Chapter

Herbal Remedies for Breast Cancer Prevention and Treatment

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Abstract

Breast cancer is among the most common type of cancer in women around the globe. Prevention of breast cancer is better than its treatment. Because of the molecular variation and complexity underlying breast cancer occurrence, its treatment by using chemotherapy and/or radiotherapy is very complicated and often leads to undesirable side effects. Plants and their extracts have been used for centuries for the treatment of almost every disease and breast cancer is not an exception. Herbal products can be trusted for cancer treatment because of their low toxicity. Besides, herbal remedies are easily accepted by the majority of woman suffering from breast cancer because of their easy availability and affordability. In the last decade, a large number of plants and their compounds were reported to show promising anticancerous effects against breast cancer cells in both *in vivo* and *in vitro* models. However, their beneficial effects on breast cancer treatment are still doubtful due to the lack of randomized clinical trials. This chapter is dedicated to reporting the potential of some herbal products for the prevention and/or treatment of breast cancer. Besides, it focused on the anticarcinogenic mechanism of those phytocompounds to report their potential chemotherapeutic role.

Keywords: herbal remedies, phytochemicals, phytoestrogens, breast cancer

1. Introduction

According to World Health Organization (WHO), cancer is the second leading cause of death after cardiovascular diseases and a growing health issue globally. Breast cancer is the most commonly diagnosed type of cancer among females accounting for approximately one-quarter of cancers in females globally. Great research efforts are in place to understand the cause of breast cancer onset, to identify the critical molecular mechanism of its progression, and to define new ways of treating it with lower and limited toxicity. These efforts are certainly encouraging since overall survival has greatly improved in several breast cancer types during the last decade. Since 1990, mortality rates of breast cancer have reduced significantly by 25%, this is at least in part due to the significant improvement in its treatment [1]. Treatment of cancer mainly relies on chemotherapy that uses cytotoxic agents for killing cancer cells. However, these agents or drugs affect both cancer cells as well as healthy cells, causing an array of side effects during the therapy or after the therapy. To overcome these problems, current research is emphasized to explore herbal remedies that selectively targets cancer cells. Besides this, unlike other

cancer types, breast cancer has diverse genetic mutations that affect several pathways [2]. These complexities aid to distinct pathological types with different clinical outcomes [3]. Therefore, response to a certain chemotherapeutic drug may differ in different patients and lack of proper treatment plan may increase the toxicity furthermore. One of the encouraging approaches to overcome drug toxicity is to look for alternative medicines that have less or selective toxicity toward cancer cells [4]. In recent years, many studies have demonstrated selective cytotoxicity of a variety of herbal compounds that can be used as potential chemotherapeutics [4]. Meanwhile, diverse herbal products were reported to prevent and/or palliate the side effects of treatment, improve quality of life, and reduce stress. However, the usefulness of herbal remedies for breast cancer prevention and/or treatment is still ambiguous due to the lack of randomized clinical trials. These objectives will be achievable only if the herbal compounds that showed promising anticancer activity can be successfully transferred to clinical trials.

2. Current scenario and future burden of breast cancer

Cancer of the breast is among the most frequently diagnosed cancer and the leading cause of cancer-related deaths in females globally. According to International Agency for Research on Cancer (IARC's) Globocan data on 2018, breast cancer caused 0.62 million deaths in 2018 and another 2.08 million new cases were identified, which is 11.6% of all cancer types recorded [5]. At the current rate, the number of incident cases is expected to rise to 3.05 million, and the mortality troll is expected to rise to a nerve-racking 6.99 million by 2040 [6]. Approximately 1 in 10 women is diagnosed with breast cancer at some time in their lives [3].

Epidemiological observation shows that the incidence of breast cancer is continuously raising in both industrialized and developing countries [7]. Breast cancer is a disease largely triggered by environmental and lifestyle factors than genetic, which is believed to be responsible for only 10–15% of all breast cancer cases [8]. Various risk factors like age (>50), family history of breast cancer, woman's reproductive history such as early menarche, nulliparity or late pregnancy, and late menopause mainly aid to breast cancer onset [9]. In addition, prolonged use of oral contraceptive and hormone replacement therapy are also known risk factors of this disease among postmenopausal women [10].

3. Molecular feature of breast cancer occurrence, progression, and treatment

The onset of cancer is a result of several sequential molecular events. Most common of them is a mutation in a DNA molecule that codes for a protein that either triggers cell division, proliferation, and growth or that signals termination of all these molecular events [11]. Therefore, damage to DNA or a protein that regulates cell cycle may lead to uncontrolled division and growth of cells, the condition is cancer. It is a hyperproliferative disease that involves molecular alteration resulting in apoptosis dysregulation, proliferation, angiogenesis, and metastasis [12].

Breast cancer is one of the commonest types of cancer and characterized by distinct pathological types with different clinical outcomes. It has different stages that arise from ductal hyperproliferation, which changes into ductal carcinoma *in situ* (DCIS), invasive carcinoma, and metastatic stage. In addition, based on the molecular mechanism of occurrence, breast cancer can be divided into estrogen receptor (ERα) and progesterone receptor (PR) expression and amplification

of human epidermal growth factor receptor (HER2), also known as epidermal growth factor receptor 2 (ErbB2) [3]. Breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) are the two most important genes that code the proteins BRCA-1 and BRCA-2, which play a key role in DNA damage repair and in maintaining genomic stability [3]. Mutation in these genes leads to 15–20 fold increases the risk of breast cancer occurrence [13]. Additionally, tumor suppressor TP53 is another important gene that codes for the protein p53 that plays a major role in the regulation of cell cycle and in apoptosis induction. Mutation in the TP53 gene increases the risk of breast cancer as well as other cancer types. Breast cancer cell survival, proliferation, motility, and cell metabolism are controlled by various signaling cascades. In around 70% of breast cancers, the phosphatidylinositol 3-kinase (PI3K)/AKT pathway has shown to be mutated [14]. Other frequently mutated signaling cascades in breast cancer are Janus kinase (JAK)/signal transducer, activators of transcription (STAT), and nuclear factor κβ (NF-κβ) pathways [3]. Classification of breast cancer based on the molecular expression has therapeutic implication as it helps in deciding the treatment plan. Based on the relative expression of the above markers, patients either receives hormonal therapy or chemo/targeted therapies. The most promising way of dealing with cancer is to interfere with modulation stages of carcinogenesis—initiation, promotion, and progression as well as altering the carcinogenesis signaling pathways [15, 16].

Breast cancer therapeutics include drugs that protect genomic stability by preventing DNA damage, inhibit the cell cycle by disrupting cellular integrity or by inducing apoptotic cell death, and block certain pathways that are responsible for abnormal cell growth (**Table 1**). Majority of breast cancer cases express the estrogen hormone receptor, which helps the cancer cells to proliferate rapidly by the growth-promoting effects of circulatory estrogens [17]. Therefore, current therapies are targeted at abrogating estrogen dependence for estrogen receptor (ER)-positive breast cancers [17]. One of the successful and efficient approaches is the employment of a selective estrogen receptor modulator (SERM) like tamoxifen, which binds to the ER that induces a conformational change in the receptor resulting in obstruction of estrogenic expression [18, 19]. However, tamoxifen like SERMs exhibits many notable side effects including—secondary cancer, cardiovascular diseases by their estrogenic activity in other tissues and organs. The efficiency of tamoxifen is challenged by the development of highly potent third-generation aromatase inhibitors (AIs) that represents a promising approach in endocrine therapy of breast cancer [20]. The aromatase inhibitor drugs like anastrozole and letrozole reduce estrogen production by competitive inhibition of the enzyme aromatase, although the long-term health effects of AIs are doubtful [21]. Another effective strategy in breast cancer treatment is the implementation of a growth factor inhibitor. One of the first identified targets of these growth inhibitors was the epidermal growth factor receptor (EGFR) that plays a vital role in the survival of cancer cells and developing multidrug resistance [22]. The effectiveness of the small molecule EGFR tyrosine kinase inhibitor like gefitinib is highly appreciated for the treatment of breast cancer; however, it failed to produce notable improvement in advance stages of breast cancer [23].

Approximately 20% of breast cancer cases show overexpression of the HER2 that results in aggressive disease and reduced survival [17]. In present, trastuzumab and lapatinib are the only marketed drugs used to inhibit the HER2-mediated growth and proliferation signaling [17]. Other than this, enzyme-mediated DNA damage is an effective approach used in cancer chemotherapy. Doxorubicin, an anthracycline drug, binds with DNA by intercalation with base pairs, which results in an elevated level of DNA-topoisomerase II covalent complexes inhibiting topoisomerase II activity [24]. Other anticancer drugs inhibit mitosis by interrupting the

Drugs	Target	Mode of Action
Doxorubin/ Daunorubicin	DNA , Topoisomerase II	Binds with DNA by intercalation between base pairs and inhibits topoisomerase II activity by stabilizing DNA-topoisomerase II complex.
Epirubicin	DNA/RNA, Topoisomerase II-α, Chromodomain-helicase-DNA-binding protein 1	It has antimitotic and cytotoxic activity. Inhibits nucleic acid & protein synthesis in many ways. Inhibits DNA helicase activity thus interferes DNA replication & transcription.
Cisplatin	DNA, DNA-3-methyladenine glycosylase, α-2-macroglobulin, serotransferrin, ATOX1	Its an alkylating agent that adds alkyl group to DNA bases, preventing DNA and protein synthesis. Forms cross-links in DNA that prevents synthesis or transcription of DNA and induce mutation by mispairing of nucleotides.
Paclitaxel	Tubulin β-1 chain, Bcl-2, microtubule-associated proteins	It's a mitotic inhibitor that interferes with microtubule growth by hyper-stabilization of their structure. Induce apoptosis by inhibiting Bcl-2 activity.
Cyclophosphamide	DNA	Cross-linking and alkylation of DNA that prevents DNA synthesis and transcription.
Tomaxifen	Estrogen Receptor (ER)	It's a selective estrogen receptor modulator (SERM) that binds to estrogen receptor (ER), inducing a conformational change in the receptor, that results in blockage or change of expression of estrogen dependent genes in the mammary tissue.
Raloxifene	Estrogen Receptor (ER)	Second generation SERM, mode of action is similar to tamoxifen.
Herceptin/ Trastuzumab	Human epidermal growth factor receptor 2 (HER 2)	It's a recombinant humanized IgG1 monoclonal antibody used in protein based therapies that blocks the extracellular ligand-binding domain of HER-2 receptor, subsequently inhibiting HER-2 mediated signaling cascade.
Gefitinib	Epidermal growth factor receptor	Inhibits the activity of EGFR tyrosine kinase, subsequently inhibiting the proliferation of malignant cells.
Bevacizumab	VEGF/ VEGFR	It's a recombinant humanized monoclonal IgG1 antibody that inhibits the activity of human vascular endothelial growth factor by preventing its interaction with VEGFR.
Capecitabine	Thyamidylate synthase	It's a prodrug that converts to fluorouracil in cancer cells and inhibit DNA synthesis.

Table 1.
Commonly used breast cancer chemotherapeutic drugs, their targets, and mechanism of action [26].

microtubule stability, hence blocking the transition from metaphase to anaphase [25]. Subsequently, the cell undergoes mitotic arrest or programmed cell death (apoptosis). For instance, vincristine and vinorelbine inhibit the polymerization of microtubules by binding to either the vinca domain or taxoid-binding domain that interferes between β- and α-subunit of tubulin [25]. On the other hand, microtubule-stabilizing drugs like paclitaxel hyperstabilizes the microtubule assembly by binding to the inner surface of the microtubule at a taxoid-binding site on β-tubulin resulting in mitotic arrest in the cell [25]. All these strategies helped in reducing mortality due to breast cancer and increased the survival rate; however, they appear with certain side effects that may be either low and short term or high and life threatening.

4. Chemotherapeutic-associated toxicity in breast cancer treatment

The role of chemotherapy in curing cancer is still doubtful [27]. Even it decreases the risk of recurrence and helps the patient to live longer with improved quality of life in case of metastatic breast cancer. But its use associated with certain risk factors or side effects—some of the side effects are short term and minor, whereas others may become more serious and life threatening [27]. **Table 2** describes a few commonly used chemotherapeutic drugs and their side effects.

Among the most common side effects of chemotherapeutic drugs is its nonselective toxicity, where it destroys the normal body cells such as those in the hair follicle,

Drugs	Common Side-Effects
Doxorubicin	Cardiotoxicity, infertility, alopecia, nausea & vomiting, low blood counts.
Daunorubicin	Alopecia, nausea & vomiting, mouth sores and low blood count. May cause infertility and cognitive heart failure in exceptional occasions.
Epirubicin	Increased risk of infectious diseases, hair loss, respiratory problems, decreased blood count.
Cisplatin	Nausea & vomiting, kidney toxicity, ototoxicity and decreased blood count.
Paclitaxel	Alopecia, pain in joints and muscles (arthralgia and myalgia), peripheral neuropathy, nausea & vomiting, diarrhea and hypersensitivity.
Cyclophosphamide	Temporary hair loss, nausea & vomiting, poor appetite, discoloration of skin and nails, low blood count, loss of fertility.
Tomaxifen	Cardiotoxicity, respiratory difficulties, abnormal vaginal bleeding, tenderness and numbness in face, hand and legs.
Raloxifen	Hot flashes, flu, joint and muscle pain, rhinitis and blood clots, including deep vein thrombosis in rare cases.
Herceptin/ Pertuzumab	Flu-like syndrome, respiratory problems, insomnia, hypersensitivity, cardiotoxicity, peripheral neuropathy, alopecia, low blood count, nausea & vomiting.
Gefitinib	Eye irritation, hypersensitivity, poor appetite, nausea & vomiting, pulmonary and respiratory problems, liver toxicity.
Bevacizumab	Upper respiratory infection, alopecia, nausea, vomiting, abdominal pain, constipation, nose bleeding, proteinuria and in rare cases cognitive heart failure and nephrotic syndrome was observed.
Capecitabine	Low blood count, risk of infection, hand-foot syndrome, hepatotoxicity, eye irritation, nausea & vomiting, poor appetite and constipation.

Table 2.
Frequently used chemotherapeutic drugs in breast cancer treatment and their common side effects associated with them [26, 28–30].

bone marrow, and cells of other important organs along with the cancer cells. Quite a few chemotherapeutic drugs affect the nerve endings or synaptic gaps in hands and feet that may result into numbness, pain, burning or tingling, sensitivity to cold or heat, or weakness in your extremities [31]. Besides, chemotherapeutic drugs may severely damage the immune cells as wells as the brain cells, making the patient vulnerable to infectious diseases and impaired cognitive functions [32]. These side effects may be temporary and may disappear after a few months of completion of chemotherapy. Other critical side effects that arise due to certain chemotherapeutic drugs may last longer—infertility is one of them [33]. Chemotherapeutics that damage ovaries may lead to menopause symptoms, like hot flashes and vaginal dryness, where menstrual cycle becomes irregular or permanently ceases making pregnancy impossible [34]. Further, early menopause in premenopausal women due to the use of aromatase inhibitor agents in adjuvant therapy causes a hypoestrogenic condition that negatively impacts bone density resulting in osteopenia or osteoporosis [35].

Besides, long-term chemotherapeutic toxicity results in cardiac diseases and may trigger secondary cancer such as marrow neoplasm or leukemia [36, 37]. Chemotherapy-linked cardiotoxicity is another major setback of cancer therapy that increases the mortality rate because of the high prevalence of cardiovascular diseases in cancer patients [38]. The cardiotoxicity leads to congestive heart failure (CHF), which is more prevalence in young and elderly patients. It has been reported

that the breast cancer patients aged between 65 and 70 years, who received adjuvant anthracycline chemotherapy, had significantly higher rates of CHF [39]. In another investigation, a widely used chemotherapeutic drug, doxorubicin, was reported to cause CHF in worryingly 26% of the patients suffering from breast carcinoma [40, 41]. Additionally, it was observed that 0.5% of breast cancer patients developed different types of marrow neoplasm (MN) or leukemia after a few years of chemotherapy [42]. The risk of developing MN is higher in the first few years after chemotherapy. Furthermore, chemotherapeutic drugs may also disrupt the normal psychological state of patients in certain cases [43, 44].

The side effects that arise due the conventional chemotherapy is mainly due to lack of specificity of the drugs for cancer cells. Majority of the widely used chemotherapeutic drugs causes adverse damage to normal cells and key organs, which limits the dose of a drug that can be used [45]. This explains the reason why cancer drugs have a low therapeutic index. Several approaches are being considered to address this issue in order to improve the effectiveness of anticancer drugs. One of the popular approaches among them is searching for natural compounds that inhibit cancer cell growth without disrupting the functioning of healthy cells.

5. Ethnomedicine and herbal compounds used for cancer treatment

Plants have played a key role in the survival and evolution of human beings as they have provided the basic need of mankind like food, clothing, shelter, and medicine since the beginning of the human race. Plants have formed the basis of traditional medicine systems like Ayurveda, Unani, and Chinese traditional medicines that have served mankind with their health needs. A larger part of the population in developing and underdeveloped countries relies on herbal medicine for solving treating their primary health issues. Traditional herbal medicines become popular because of their cost-effectiveness, abundancy, and less or no side effects. In recent years, global emphasis on plant research has increased to find out drug-like substances from traditionally used medicinal plants. Moreover, several naturally occurring plant-based compounds like curcumin, resveratrol, quercetin, and many more showed promising anticancerous effects and are gaining interest as an adjuvant chemotherapeutic agent. Besides, naturally occurring compounds cause less toxicity to healthy cells and in certain cases show selective toxicity against abnormal or diseased cells [46]. This might be the reason that today a large number of drugs being marketed are structurally similar to the structure of naturally occurring compounds.

Herbal compounds show a variety of anticancer activity mainly antioxidant, anti-inflammatory, antimutagenic, and apoptosis-inducing activity that may help prevent cancer development in the early stage (**Figure 1**). Dietary consumption of adequate quantity of these herbal products may help in prevention and treatment of breast cancer by cell cycle arrest, induction of apoptosis, regulating carcinogen metabolism and oncogenic expression, inhibiting cell adhesion, proliferation and migration, and blocking signaling pathways that are essential for cancer progression [47].

Between the year 1981 and 2014, 136 anticancer drugs were brought to use around the globe, almost 83% of which were either herbal compounds or their derivatives [48]. A number of anticancer drugs have already in use for the treatment of breast cancer—including vincristine, vinblastine, paclitaxel, and docetaxel [49]. Despite the success of herbal products in curing breast cancer and its associated complexities, not many herbal products are making through preclinical or clinical

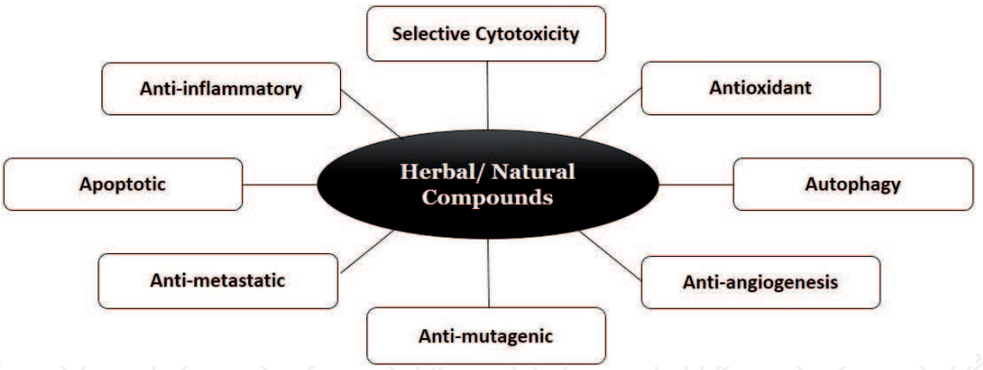


Figure 1.
Features of herbal compounds that attribute to their anticancer activity.

trials. Hence, greater effort is necessary to successfully transfer these agents to an ideal clinical setting to assess their potential for herbal therapies.

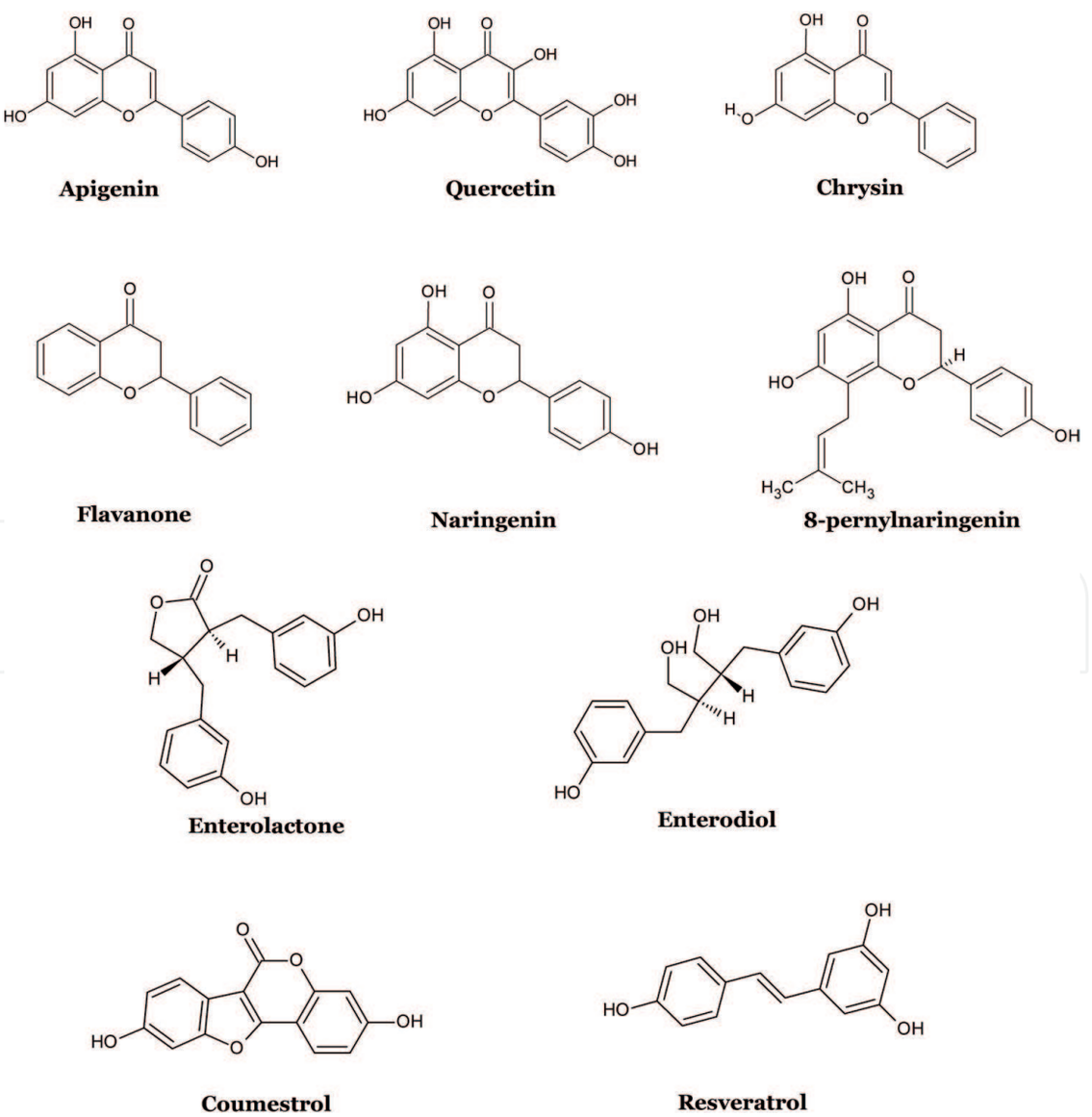


Figure 2.
Some important members of different classes of phytoestrogens [61].

6. Herbal products used for prevention of breast cancer

Breast cancer is a preventable disease [50]. Estrogens play a major role in promoting the proliferation of normal breast cells as well as neoplastic breast epithelium [51]. Almost 40–70% of breast cancers are estrogen receptor positive [52]. Hence, blocking the estrogen receptor for the treatment and chemoprevention of breast cancer is one of the significant approaches. Plant-based estrogen-like compounds or phytoestrogens were originally proposed as cancer-protective agents. This claim was strongly supported by an epidemiological study that revealed a low breast cancer incidence in the soy-consuming population [53, 54]. Phytoestrogens are structural analogues of the mammalian hormone, estrogen, and thus can bind weakly to the hormone receptor [55]. Structurally, phytoestrogen can be grouped into flavones, flavanones, lignans, coumestans, and stilbenes [56]. The structure of important members of different classes of phytoestrogens is given in **Figure 2**. Soybean and soy product is a rich source of isoflavones [57]. Other phytoestrogen classes are legumes and lignans found in seeds, nuts, whole grains, fruit, and vegetables [57]. Historically, the rate of breast cancer occurrence in the United States is 4–7 times higher than that of Asian population where the consumption of dietary isoflavones is comparatively as higher as 20 to 80 mg/d [58]. In addition, epidemiological observations also revealed a modest 30% reduction in breast cancer risk for women with a higher percentage of dietary lignan intake [57]. Therefore, consumption of phytoestrogen-rich diet is one of the many potential protective lifestyles against breast cancer. Recently, there are increasing pieces of evidence that phytoestrogen activity inhibits key steroidogenic enzymes activity involved in the synthesis of estradiol from circulating androgens and estrogen sulfate [7]. Consequently, this activity could play a major role in protection against breast cancer. Besides inhibiting the estrogenic activity, phytoestrogens were also reported to activate the G-protein coupled receptor, GPR30 or GPER-1, described as a novel estrogen receptor and play a significant role in estrogen-dependent diseases like breast cancer [59]. However, the activity of phytoestrogens is unclear and depends on more than one factors that include—its structure, metabolism, its relative availability compared to that of endogenous estrogen [60, 57].

Naturally occurring phenolic compounds namely phenolic acids, flavonoids, tannins, quinones, anthocyanins, and others play an important role in cancer prevention and/or treatment [47]. These phenolic compounds are ubiquitous and rich in medicinal herbs and dietary plants. Several phenolic compounds contribute toward inhibiting carcinogenesis mechanism and show chemopreventive activities by their diverse range of biological activities [62] (**Table 4**).

7. Herbal products used for treatment of breast cancer

A recent population-based survey showed that almost 80% of the women suffering from breast cancer use some form of complementary or alternative medicine for the treatment of cancer [63]. Herbal remedies are the most common and popular form of alternative medicine among them, which is frequently used by women suffering from breast cancer. Here is some evidence that can help to treat breast cancer and its associated toxicity:

7.1 Choosing a selectively cytotoxic herbal cure

One of the interesting features for herbal remedies is their selective toxicity toward cancer cells. There are a number of phytocompounds reported that have

Chemotherapeutic Drugs	Cancer type	Plant Source	Anticancer activity	Clinical status
Paclitaxel	Breast cancer, ovarian cancer	*Taxus brevifolia* L.	Mitotic inhibitor, Microtubule disruptor, Apoptosis inducer	Approved
Docetaxel	Breast cancer, Lung cancer	*Taxus baccata*	Anti-mitotic, Apoptotic	Approved/ Investigational
Sulphoraphane	Breast cancer	Cruciferous vegetables/ Brassica	inhibits tumor growth, anti-proliferative effects	Investigational
Epipodophyllotoxin	Lymphomas, Testicular cancer	*Podophyllum peltatum* L.	Cell cycle disruption, apoptosis	Investigational/ Approved
Vincristine	Breast cancer, Leukemia		Anti-mitotic	Approved, Investigational
Vinblastine	Breast cancer, Lymphoma		Mitotic arrest, cell death	Approved
Vinorelbine	Breast cancer, Hodgkin lymphoma, Lung Cancer	*Catharanthus roseus*	Anti-mitotic, apoptosis	Approved, Investigational
Vindesine	Acute leukaemia, Malignant lymphoma, Hodgkin's disease		Antineoplastic activity, Anti-mitotic, immunomodulatory agent	Approved, Investigational
Vinflunine	Urothelial carcinoma of the bladder		Antineoplastic activity, Anti-mitotic, immunomodulatory agent	Approved, Investigational
Pomiferin	Breast, Lung, prostate and colon cancer	*Maclura pomifera; Dereeis malaccensis*	Inhibits histone deacetylases, prevents DNA damage, Apoptotic	Investigational
Epigallacotechin-3-gallate	Prostate cancer, breast cancer	Catechin; green tea; *Hibiscus sabdariffa* L.	Anti-mutagenic, DNA protective, anti-proliferative	Experimental
Combretastatin A-4 phosphate	Anaplastic thyroid cancer,	*Combretum caffrum*	Anti-angiogenic, induce necrosis in tumors	Investigational
Roscovitine	Lung cancer, nasopharyngeal carcinoma	*Raphanus sativus* L.	Interfere cell cycle, inhibits cyclin dependent kinases	Experimental
Flavopiridol	Lung cancer, Esophageal cancer, Leukemia, Lymphoma	*Dysoxylum binectariferum*	Inhibits cyclin-dependent kinases, arrests cell cycle, apoptotic, immunomodulatory	Experimental
Noscapine	Lymphoma, Lymphoid leukemia, Multiple myeloma.	*Papaver somniferum*	Anti-proliferative, interfere microtubule stability	Approved/ Investigational

Table 3.
Plant-based cancer therapeutics in different stages of clinical trials and research [68].

selective toxicity toward breast cancer cells. Artemisinin is one among them, isolated from *Artemisia annua* L. proved to be selectively cytotoxic toward breast cancer cells when an adequate amount of iron (i.e., ferrous iron) is present in the cells. Because cancer cells have a higher iron influx, therefore, artemisinin and its analogues can selectively destroy cancer cells under high iron concentration [64]. Besides, polyphenols from *Artemisia annua* L. were reported to inhibit the adhesion and epithelial-mesenchymal transition (EMT) of highly metastatic breast cancer cells, MDA-MB-231 [65]. Other than this, polyphenol-rich extracts of *Hibiscus sabdariffa* and aqueous extract of *Brucea javanica* were also reported to show selective cytotoxicity toward *MCF7* and HTB-126 breast cancer cell lines, respectively [66, 67]. However, further exploration is necessary to isolate the selective cytotoxic ingredients of these plants (**Table 3**).

7.2 Combination therapy by herbal remedies and synthetic drugs

Combination therapy of herbal therapy and synthetic drugs possibly be the last resource for patients in the final stage of breast cancer, where surgery is not possible [69]. The combinatory effect of a herbal drug with conventional cancer drugs might improve the bioavailability of one of them making the treatment more effective [69, 70]. Additionally, the combinatory use of herbal remedies with chemotherapy will reduce the dose of standard medicine resulting in lower toxicity and side effects [71]. Several researchers have suggested that herbal compounds can be used in a therapeutic modality as it enhances the anticancer activity of current drugs. Curcumin, a renowned anticancer herbal compound down-regulated the expression of breast cancer markers *in vivo* and *in vitro* when administered along with

chemotherapeutic drugs cyclophosphamide and paclitaxel that made the cancer cells more viable to the drugs [72, 73]. Similarly, 20S-protopanaxadiol, a metabolite of ginsenosides, inhibited cell proliferation in MCF-7 cells by interfering with estrogenic gene expression when used in combination with tamoxifen [74]. Besides, this combination asynergistically improved the cytotoxicity of tamoxifen in an ER-independent manner [74]. Hence, the benefits of these herbal compounds in synergistic therapy are considerable, and this might help to overcome chemotherapeutic drug resistance and toxicity in breast cancer treatment.

7.3 Herbal supplements and nutraceuticals for breast cancer therapy

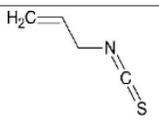
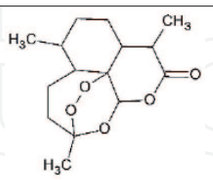
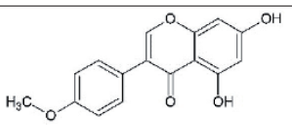
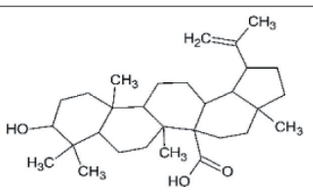
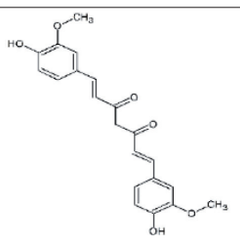
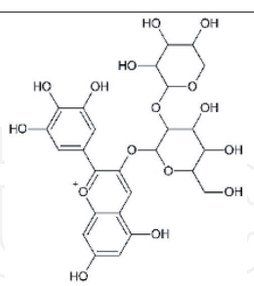
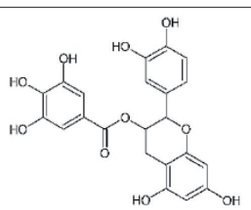
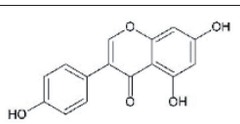
Cancer has been shown to be a preventable disease with changes in nutrition and dietary changes. A previous investigation showed that almost 35% of cancers are related to diet [75]. There are several confirmations from epidemiological and laboratory studies that sufficient intake of fruit, vegetables, and herbal supplements is inversely linked with breast cancer occurrence. A diet composed of adequate quantity of phytoestrogens, polyphenols, and rich sources of other chemopreventive agents helps in reducing breast cancer risk. Dietary supplements of the herbal source are less toxic and easily metabolized. Besides, dietary consumption of these herbal remedies helps in fighting side effects in postchemotherapy patients. One of the primary symptoms of adjuvant chemotherapeutic damage in posttherapy breast cancer patients is hot flushes. Black cohosh or *Actaea racemosa* plant is popularly used by patients of breast cancer to treat hot flushes, which gives conflicting but promising results [76].

8. Molecular mechanism of anticancerous activity of herbal compounds on breast cancer

As discussed in the earlier section, herbal compounds show a verity of anticancer actions—including antioxidant, cytotoxic, antiproliferative, apoptotic activity, etc. Plant-based cancer agents broadly classified into five groups that include—methyltranferase inhibitors, DNA protecting agents, antioxidants, histone deacetylases inhibitors, and mitosis disruptors. Generally, plant-derived compounds contribute toward the anticarcinogenesis mechanism by their antioxidant, cytotoxic, antimitotic, and apoptotic activity (**Table 4**). Others help in chemoprevention by preventing DNA damage, modulating carcinogenesis signaling, and inducing apoptotic cell death (**Table 4**). Several *in vitro* and *in vivo* investigations support the activity of herbal compounds that linked with their anticancer activity. Here's is a few examples of the anticancer mechanism of herbal compounds.

8.1 Antioxidant activity of herbal compounds

Antioxidant activity of herbal compounds of oxidative stress is developed when the balance between the production of reactive oxygen species (free radicals) and antioxidant defense is disturbed [77]. Oxidative stress development and consequent reactive oxygen species (ROS) generation are linked with several disease pathogenesis including cancer. Oxidative stress is dealt with by the body's antioxidant mechanism and several herbal compounds help boosting this machinery. For instance, curcumin enhances the activity of antioxidant enzymes resulting in enhanced cellular resistance to oxidative damage [78]. In addition, curcumin was also found to rise hepatic GSH, SOD, GPx, GR, GST, and CAT activities in paracetamol-treated rats [79]. Other plant-based compounds like epigallocatechin gallate, a component

Compound	Structure	Herbal source	Activity	References
Allyl isothiocyanate		*Brassica nigra, Brassica juncea*	Chemoprevention, detoxification, and reduces cancer risks. Inhibits mitosis and angiogenesis. Shows selective cytotoxicity.	[86, 87]
Artemisinin		*Artemisia annua*	Selective cytotoxicity, mitotic arrest, apoptosis, inhibition of angiogenesis, and ferroptosis.	[88, 89]
Biochanin A		*Trifolium pratense*	Breast cancer preventive agent inhibits tumor growth.	[90, 91]
Bacosine		*Bacopa monnieri*	Anti-metastatic activity.	[92, 93]
Curcumin		*Curcuma longa*	Chemopreventive and antitumoral activities, anti-metastatic, apoptotic, modulate carcinogenesis signaling, help reducing drug toxicity.	[94–96]
Delphinidin 3-sambubioside		*Hibiscus sabdariffa*	Antioxidant, cytotoxic, apoptotic, induces autophagy and necrosis.	[97, 98]
Epicatechin gallate		*Parapiptadenia rigida, Hibiscus sabdariffa,* component of green tea	Induces apoptosis and inhibits tumorigenesis, potential cancer chemopreventive agent.	[99–101]
Genistein		Component of soy products	Chemoprevention, estrogenic activity, inhibition of tumorigenesis, inhibit topoisomerase II activity and angiogenesis	[102–104]

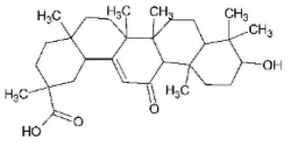
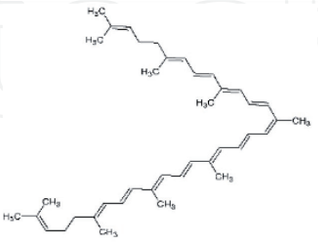
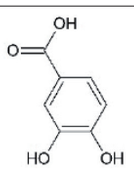
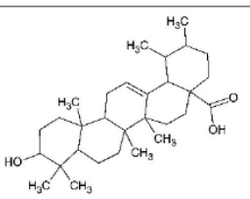
Compound	Structure	Herbal source	Activity	References
Glycyrrhetinic acid		*Glycyrrhiza glabra*	Inhibition of cell proliferation, synergistic effect in combination with an anticancer drug, etoposide. Antineoplastic effect including apoptosis.	[105, 106]
Lycopene		Component of tomatoes, pink grapefruit, apricots, red oranges.	Inhibition of cell cycle progression	[107, 108]
Protocatechuic acid		Dietary polyphenol found in many foods including *Hibiscus sabdariffa, Ginkgo biloba, Hypericum perforatum*	Apoptosis-inducing agent, anti-metastatic.	[109–111]
Ursolic acid		Many plants including *Malus domestica*, *Origanum majorana*	Antitumor, antioxidant, anti-inflammatory, and anti-angiogenesis activity.	[112–114]

Table 4.
Some novel compounds from herbal sources that showed promising anticancerous activity in both in vivo *and* in vitro *studies.*

of in green tea, found to reduce the levels of lipid peroxidation and protein carbonyl content in rats, possibly by enhancing the GSH redox status significantly when administered orally [80]. Likewise, several herbal compounds help to reduce oxidative stress, hence play a preventive role against cancer onset.

8.2 Anti-angiogenesis activity of herbal compounds

Quite a few herbal compounds help to inhibit angiogenesis in breast cancer. Genistein, a flavonoid phytoestrogen, is the most potent angiogenesis inhibitor linked with reduced expression of VEGF, PDGF, uPA, and MMP-2 and MMP-9 [81]. Curcumin was even found to be an effective inhibitor of angiogenesis that reduces the expression of various proangiogenic proteins such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor [82]. Resveratrol and quercetin inhibited the migration and tube formation in bovine aorta endothelial cells consequently inhibiting angiogenesis in those cells [83, 84]. In addition, catechin derivatives, such as epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG), present in green tea are potent angiogenesis inhibitors [85]. The anti-angiogenic activity of EGCG was demonstrated by inhibition of vascular endothelial growth factor (VEGF) production and reduction of matrix metalloproteinase-2 (MMP-2) activity in MDA-MB231 breast cancer cells [85].

8.3 Apoptosis-inducing activity of herbal compounds

The apoptosis-inducing activity of herbal compounds is another favorable feature that contributes toward their anticancer effect. Curcumin was found to inhibit the proliferation and inducing apoptosis in several cancer cell lines including breast cancer cells such as T47D, MCF7, MDA-MB-231, and MDA-MB-468 [115]. Curcumin inhibited the phosphorylation of protein kinase B (Akt)/mammalian target of rapamycin (mTOR), decreased BCL2 expression, and elevated BAX expression and cleavage of caspase 3, subsequently inducing apoptosis of breast cancer cells [115]. Protocatechuic acid was also found to be a potent apoptosis inducer in five types of human cancer cell lines including breast, lung, liver, cervix, and prostate cancer cells [111], which was confirmed by DNA fragmentation, changes in mitochondrial membrane potential, and measurement of caspase activity. The flavonoid 8-prenylnaringenin (8PN), a constituent of *Humulus lupulus*, is an effective phytocompound known for its growth-inhibiting and apoptotic activity in various human cancer types including breast cancer [116]. This activity of 8PN in MCF7 breast cancer cells was possibly mediated by interference with an ER-associated PI3K pathway [116]. Other herbal compounds like lycopene inhibit cell cycle progression by reducing cyclin D expression and retention of p27 in cyclin E–cdk2, thus leading to inhibition of G1 CDK activities in human breast cell line MCF-7 and T-47D along with endometrial (ECC-1) cancer cells [108].

Interestingly, artemisinin, which is an ancient Chinese herbal compound for malarial fevers, has been recently found to have potent and selective toxicity against cancer cells. It reacts with iron to form free radicals with alkylating capacity that can kill cells. As cancer cells require a large quantity of iron uptake to proliferate, making them more susceptible to the cytotoxic effect of artemisinin [117]. Besides, oral administration of artemisinin delayed the onset of breast cancer in 7, 12-dimethylbenz [a] anthracene (DMBA)-induced rats [118]. This encouraging results might lead to design novel chemotherapeutics with effective anticancer property and low toxicity.

9. Conclusion

Though, advances in healthcare research lead to the identification and characterization of most breast cancer types and corresponding cure. However, incidence and prevalence of breast cancer is rising in terrifying rate in both developed and developing countries because of various risk factors. Improved synthetic drugs and hormonal therapy emerged in a decline in breast cancer incidences, increased survival, and better life quality. However, prolonged use of synthetic anticancer drugs is linked with several health risks or side effects that consequence from the toxic effect of these drugs in normal cells. Chemoprevention by herbal compounds is of great interest and is considered to be an inexpensive, readily applicable, acceptable, and accessible approach to cancer control and management. Herbal remedies play a significant role in the management of breast cancer and the associated therapeutic toxicity. The adjunct use of herbal products and chemotherapy can be an efficient and cost-effective way to treat breast cancer. Such adjuvant therapy proved to produce a synergistic anticancer effect that reduced the drug toxicity, suppresses drug resistance, and provides quick drug action enhancing the quality of treatment. Besides, combinatory therapy might also increase the therapeutic index of the synthetic partner by improving the efficiency of the drug. Plant-derived anticancer drugs such as vinblastine, vincristine, taxols, etc. showed encouraging chemotherapeutic potential that is currently used in breast cancer treatment and a large number of them are in preclinical or in clinical trials. In the last decade, a vast number of phytochemicals were identified that showed encouraging anticancer

activity *in vivo* and *in vitro* breast cancer models. Interestingly, several compounds like artemisinin and isothiocyanates showed selective toxicity toward cancer cells, which recommend clinical trials of these compounds. Furthermore, phytoestrogens with affinity and capacity to produce functional responses through estrogen receptors revealed unique possibilities of using them in hormone replacement therapy. Overall, this chapter can conclude that understanding the molecular mechanism of interaction between herbal compounds and cancer cells in the tumoral environment can help us to design novel anticancer drugs that are less toxic and affordable. This reflects the fact that these goals will only be attainable if the herbal compounds that showed promising anticancer activity can be successfully transferred to an ideal clinical setting for the use of herbal therapies.

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