability, which can be overcome by designing micro and nanoparticle-based formulations of this molecule. In a fascinating study, *Braicu* et al. proposed that the combination of *p53* siRNA and EGCG, through the activation of apoptosis and autophagy, potentiated the antitumor effects of EGCG in Hs578T cells[44].

Apigenin

Apigenin is a yellow crystalline water-soluble flavone found in various plants such as parsley, celery, artichokes, chamomile, oregano, and vine spinach. It has gained attention due to its traditional use in chamomile tea for insomnia and anxiety. Apingenin is a multi-targeted molecule with several mechanisms of action. One of the main pathways through which apigenin exerts its effects is the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway. It inhibits aromatase and fatty acid synthase (FAS), which are involved in hormone metabolism and synthesis. It also downregulates the expression of VEGF, NF-Kb, and erythroblastic oncogene B (*ErbB2*).

Additionally, it also works by suppressing mitogen-activated protein kinase (*MAPK*). It has also proven to show synergistic activity with many antineoplastic agents. An interesting observation in studies with apigenin-treated mice was that the diameter of blood vessels supplying cancer cells was smaller, leading to restricted nutrient flow to the tumors. This starvation of cancer cells could impact tumor growth and spread. In a study conducted by *Long* et al*., 2008* apigenin was shown to be a potent inhibitor of antiestrogen-resistant BC cells at concentrations of 10 μM or higher. This activity was attributed to several mechanisms, including the inhibition of estrogen receptor alpha (ERα) mobility, downregulation of nuclear receptor coactivator 3 (*NCOA3*) expression levels, and inhibition of various protein kinases such as Mitogen-activated protein kinase (*MAPK*), *AKT*, and *PKA*[45].

Overall, apigenin exhibits diverse mechanisms of action and shows potential as a therapeutic agent in cancer treatment, particularly in BC and antiestrogen-resistant cases. However, further research is needed to understand its effectiveness and potential clinical applications fully.

Genistein

Genistein, an isoflavone, is a phytoestrogen obtained mainly from plants belonging to the soy family. It exhibits its anti-cancer property in BC via multiple mechanisms. One prominent mechanism is its ability to induce apoptosis, or programmed cell death, in these cells. This apoptotic effect is believed to be mediated by activating the Peroxisome Proliferator-Activated Receptor-gamma (*PPARγ*) pathway. Furthermore, genistein exerts its influence by downregulating the expression of cyclooxygenase-2 and prostaglandin E2.

Additionally, genistein inhibits the growth of BC cells by downregulating the Hedgehog-Gli1 signalling pathway. Although the specific mechanism of action in BC cells is not extensively studied for this compound, it has been found to promote apoptosis by enhancing the expression of ER stress-associated proteins like calpain 1, leading to the activation of apoptotic protease activating factor 1(*APAF1*). Another study demonstrated that genistein induces apoptosis by upregulating the expression of GRP78, which triggers ER stress and enhances the activity of PERK, subsequently activating the transcription factor CCAAT/enhancer-binding protein homologous protein (*CHOP*). Regarding proliferation prevention, genistein blocks the activation of NF-B, directly or indirectly, by inactivating EGF and Akt, which plays a vital role in preventing the proliferation of BC cells [64]. In an ovariectomized nude mouse breast cancer xenograft model, genistein and cisplatin were administered in vitro at a dose of 5 mg/kg/day each. The average concentration of total genistein metabolite equivalent in the xenograft tumor tissues reached 0.2729 nmol/g of dry weight. Upon reaching this threshold, genistein significantly enhanced cisplatin's cancer-protective effects, demonstrating the potential of genistein in treating breast cancer [46].

Overall, genistein's multifaceted mechanisms contribute to its anti-cancer effects in BC, including apoptosis induction, downregulation of specific gene expressions, and inhibition of proliferation-related pathways such as NF-B. Further research is warranted to fully elucidate the precise molecular mechanisms underlying genistein's effects in BC.

Thymoquinone

Thymoquinone, the principal constituent of Nigella sativa from the Ranunculaceae family, exhibits a wide range of therapeutic properties and is utilized in various traditional systems of medicine.

Its apoptotic properties, and various inhibitory mechanisms, contribute to its anti-cancer effects. Studies have demonstrated that Thymoquinone interferes with *PI3K/Akt* signalling, leading to G1 arrest. Additionally, it induces apoptosis by upregulating the expression of P53. Thymoquinone was studied to regulate this *EMT* process by down-regulating Twist-related protein 1 (*TWIST1*) expression. Studies by Woo et al., 2011 show *PPAR- γ* to be yet another molecular target for Thymoquinone activity [47]. Literature indicates that thymoquinone is effective against breast cancer with a dose of 20 mg/kg body weight for oral administration and 5 mg/kg body weight for intravenous administration. This study was conducted on layer chickens [48].

Thymoquinone exhibits therapeutic properties and has demonstrated promising anti-cancer effects against BC cell lines. Further research is needed to fully understand the molecular mechanisms underlying its actions and potential as a therapeutic agent in BC treatment.

Limitations of phytomolecules

Despite the promising anticancer properties exhibited by phytochemicals, including their ability to decrease cellular proliferation, induce apoptosis, and modify signal transduction pathways, their utilization presents several challenges [49, 50]. One significant hurdle is the variability in treatment effectiveness. The impact of phytochemicals can vary greatly depending on the specific type of phytochemical and the individual subtype of BC. This diversity makes it challenging to establish the optimal dosage and delivery regimen [51]. For instance, although resveratrol has demonstrated the ability to suppress TNBC cell growth in laboratory settings, its effectiveness in animal models and human studies has been inconsistent [52]. Another limitation is the lack of comprehensive understanding regarding the pharmacokinetics

and pharmacodynamics of phytochemicals. This gap in knowledge makes it difficult to predict their efficacy and safety in clinical settings. Additionally, it poses challenges in identifying potential interactions with other medications that could influence treatment outcomes [53]. Thorough understanding of the mechanisms underlying herb-drug interactions is crucial for conducting comprehensive clinical risk assessments. This knowledge is indispensable for healthcare professionals striving to minimize risks and ensure the safety of patients using herbal medicinal products [54]. Moreover, the considerable variation in phytochemical sources in terms of content and quality presents a significant obstacle. This diversity complicates the standardization of phytochemical-based therapies and undermines their consistent therapeutic efficacy. Factors such as growing conditions, seasonality, and harvesting methods can influence the composition of plant extracts, affecting the concentration and stability of phytochemicals [55].

As discussed, addressing obstacles like limited solubility, inadequate bioavailability, and safety considerations is essential for the successful transition of these bioactive phytochemicals from laboratory investigation to clinical application. For instance, among the phytomolecules discussed in the current review, berberine presents challenges such as poor absorption, rapid metabolism, and rapid systemic elimination, resulting in diminished plasma and tissue concentrations. Numerous researchers have pursued various strategies to address this hurdle and improve the bioavailability of berberine. These approaches encompass the development of innovative formulation techniques, utilization of novel drug delivery systems (NDDS) like liposomes, nanosized formulations, phospholipid complexes, mucoadhesive microparticles, and microemulsions, incorporation of adjuvants, and designing of structural analogs of Berberine [56]. Another phytomolecule, Curcumin, also faces obstacles such as poor water solubility, particularly in acidic and neutral environments, chemical instability, especially under neutral and alkaline conditions, rapid enzymatic metabolism in the human body, and limited bioavailability. Consequently, only a small portion of ingested curcumin is effectively absorbed into the bloodstream. However, these challenges are also addressed through the application of encapsulation technologies, which involve entrapping curcumin within minute particles. Commonly employed edible microparticles or nanoparticles for this purpose include micelles, solid lipid particles, liposomes, emulsions, and biopolymer particles [57]. Despite numerous pharmacological benefits and extensive history of use of quercetein as a nutraceutical, its clinical research utilization as a therapeutic molecule is restricted due to challenges like poor water solubility, significant first-pass metabolism, and resulting low bioavailability. Researchers have explored various drug delivery approaches in pre-clinical and clinical settings, including nanoparticles, inclusion complexes, nano emulsions, micelles and solid dispersion [58]. Lycopene undergoes isomerization or degradation when subjected to light, oxygen, and fluctuations in temperature, resulting in a loss of its biological activity. Furthermore, lycopene faces challenges related to poor oral bioavailability and water solubility, posing obstacles for the formulation of commercial products containing carotenoids. Utilizing nanobiotechnology, such as the creation of lipid-core nano capsules featuring a poly-ε-caprolactone wall coated with polysorbate 80, has demonstrated efficacy in enhancing the stability of lycopene [59]. Bioavailability and stability are the challenges associated with even other molecules like Sulforaphane [60], Resveratrol [61], EGCG [46], Apigenin [62], Genistein [46], and Thymoquinone [63].

In summary, while phytochemicals hold promise for targeting various BC pathways, addressing these limitations is essential before they can be widely adopted as a therapeutic option. Further research is imperative to gain a deeper understanding of their pharmacokinetics, pharmacodynamics, and potential interactions, as well as to establish protocols for standardization and quality control. Incorporating nanotechnology alongside other cutting-edge methods such as high throughput screening and rational drug design holds promise for optimizing the development and application of plant-based drug molecules. It is also imperative to exert concerted efforts in research, isolation, quality control, and market establishment to fully leverage the potential of phytochemical resources in treating diseases, thus transitioning them from preventive measures to effective therapeutic solutions. It is also important to note that only 10% of the 300,000 identified plant species have been studied for biological activity, leaving a vast majority of phytochemical diversity untapped for potential pharmaceutical applications. Many of these unexplored plant compounds could be promising candidates for future drug development [64].

Nutriceutics in the treatment of early breast cancer

In the nineteenth century, Hippocrates' put forth the philosophy of "let food be thy medicine and medicine be thy food," and emphasized the relationship between nutrition and human health. Later, in 1989, Stephen DeFelice first introduced the term "Nutraceuticals." This newly coined word blends "nutrition" and "pharmaceutical" and was defined by him as encompassing "food components or active ingredients in food that offer beneficial effects on overall health and well-being, including their potential in preventing and treating various diseases". It is since

then that the use of food constituents, extracts, and phytomolecules became an emerging area of research focus in the prevention and effective management of chronic diseases. Numerous research studies have also shown that they could function as a valuable complement to pharmaceutical drugs in mitigating undesirable side effects. The current review focuses on 'nutriceutics', the term that authors use to define the use of various phytomolecules in combination with FDA approved drugs to prevent, manage and treat a particule disease, here breast cancer in specific. 'Nutreceutics' also focuses on employing nanotechnology and the novel methods of drug delivery for effective treatment.

Benefits and challenges associated with nutriceutics

Many cancer patients opt to incorporate herbal medicine alongside conventional chemotherapy for various reasons. Some seek to alleviate the adverse effects of conventional chemotherapy, while others believe in the potential health benefits of herbal remedies, such as enhancing overall well-being, managing disease symptoms, and boosting immunity. In addition to patients voluntarily using herbal products, ongoing research explores the integration of herbal medicines into cancer treatment protocols with the aim of mitigating the side effects of chemotherapy (Table 2). Combining phytochemicals with conventional anticancer drugs also results in pharmacodynamic interactions, which can be either synergistic or antagonistic[65]. The summary of combinational therapy explored for BC is provided in Table 3. Based on the numerous studies reviewed, it can be deduced that combining phytochemicals with standard anticancer drugs offers several advantages. These combinations help overcome associated toxicities, exhibit synergistic effects, act as chemosensitizers, counteract drug resistance, suppress chemoresistance, upregulate the expression of desirable genes while downregulating the expression of undesirable ones, improve apoptosis (programmed cell death), and enhance the intracellular accumulation of standard anticancer drugs in some cases. Therefore, it is reasonable to state that combining phytomolecules with standard anticancer agents can improve the overall quality of life for patients.

Traditional single therapies often require high doses of standard anticancer agents. In contrast, the increased effectiveness of combination makes it possible to lower the dosage of the chemotherapy medication, resulting in a decreased occurrence of both toxicity and drug resistance. This approach not only improves the affordability of the treatment but also supports the use of higher quantities of dietary phytomolecules, making the formulation more accessible. Therefore, combinations can also address the issue of affordability, which is yet another drawback of cancer chemotherapy.

Pre-clinical studies have demonstrated that chemo-herbal drug combination therapy enhances the therapeutic efficacy through various mechanisms, however, it's essential to emphasize that some of the preclinical findings do not readily translate into practical applications in clinical settings. Hence, safety concerns regarding the combination of chemotherapy and herbal drugs have become a significant focus for both health authorities and the general public. Consequently, there is an urgent need for safety pharmacology assessments of this combination therapy to uncover any potential undesirable pharmacodynamic effects.

To bridge the gap between experimental data and the clinical utilization of herbal drugs as adjuvant therapy in the management of cancer two key steps would be necessary. Firstly, an in-depth mechanistic evaluation of chemo-herbal drug combination therapy, utilizing advanced methods like network-based optimization approaches and cutting-edge facilities to generate dependable data that can be predictive for human applications and secondly multicentre clinical trials to expedite the adoption of chemo-herbal drug combination therapy for cancer treatment.

Future of nutriceutics

The future of nutriceutics lies in their customization to individual patient needs, enabling clinicians to maximize therapeutic benefits while minimizing side effects. These personalized regimens, guided by genetic and metabolic insights, can address unique patient characteristics, potentially enhancing treatment efficacy and improving overall quality of life. For example, Soy products contain isoflavones that can mimic estrogen in the body. Some breast cancer patients with hormone receptor-positive tumors may benefit from personalized advice to limit or incorporate soy into their diet based on their specific hormonal profile. As genetics and pharmacogenomics research advances, we can anticipate more precise and patient-centric approaches to breast cancer management through tailored nutraceutical interventions, offering the potential for improved outcomes and enhanced well-being for those dealing with this diagnosis.

Emerging trends

While nutraceuticals have shown promise in combating breast cancer, their effectiveness was not adequately addressed until about a decade ago, particularly in terms of their absorption, metabolic processing, and their ability to target breast tissue. Recent research has been dedicated to improving these aspects, and one notable approach is the integration of nanotechnology. This

Table 3 Combination-based formulations studied in BC

Combination studied	Dose	Model	Formulation designed	Pharmacological effects	References
Paclitaxel + Curcumin	Paclitaxel 0.1 M + Curcumin 1 µM at 37 °C for 24 h	MCF 7 cell lines	Liposomes	Improved chemotherapeutic efficiency was observed due to induced stronger G_2/M arrest	[110]
Doxorubicin + Curcumin	Curcumin50 mg/Kg + Doxorubicin 50 mg/ Kg Once a week for 7 weeks	BALB/c mice xenograft model (MCF- 7 cell lines injected)	Transferrin-decorated nanoparticles	Effective targeting, stronger antitumor effect and decreased cytotoxic effects of doxorubicin in bc xenograft mouse model	[111]
Doxorubicin + Curcumin	Doxorubin 10 mg /kg (i.v) + Curcumin 10 mg/kg (i.v) injected every other 2 days for 12 days	Female Balb/C mice	Micellar delivery system	Better tumor targeting and accumulation of drugs. It even efficiently inhibited tumor growth It showed minimal damage to cardiac tissue compared to using doxorubicin alone due to the potential myocardial effect possessed by curcumin	[112]
Vincristine + Quercetin	Vincristine 1.33 mg days/kg (two-thirds of the maximum tolerated dose in severe combined immunodeficiency disease (SCID) mice) + Quercetein 0.24 mg/kg. At these values, the molar ratio of vincristine/quercetin was 2:1	SCID mice xenograft model (JIMT-1 cell lines injected)	Liposomes	Significant antitumor activity was observed even when two-thirds of the maximum tolerated dose of Vincristine was used	[36]
Tamoxifen + Resveratrol	Tamoxifen 1.02 mg/kg (oral) and Resveratrol 10.20 mg/kg (oral) once	Albino Wistar rats	Self-nano emulsifying drug delivery system (SNEDDS)	The oral bioavailability of TAM from SNEDDS was significantly higher, being 1.63 times greater ($p < 0.05$) than the combination suspension and 4.16 times greater ($p < 0.05$) than the TAM suspension	[72]
Doxorubicin + Berberine	Berberine (12 mg/ Kg) and Doxorubcin (1.2 mg/ Kg) for 16 days	Female BALB/c mice	Liposomes	Significant tumor growth inhibition in 4T1 murine mammary carcinoma compared to Doxil prevented the myocardial toxicity caused by Doxil	[113]
Doxorubicin + Berberine	25 µM + 25 µM incubated for 48 h	MDA-MB-231 and T47D cells	PLGA nanoparticles	The formulation demonstrated the excellent anti-proliferative effect compared to the individual drugs/bioactives against MDA-MB-231 and T47D cells	[114]
Doxorubicin + Quercetin	0.156 µg/mL + 40 µg/mL for 72 h	MCF 7 cell lines	PEGylated niosomes	The formulation exhibited higher toxicity against BC cells compared to the unencapsulated forms and showed a synergistic effect	[115]

Table 3 (continued)

Combination studied	Dose	Model	Formulation designed	Pharmacological effects	References
Docetaxel + Gemcitabine	Docetaxel 2 mg/Kg (i.v) + Gemcitabine 10 mg/Kg (i.v.) per day via tail vein for 7 days	Female Sprague Dawley Rats	Albumin nanoparticles	The AUC increased by 6.12 and 3.27-fold and $T_{1/2}$ by 6.28 and 8.9-fold of docetaxel and gemcitabine as compared to Taxotere® and Gemzar®	[116]
Pemetrexed + Ellagic acid	Pemetrexed 34 µg/mL + Ellagic acid 26 µg/mL for 24 h	MCF-7 cell lines	Mesoporous silica nanoparticles	The formulation demonstrated a sequential faster release of ellagic acid followed by a sustained release of pemetrexed It showed the highest cytotoxicity against MCF-7 BC cells, as revealed by the lowest combination index compared to free drugs	[117]
Paclitaxel + Curcumin	Paclitaxel 13.54 µg/mL and Curcumin 44.60 µg/mL for 48 h Paclitaxel 30.75 µg/mL + Curcumin 76.71 µg/mL for 48 h	MCF-7 cell lines MCF- 10 A cell lines	PEGylated niosomes	The Curcumin and Paclitaxel IC_{50} value was reduced by threefold and 3.6-fold, respectively Combination formulation was effective in enhancing the cytotoxicity activity against MCF-7 cells	[118]
Methotrexate + Curcumin	5 mg Methotrexate (i.v) + 2.5 mg Curcumin (i.v.) both for 4 weeks	Sprague Dawley rats	PLGA nanoparticles	Co-delivery demonstrated a synergistic effect on inhibiting the progression of BC	[119]
Paclitaxel + Doxorubicin + Cannabidiol	Paclitaxel 5.52 nM + Doxorubcin 0.03 µM + Cannabidiol 20 µM for 48 h Paclitaxel 22.86 nM + Doxorubcin 1.41 µM + Cannabidiol 10 µM for 48 h	MCF-7cell lines MDA-MB-231cell lines	Polymeric microparticles	A Significant reduction of the effective concentration of antineoplastic agents in MDA-MB-231 and MCF-7 cells was observed	[120]
Guanidine + Curcumin	Guanidine 25 µM + Curcumin 30 µM for 72 h	MCF-7 Cell lines	Mesoporous silica nanoparticles	The formulation induced delayed apoptosis and necrosis at 48 and 72 h compared with individual-drug-treated cells An Increase in the phosphorylation of oncogenic proteins inducing cell death in MCF-7 cells was observed	[121]

technology is primarily employed to enhance the development of nutraceutical products with improved bioavailability, reduced toxicity, and greater sustainability. Additionally, nanostructures can facilitate photothermal and photodynamic therapy for breast tumor ablation by inducing cell death. These nanoparticles also remodel the tumor microenvironment and repolarize macrophages to enhance antitumor immunity. Stimuli-responsive nanocarriers, such as those sensitive to pH, redox, and light, enable targeted suppression of breast tumors[66]. Notable examples of nanotecapproach include Curcumin encapsulated casein nanoparticles, Curcumin encapsulated lipidic nanoconstructs, Piperine encapsulated lipid polymer hybrid nanoparticles, Thymoquinone-loaded lipid-polymer hybrid nanoparticles. In addition to the approaches, further advancements include the development of surface-engineered nanosystems like hyaluronic acid modified mesoporous silica nanoparticle loaded with curcumin, Curcumin-loaded ZnO nanoparticles, Resveratrol-loaded folic acid functionalized nanostructured lipid carriers, Folic acid engineered sulforaphane loaded microbeads were designed to specifically target breast cancer cells, marking a promising direction in cancer research. Chitosan (CS)-based nanoparticles too have been incorporated into breast cancer therapy to improve the targeted delivery of drugs and genes to the tumor site. These CS nanostructures are studied to inhibit tumor growth by enhancing the precision of drug and gene delivery and ensuring their accumulation in tumor cells. Tumor cells internalize CS-based nanoparticles via endocytosis [67].

Formulation design

The combination of drugs can be effective only when delivered by choosing an appropriate Drug Delivery System (DDS). A DDS can potentially enhance drug concentration in the cells, thereby increasing the therapeutic efficacy. It can even help in reducing the dose and, thereby, toxicity. Enhancement of the residence time in target cells is another advantage that DDS can offer [68]. Novel nanotechnology-based drug delivery system is being widely explored to solve the drawbacks associated with chemotherapy. The various formulation being studied for delivering the combination of molecules and their outcomes is

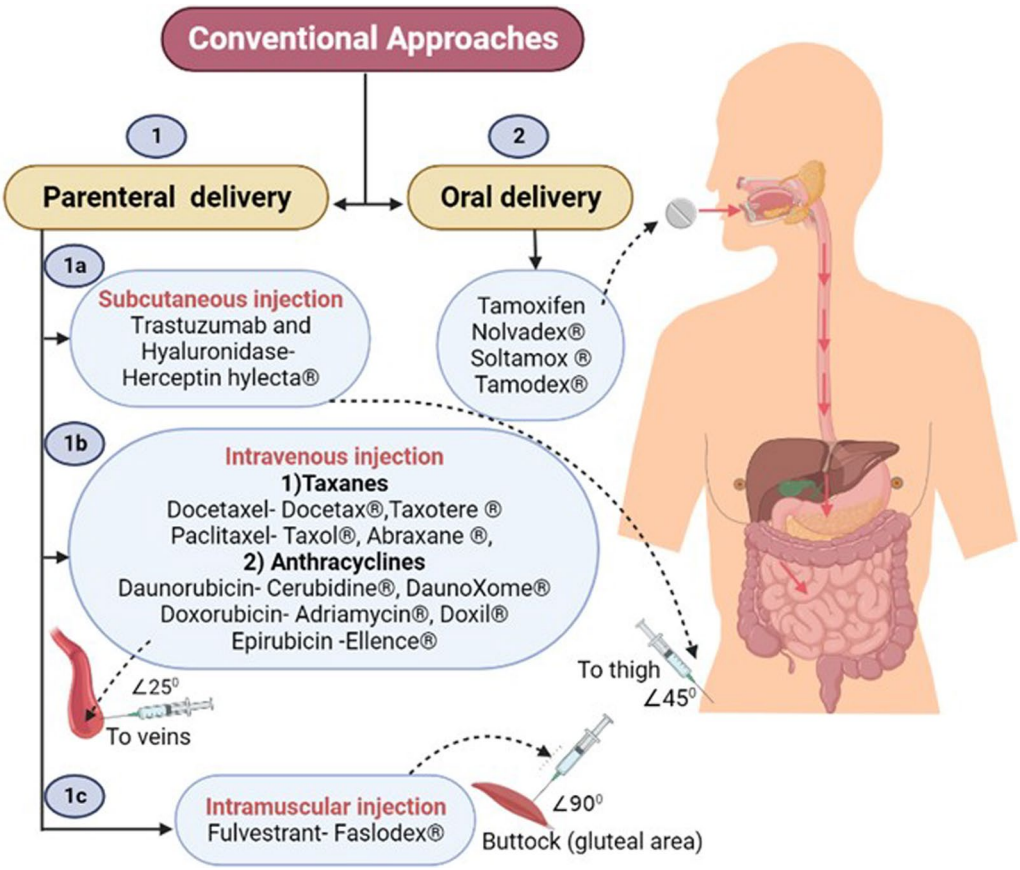


Fig. 6 Conventional drug delivery approaches for early Breast Cancer treatment (Created with BioRender.com)

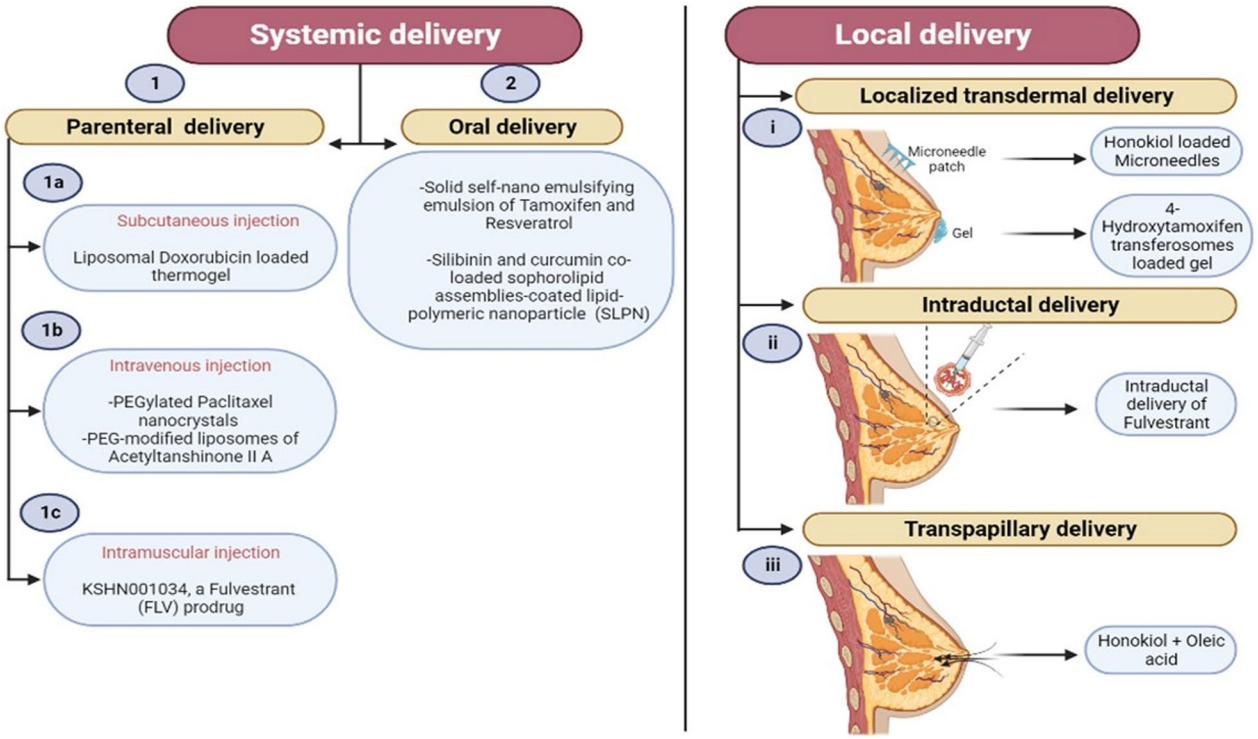


Fig. 7 Schematic representation of novel routes and formulation approaches for drug delivery in early Breast Cancer (Created with BioRender.com)

discussed in Table 3. Conventional approaches followed to deliver the drug is depicted in Fig. 6**.** The novel DDSs include nano-vehicles meant to act as drug- reservoirs and deliver the drug to the target site. It is also meant to improve the pharmacological and therapeutic properties of drug. Some such nano-vehicles are depicted in Fig. 7.

Solid lipid nanoparticles (SLNs) are biocompatible ingredients comprising of solid core lipid nanocarriers capable of accommodating lipophilic and lipophobic drugs and therefore are one of the preferred choices for drug delivery. Their surface modification can support achieving targeted delivery. Though they comprise soluble lipids, their stability is a concern. Polymerosomes are vesicles formed by the self-assembling of amphiphilic polymers and can load both lipophilic and lipophobic drugs. Their stability and storage capacity are often compared with liposomes made of phospholipids. Polymerosomes have been proven to be superior to liposomes in both these terms. Polymeric nanoparticles are colloidal systems that bind polymeric matrix with a copolymer. Based on the preparation method, they are further classified as nanospheres, in which the drugs are evenly dispersed in the matrix system, and nanocapsules, where the drugs are enclosed in a polymer membrane. They are mainly designed to obtain targeted and sustained drug delivery.

Dendrimers are radially symmetric, highly branched, three-dimensional molecules with well-defined, homogeneous structures possessing a low polydispersity index. They have tree-like arms or branches, and the layers formed between each branch's cascade point are termed "generations." Both hydrophilic and hydrophobic drugs can be loaded in them.

Liposomes are spheres of concentric phospholipid bilayers separated by aqueous compartments, capable of accommodating lipophilic and lipophobic drugs. They have a outer hydrophilic head and an inner hydrophobic fatty acid tail. Lipodox® and Lipodox 50® administered as intravenous injections are doxorubicin-based liposomal formulations approved by FDA. Combisomes, a novel term coined by *Dubey* et al. indicates fourth-generation liposomes containing both food bioactives and anticancer drugs in the vesicles [69]. Liposomes and lipid nanoparticles are lipid-based formulations, but unlike liposomes, lipid nanoparticles do not possess a bilayer and are primarily made up of cationic lipids. Thus, lipid nanoparticles are the advanced version of Liposomes. Lipid nanoparticles are the most popular non-viral gene delivery system. The colloidal particles made of amphiphilic copolymers that can self-assemble in aqueous medium are called polymeric micelles. They can accumulate lipophilic and lipophobic drugs because of their

hydrophobic core and hydrophilic surroundings. They have proven to increase the intracellular concentration in doxorubicin-resistant MCF-7 cells because of their ability to decrease p-glycoprotein efflux. Genexol-PM, administered as an IV infusion, is an FDA-approved polymeric micelle used to treat BC. Studies have proven it to possess greater anti-tumour activity and accumulation in tumor cells than conventional Paclitaxel therapy. It has shown a higher anti-tumour activity and more accumulation in tumor tissue compared to conventional paclitaxel therapy [70].

Quantum dots are an interesting class of fluorescent nanomaterials. Since it is easy to modify their surface and optical properties, and since they have high quantum yields, they are used as multifunctional nano-vehicles. Ghanbari et al. formulated glucosamine-conjugated graphene quantum dots (GQDs) for the targeted delivery of curcumin to the breast and observed positive outcomes [71]. Mesoporous nanoparticles made of silica are biocompatible, thermostable, and facilitate effective drug loading.

The other biocompatible DDS being explored for gene and drug delivery include silver nanoparticles, gold nanoparticles, nanorods, nanospheres, nanoshells, nanosponges and many others. The above discussed drug delivery systems are depicted in Fig. 8.

Drug delivery approaches

The route of administration has a vital role in therapeutic outcomes and quality of life of the patients. The choice of route depends on the pharmacokinetics and pharmacodynamic profile of the drug, in addition to convenience and compliance. Each route has its pros and cons. Hence, it is crucial to understand the characteristic properties of each route. The administration route used in conventional and novel approaches can be broadly categorized into systemic and local, as depicted in Figs. 6 and 7.

Systemic delivery

Oral delivery

The most used route for medication administration is the oral route owing to its convenience for patients who can swallow and tolerate oral medications. It is widely accepted by patients due to its cost-effectiveness and ease of administration. When a drug is taken orally, the small intestine is the primary site where it is absorbed into the bloodstream, affecting its bioavailability. The harsh gastrointestinal environment also affects the bioavailability of orally administered drugs; many novel drug delivery systems (NDDS) are being explored to improve the same. For instance, in a study, a solid self-nano emulsifying emulsion of tamoxifen and resveratrol showed improved oral bioavailability, higher intestinal drug permeation, and increased cytotoxicity and cellular internalization in MCF-7 cells compared to an oral suspension of tamoxifen and resveratrol [72]. In another study, a novel oral nanocarrier, sophorolipid assemblies-coated lipid-polymeric nanoparticle (SLPN), was developed to exhibit bio-responsive mucus diffusion. The sophorolipid assemblies in the mucus presented a stronger affinity for mucin than for the inner shell of the nanoparticles, leading to their dissociation during mucus penetration and perhaps interacting with the mucin binding sites for nanoparticles, thus allowing nanoparticle mucus diffusion. Silibinin and curcumin co-loaded SLPNs were shown to reduce BC

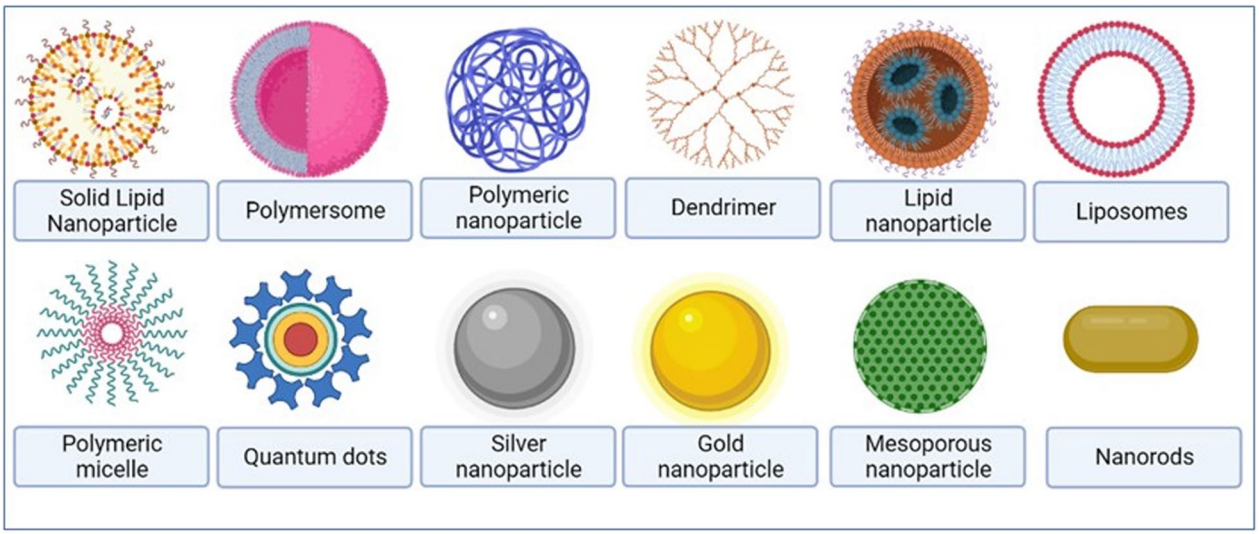


Fig. 8 Drug delivery systems employed for combined delivery of drugs in Breast Cancer (Created with BioRender.com)

metastasis in 4T1 tumor-bearing mice [73]. Drug degradation due to fluids present in the digestive tract, the inability of drug molecules to effectively traverse intestinal epithelium to reach the systemic circulation, drug insolubility due to low pH levels in the digestive tract, and the first-pass effect are some of the other limitations of oral drug delivery.

Parenteral delivery

Intravenous injection Intravenous (IV) administration is the most common alternative to oral drug delivery for patients who cannot tolerate oral medications, including critically ill and comatose patients. This route allows for direct administration of the medication into the systemic circulation, ensuring nearly complete bioavailability. Moreover, intravenous administration offers the advantage of bypassing the first-pass metabolism. It is also the most extensively studied route of administration for combination drugs. Various nanoparticles, micelles, and liposomes have been designed and evaluated to deliver combination drugs through the intravenous (IV) route. These formulations have efficiently inhibited tumor growth and improved tumor targeting, thereby reducing cytotoxicity against healthy cells. However, it is important to note that intravenous injection can cause discomfort or pain at the administration site. These factors should be considered when utilizing intravenous administration for drug delivery.

Intramuscular injection Intramuscular (IM) injection is commonly used when oral drug absorption is erratic or incomplete, when the drug undergoes significant first-pass metabolism, or when patients are non-compliant with oral medications. Similarly, unlike IV administration, IM route enables depot formation and release of the drug in a sustained manner for a prolonged period. Currently, Faslodex® (500 mg) is administered via the IM route as a depot formulation and is studied to achieve steady-state plasma concentrations of 24–28 ng/mL of fulvestrant from the 28th day. However, studies prove that this dose does not provide sufficient blockade of the ERα receptor. Hence, Pandya et al., 2022 modified the solubility of fulvestrant by developing a prodrug, KSHN001034, which increased aqueous solubility up to ~ 1100 fold higher than fulvestrant. Compared to Faslodex®, the relative bioavailability of fulvestrant after KSHN001034 administration was sixfold higher in rats and 2.5-folds higher in dog. Treatment with KSHN001034 inhibited Estradiol (E2)-mediated uterine stimulation, showing a considerable reduction in uterotrophic activity (85%) in comparison to fulvestrant (73%)[74]. The drug combinations that have synergistic effects against BC can be administered through IM route for a sustained drug release pattern. However, IM injection causes pain at the injection site and can lead to complications such as abscess, peripheral nerve injury and hematoma.

Subcutaneous injection Subcutaneous injection involves drug administration to the cutis skin layer, just below the dermis and epidermis layers. The medications injected are absorbed slowly and sustainably to the blood vessels in subcutaneous tissue. SC route is employed when the molecular size of the drug is too large to be effectively absorbed in the intestine, when higher bioavailability is required, or when a faster absorption rate is required than that of oral administration. The patients have widely accepted SC administration as the medication can be self-administered. Liposomal doxorubicin loaded poly(lactic acid-co-glycolic acid)-block-poly(ethylene glycol)-block-poly(lactic acid-co-glycolic acid) (PLGA-PEG-PLGA) based thermogel was developed for sustained local drug delivery for the treatment of BC, which resulted in prolonged doxorubicin release, and significantly inhibited the tumor growth, and reduced cardiotoxicity. Further, combination therapy consisting of an anti-cancer agent and bioactive compound could be explored for their anti-cancer potential through SC administration. However, the SC administration causes irritation and pain at the injection site, and frequent change in the injection site is necessary to prevent the build-up of unabsorbed medication.

Local delivery

The local delivery of the active therapeutic molecules enables direct delivery to the breast tumor region with negligible systemic exposure and minimal adverse effects of the drug. Following are the various mechanisms of localized drug delivery.

Localised transdermal delivery

The administration of active drugs through the breast skin, resulting in high concentrations in the breast with limited or no systemic exposure, is known as local transdermal therapy (LTT). This drug delivery approach is non-invasive, self-administered, and independent of hepatic metabolism. In contrast to drugs applied to the skin on other body regions, where the medication reaches the systemic circulation and is then distributed throughout the body, investigations have demonstrated that drugs applied to the breast skin are selectively localized in the breast due to the embryological origin of the breast as a skin appendage. The breast has a modified eccrine gland, has a well-built internal lymphatic system ensuring selective localization of therapeutic molecules applied topically to the region.

Researchers developed a 4-hydroxytamoxifen (4-OHT) transferosome-loaded gel formulation for local transdermal application and demonstrated its equivalent efficacy to orally administered tamoxifen in studies on tumor volume and necrosis in the BC mouse model. In addition, the researchers also proved significantly lower plasma levels of 4-OHT transferosomes compared to the oral tamoxifen group. In conclusion, local transdermal administration of 4-OHT to the breast could avoid the toxicity of oral tamoxifen while maintaining efficacy [75, 76]. Gao et al., 2018 developed and investigated a microneedle patch loaded with honokiol, a natural anticancer phytomolecule. The study proved that this approach could increase the delivery of honokiol by nearly three-fold. Microneedles disrupt the stratum corneum and enhance the delivery of drugs into epidermal or dermal layers without reaching dermal nerves. The needles do not reach the dermal nerves, and there will be no stimulation to pain. Hence, it is a painless technique [77].

Intraductal delivery

Drug delivery by direct intraductal injection can also be categorized under local delivery. This method involves injecting the drug directly into the mammary duct and hence, a painful method, making it less patient-friendly. This method ensures a high drug concentration level in the breast, hence, minimum systemic exposure. A preclinical study by *Wang* et al. proved intraductal fulvestrant to be effective compared to conventional intramuscular therapy in early BC [78]. However, small molecules like 5-fluorouracil undergo rapid clearance increasing systemic exposure, limiting the efficacy, and demanding frequent administration. However, developing the nano-formulations can help overcome this drawback. Locating a single duct demands great skill and experience making administration challenging. Although intraductal is a great approach, this method requires modifications at various steps to improve patient compliance.

Transpapillary delivery

Drug delivery through mamillary papillae is another promising approach for the localized delivery of anticancer drugs. The papillae are a leaky tissue with the epidermis of the papillae-areolar complex thinner than that of skin in other regions. In addition, numerous glands, including sweat glands, sebaceous, and eccrine glands, facilitate drug transportation via this route. The extent of distribution depends on the lipophilicity of the therapeutic moiety. Lipophilic drugs will be localized to the ducts, while lipophobic drugs will mostly be found in ducts and the surrounding tissue. *Gao* et al. explored compared transpapillary route and microneedles for delivering honokiol. They used a permeation enhancer, oleic acid, and honokiol, resulting in an effective route than microneedles [77, 79].

An anti-cancer agent combined with a bioactive synergistic effect followed by encapsulation into nano-carriers could allow for a dose reduction of the anti-cancer agent, providing a safe platform for the efficient management of BC. This treatment approach is expected to have more patient compliance as it does not involve invasive procedures and is less expensive than the available treatment options so that every person in need could benefit from it.

Designing a combination-based drug delivery system- how to start?

Considerable research is underway to investigate the effects of combining dietary phytomolecules with FDA-approved anticancer drugs (Table 3). The ultimate objective of these combination-based formulations was to enhance the overall therapeutic outcome with a minimal dosage of synthetic molecules and a significantly higher dosage of dietary phytomolecules, wherein determining the correct dosage was a critical step.

Standard anticancer drugs have a narrow therapeutic window and exhibit a strong dose–response relationship, which presents a challenge in determining the optimal dosage when combined with dietary phytomolecules. Achieving the right dosage may require extensive trials, as an insufficient dose could result in poor therapy, while an excessive dose may lead to adverse effects. Additionally, hepatic, and renal clearance should be considered when adjusting the dosage. Studies have proposed proportions such as 80:20, 70:30, and 60:40 of dietary phytomolecule to standard anticancer drugs as starting points for evaluating the anticancer potential[69, 79]. However, pre-clinical studies and Phase I and II clinical trials can only establish the final dose–response and dose-toxicity relationships.

Moreover, an effective drug delivery system and route of administration can facilitate targeted delivery and concentration of the drug at the intended site, thereby improving therapeutic outcomes. It is important to note that further research, including clinical studies, is necessary to fully establish the efficacy and safety of combining dietary phytomolecules with standard anticancer drugs and to optimize the dosage and treatment protocols.

Regulatory considerations

Regulatory bodies evaluate the safety, efficacy, and quality of new treatments. Regulatory considerations become crucial in the clinical application of combination therapies. Using phytochemicals alongside existing anti-cancer molecules requires rigorous assessment of their safety profiles, potential drug interactions, and standardized

production processes. Additionally, the development of novel approaches, including new delivery systems and routes of administration, must adhere to regulatory guidelines for approval and clinical use. Regulatory considerations also evaluate the outcomes of clinical studies, emphasising long-term effects and ensuring appropriate labelling and patient information. The ultimate objective is to ensure that these innovative approaches enhance patients' quality of life and meet the necessary standards for long-term safety and efficacy. By addressing regulatory aspects, researchers and clinicians can facilitate the successful integration of patient-friendly and effective BC treatments into clinical practice.

The U.S. Food and Drug Administration (FDA) critically regulates combination therapies and novel drug delivery systems for cancer treatment. Regarding combination therapies, the FDA is also concerned with the long-term safety and efficacy of the combinational approach. The agency assesses the rationale behind combining specific drugs, the proposed mechanism of action, and the potential benefits compared to individual therapies. Clinical trials are typically required to demonstrate the safety and efficacy of the combination therapy, including considerations for dosing, potential synergistic effects, and possible drug interactions involved. They collaborate with Drug discovery and formulation scientists and clinicians to facilitate the development and approval of innovative therapies while maintaining high standards of patient safety and care.

The European Medicines Agency (EMA) is the regulatory authority responsible for evaluating and supervising medicinal products in the European Union (EU). The EMA follows a rigorous regulatory mechanism regarding combination products and novel drug delivery systems for cancer treatment to ensure patient safety and efficacy. The EMA's regulatory approach aims to ensure the medicinal product's safety, quality, and efficacy throughout the EU. They work closely with national regulatory authorities and follow established guidelines and procedures to evaluate combination products and novel drug delivery systems for cancer treatment, ensuring that patients have access to safe and effective treatments.

Conclusion and future prospects

The quality of life for cancer patients, especially those with early-stage BC, is very important. The advancements in technology for early detection of BC have contributed significantly. While chemotherapy with anthracyclines and taxanes remains a common treatment option, it has drawbacks and the potential for over-treatment in early BC, which highlights the need for alternative strategies. In this context, phytomolecules derived from dietary sources is gaining tremendous interest and have shown immense potential in addressing the limitations of current chemotherapy regimens.

Combining these natural phytomolecules with standard anticancer agents and delivering them through appropriate drug delivery systems and routes of administration is gaining significant interest. By undertaking concerted efforts and meticulous investigations, it is possible to assess the efficacy and safety of combination therapies thoroughly. It is noteworthy that regulatory bodies have also recognized the importance of this emerging field. Rigorous clinical trials and establishing regulatory guidelines are crucial to ensure the success of combination-based therapies. With continued advancements and scientific exploration, integrating dietary phytomolecules with conventional chemotherapy is poised to become a frontline approach in near future. This approach can potentially improve treatment outcomes, minimize side effects, and enhance the overall quality of life for cancer patients, particularly those with early-stage BC. Subsequently, further research on combinational therapies should focus on conducting comprehensive clinical trials validating the efficacy, safety, and long-term outcomes. Additionally, regulatory authorities must collaborate closely with scientists, healthcare professionals, and industry stakeholders to establish standardized guidelines for developing and approving these innovative treatment approaches. By harnessing the potential of combination therapies incorporating dietary phytomolecules, we can strive to enhance treatment outcomes while minimizing the adverse effects and preserving the quality of life for BC patients. Continuous collaborated research in this field holds the key to a more patient-centred and effective approach to early BC treatment in the future.

Incorporating dietary phytomolecules into standard cancer treatment regimens not only addresses the limitations of current chemotherapy but also is likely to create new opportunities for personalized medicine. Phytomolecules offer a diverse array of bioactive compounds that can be tailored to individual patient profiles, enhancing the specificity and effectiveness of cancer therapies. As our understanding of the molecular mechanisms underlying cancer progression deepens, the ability to select and combine specific phytomolecules with targeted chemotherapy agents can result in more precise and less toxic treatment options. This personalized approach aligns with the growing trend towards precision medicine in oncology, promising a future where cancer treatment is customized to the unique genetic and biochemical makeup of each patient.

Additionally, the economic implications of integrating dietary phytomolecules into cancer treatment are significant. Traditional chemotherapy can be prohibitively expensive, often leading to financial strain for

patients and healthcare systems alike. Phytomolecules, derived from readily available dietary sources, present a cost-effective alternative or complement to conventional treatments. By reducing reliance on expensive synthetic drugs and minimizing side effects that require additional medical interventions, phytomolecule-based therapies could significantly lower healthcare costs. This economic benefit, coupled with the potential for improved patient outcomes, highlights the importance of further investment and research in this promising field. The future of cancer treatment lies in a multidisciplinary approach that integrates the best of both natural and conventional medicine, ultimately enhancing the quality of life for patients and making effective cancer care more accessible to all.

Furthermore, the role of patient education and awareness in the successful integration of dietary phytomolecules into cancer treatment cannot be overstated. Educating patients about the potential benefits and safety of phytomolecule-based therapies can empower them to make informed decisions about their treatment options. Additionally, healthcare providers must stay updated on the latest research and advancements in this field to offer evidence-based recommendations. By fostering a collaborative environment where patients and healthcare professionals work together, we can ensure that innovative treatments are effectively implemented, leading to better health outcomes and an improved quality of life for cancer patients. This holistic approach, combining advanced scientific research with patient-centered care, represents the future of oncology and holds promise for revolutionizing cancer treatment.

Abbreviations

(AP-1)	Activating protein-1
(AIIA)	All India institute of ayurveda
(ATRA)	All-trans retinoic acid
(Akt)	Ak strain transforming
(APAF1)	Apoptotic protease activating factor 1
(ARE)	Antioxidant response elements
(AUC)	Area under the curve
(Bax)	BCL2 associated X
(BBR)	Berberine
(CEA)	Carcinoembryonic antigen
(CHOP)	C/EBP homologous protein
(c-Myc)	Cellular Myc
(CIPN)	Chemotherapy-induced peripheral neuropathy
(CXCR4)	Chemokine receptor type 4
(CXCL-1)	Chemokines involved in recruiting immune cells
(CAM)	Complementary and alternative medicine
(Cdks)	Cyclin-dependent kinases
(IL)	Cytokines like interleukin
(DNA)	Deoxyribonucleic acid
(DHA)	Docosahexaenoic acid
(DOX)	Doxorubicin
(DDS)	Drug delivery system
(EPA)	Eicosapentaenoic acid
(EGCG)	EGFR (Epidermal growth factor receptor) epigallocatechin gallate
(ELISA)	Enzyme-linked immunosorbent assay
(LSD 1)	Ephrin-B2 Histone lysine demethylase 1
(EGFR)	Epidermal growth factor receptor
(EGF)	Epidermal growth factor
(EGCG)	Epigallocatechin gallate
(EMT)	Epithelial–mesenchymal transition
(ER)	Estrogen
(EMA)	European medicines agency
(EU)	European union
(ERK)	Extracellular signal-regulated kinase
(FASN)	Fatty acid synthase
(FDA)	Food and drug administration
(GGT1)	Gamma-glutamyltransferase 1
(5-FU)	5- Fluorouracil
(GST)	Glutathione S-transferases
(GQDs)	Glucosamine-conjugated graphene quantum dots
(HGF)	Hepatocyte growth factor
(4-OHT)	4-Hydroxytamoxifen
(HER2)	Human epidermal growth factor receptor 2
(HIF-1)	Hypoxia-inducible factor 1
(hTERT)	Human telomerase reverse transcriptase
(ICAM-1)	Intercellular adhesion molecule 1
IκB	(Inhibitor of NF-κB)
(ICMR)	Indian council of medical research
(IM)	Immunomodulatory
(iNOS)	Inducible nitric oxide synthase
(IL-6)	Interleukin-6
(IL-8)	Interleukin 8
(IARC)	International agency for research on cancer
(IGF1R)	Insulin-like growth factor1 receptor
(IM)	Intramuscular
(IV)	Intravenous
(JAK)	Janus tyrosine kinase
(LTT)	Local transdermal therapy
(LAR)	Laryngeal adductor reflex
(MES)	Mesenchymal
(MIP)	Macrophage inflammatory protein
(MRI)	Magnetic resonance imaging
(mTOR)	Mammalian Target of Rapamycin
(Mn-SOD)	Manganese superoxide dismutase
(MMP)	Matrix metalloproteinases
(MCF-12A)	Michigan cancer foundation-12A
(MAPK)	Mitogen-activated protein kinase
(MOMP)	Mitochondrial outer membrane permeabilization
(MDR)	Multidrug resistance
(MCL1)	Myeloid cell leukaemia sequence 1
(MDSC)	Myeloid-derived suppressor cells
(NCDIR)	National centre for disease informatics & research
(NGF)	Nerve growth factor
(NFκB)	Nuclear factor-kappa B
(pCR)	Pathological response
(PPARγ)	Peroxisome proliferator-activated receptor-gamma
(P-gp)	P- glycoprotein
(PI3K)	Phosphoinositide 3 kinase
(PEG)	Polyethylene glycol
(PET)	Positron emission tomography
(PLGA)	Poly(lactic-co-glycolic acid)
(PLGA-PEG-PLGA)	Poly(lactic acid-co-glycolic acid)-block-poly(ethylene glycol)-block-poly(lactic acid-co-glycolic acid)
(PR)	Progesterone
(PGE-2)	Prostaglandin E2
(QoL)	Quality of life
(RCTs)	Randomized control trials
HER2	Receptors like
(ROS)	Reactive oxygen species
(RSV)	Resveratrol
(RA)	Retinoic acid
(SIK3)	Salt-inducible kinases 3
(SNEDDS)	Self-nano emulsifying drug delivery system
(STAT3)	Signal transducer and activator of transcription 3
(SLNs)	Solid lipid nanoparticles
(SLPN)	Sophorolipid assemblies-coated lipid-polymeric nanoparticle

(SC)	Subcutaneous
(TRAIL)	TNF-related apoptosis-inducing ligand
(TCM)	Traditional chinese medicine
(TNBC)	Triple-negative BC
(TNF)	Tumour necrosis factor
(Tp53)	Tumor suppressor protein 53
(TWIST1)	Twist-related protein 1
(uPA)	Urokinase plasminogen activator
(uPAR)	Urokinase-type plasminogen activator receptor
(VEGF)	Vascular endothelial growth factor
(WHO)	World health organization

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Conception and design have been done by Pavithra P.P and Akhilesh D. Writing, reviewing, and revising the manuscript have been done by Barsha M., Cynthia L.L., Sri Renukadevi B., Amitha S., Manohar M., Singh P. Critical review of the manuscript by Perumalsamy H., Ivan M. All authors have seen the manuscript and have agreed to the submission.

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Availability of data and materials
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Declarations

Competing interests
The authors declare no competing interests.

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