Plant-based anticancer compounds with a focus on breast cancer

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Abstract

Cancer as a terrible disease ranks among the most important healthcare issues confronting humanity, necessitating a proactive approach to treatment. Numerous signaling cascades are involved in the complex process of carcinogenesis. Despite its success, chemotherapy has had some undesirable side effects. Plants offer a rich source of novel substances and represent an exciting new option for cancer research. Plants and plant-derived products are revolutionizing themselves because they are less poisonous, quicker, cheaper, safer, and simpler than standard treatment procedures. Natural products are viewed as viable candidates for the creation of anticancer medicines because of their pleiotropic effects on target events in a variety of ways. The actions of plant-derived products are selective; they damage cancer cells and have no significant effect on healthy cells. Several researches are being conducted on the production of potential candidates from these plant-derived products that can stop or inhibit cancer cell proliferation without causing adverse effects. Numerous plant-derived products and the analogs from which they were derived have been identified as potential anticancer therapeutic possibilities. In this review, we summarize research on botanical products with significant and active anticancer activity and their anticancer constituents, with a focus on breast cancer. This review sought to highlight the most recent advances and key successes in plant-derived products and cancer therapies focusing on nuclear and cellular structures. Furthermore, cancer drugs and their problems are discussed.

Introduction

Cancer and tumorigenesis

A set of illnesses known as cancer involve abnormal cell proliferation and can infiltrate or spread to other regions of the body. In 2020, 18.1 million new cases of cancer occurred, which were 9.3 million male cases and 8.8 million female cases (1). Its etiology is largely related to genetic, immunological, and environmental factors. Defects in immune responses, cell apoptosis, and DNA repair functions have fundamental role in its development and progression (2, 3). Oncogenes, as important genes involved in cell cycle regulation and apoptosis, can undergo genetic or epigenetically driven alterations that lead to cancer (4, 5). The information required to determine cancer risk factors is provided by epidemiological studies (**figure.1**). Random mistakes in DNA replication occur at varying rates in various organisms are among the risk factors for developing cancer. Ionizing radiation, carcinogens, bacteria, fungi, or viruses, DNA damage response, metabolism, xenobiotic, immune system, hormone levels, and lifestyle elements such as smoking, hormone therapy, dietary consumption, and physical activity are considered as some environmental risk factors (6, 7).

The biological reactions to ionizing radiation are influenced by several factors including the type and energy of the radiation particle, the dosage rate, the types of DNA damage, the cell type, etc. Ionizing radiation has the ability to damage nucleic acids, which could lead to alter the regulation of ordinarily expressed DNA (8, 9). Some types of cancer have been linked to infections caused by specific organisms. For instance, stomach cancer correlated to Helycobacter pylori bacterial infections, gallbladder or colon cancer to Salmonella,

hepatitis C and B to liver cancer, Kaposi sarcoma to the herpes virus, and cervical cancer to the human papillomavirus infections (10, 11).

Toll-like receptor pathways (TLR), nuclear factor-kappa β (NF-kβ), cGAS/STING, Janus kinase/signal transducers and activators of transcription (JAK-STAT), inflammation, and mitogen-activated protein kinase (MAPK) have reported as the important factors related to the occurrence of cancer. Interferon (IFN), Interleukins (ILs), and tumor necrosis factor (TNF)-like cytokines, chemokines, growth factors such as transforming growth factor (TGF), and vascular endothelial growth factor (VEGF) play key roles in cancer development. Some inflammatory metabolites, such as thromboxane, leukotrienes, prostaglandins, and specific proresolving mediators (SPM), serve as significant regulators in the initiation and resolution of inflammation in cancer (12, 13).

Breast cancer

Breast cancer, one of the most prevalent malignancies and the primary cause of cancer-related death in women worldwide, disrupts the lives of millions of women (14, 15). For many years, breast cancer has consistently been ranked among the most lethal cancers in terms of incidence and mortality (16-18). Similar to other cancers, it is influenced by a person's lifestyle, environmental circumstances, and genetic predisposition. Age and breast density are two examples of natural characteristics that can increase the risk of breast cancer. In addition, alterations in circadian rhythm, alcohol consumption, and tobacco chewing or smoking are associated with the increased risk of breast cancer (19). These circumstances can result in cellular stress, the increased production of free radical oxygen species, and changes in progesterone and estrogen hormones, all of which enhance tumor aggression (20, 21). Common therapies for breast cancer include chemotherapy, radiation therapy, and surgery, however these methods have a poor prognosis and long-term negative effects. Breast cancer therapy is impeded through metastasis, recurrence, and drug resistance, like treatment for other cancers (22, 23). Scientists are focusing on nutraceuticals as an emerging medicine with less side effects to address the issue with breast cancer treatment. Due to lower drug-related adverse effects and resistance phenomena, nutraceuticals can also be used as an adjuvant therapy with currently available chemotherapeutic medicines (24, 25). Since ancient times, people have used natural remedies made from various plants or non herbal sources to treat a variety of ailments, with many encouraging results. The need for developing various herbal and non herbal drugs with therapeutic potential is growing as a science and technology advance. As a result, there is plenty of room for innovative, healthy nutrition substrates. In 2017, it was estimated that the global market for nutraceuticals would reach 734 billion US dollars by 2026 (26, 27). Therapeutic compounds known as nutraceuticals have drug-like qualities and are used to treat serious illnesses like cancer, diabetes, atherosclerosis, neurological diseases, and hematological disorders. According to study, health food products contain polyphenols, terpenoids, tannins, alkaloids, and flavonoids, which have a significant potential to combat these fatal diseases (25, 28, 29). In this review, specific important and pertinent breast cancer processes are highlighted, and nutraceuticals are assessed along with their processes and potential in breast cancer prevention.

Breast cancer pathophysiology

Breast cancer typically starts as ductal hyperplasia and progresses through benign tumors and even metastatic cancer because of numerous toxins stimulating it. The effect of stroma and tumor microenvironment, including macrophages, play a critical role in the onset and progression of the cancer. Macrophages have the ability to create an immune system-rejecting and mutagenic milieu that promote angiogenesis and permits cancerous cells to spread (30). The cancer stem cell and the stochastic theories are two hypotheses that may help to explain the development and spread of breast cancer. The stochastic hypothesis postulates that each tumor subtype is derived from a single cell type, differentiated progenitor, or stem cell. Any breast cell can get random mutations over time, and when enough mutations have accumulated, the cell is eventually become a tumor cell. Based on the cancer stem cell theory, various tumor subtypes develop via identical progenitor cells or stem cells. Epigenetic and genetic alterations in precursor cells or stem cells have fundamental role in determining different tumor features (31).

Limitations of cancer treatments and anticancer drugs

A growing body of studies has performed to develop novel drug delivery and targeting methods, enhance drug accumulation and its efficacy, and minimize the negative side effects of medications during the course of cancer therapy (32). The most current approaches to cancer treatment include surgery, radiotherapy, chemotherapy, immunotherapy, cancer vaccines, photodynamic therapy, stem cell transformation, and/or combinations of these options. These methods are largely related to serious side effects, including restricted metastasis, toxicity, nonspecificity, and reduced bioavailability (33-35). Cancer treatments are dependent on the type, stage, and site of cancer. Cytotoxic and cytostatic drugs used in chemotherapy can exert their potential impacts alone and/or in combination with other forms of cancer therapy. Alkylating compounds, such as carboplatin, cisphamide, oxaliplatin, and melphalan, may lead to cardiovascular, gastrointestinal, hematologic, pulmonary toxicities, diarrhea, sensory neuropathy, and neutropenia (36-38). These compounds are highly successful in treating numerous malignancies, but they have serious side effects, are expensive, complex, toxic, and unfriendly to the environment. Some cells, such as those located in the gastrointestinal tract, bone marrow, and hair follicles, develop quickly under usual physiological conditions. The contemporary anticancer medications also target these rapidly growing healthy cells. These anticancer drugs can lead to GIT inflammation, hair loss, immunosuppression, cardiac conditions, reduction in blood production, and neurological issues (**Table 1**).

It is reported that genetic conditions participate in the development of drug resistance in the cancer cells. *ABCA4* and *ABCA12* are mentioned as drug resistance genes related to breast cancer. Previous studies have indicated overexpression of these genes in human MCF-7 cells after docetaxel treatment. However, their expressions were downregulated when the phytochemical curcumin was combined with docetaxel (39). These observations suggest that cancer treatments need a combination of current therapeutic approaches. Consequently, plant-derived compounds and related products may provide the most effective and safest methods for treating different cancers, based on the findings of many studies (40) .

Plant-derived anticancer compounds

Newman and Cragg provide a full explanation of the functions of natural chemicals as medications or a foundation for the creation of new medications (5). They found that 929 new drugs (antiviral, antifungal, antiparasitic, antibacterial, antitumor, etc.), approved in the last forty years, had a natural origin. Approximately 29 of the 240 anticancer medications are purely synthetic, which may be due to natural compounds' benefits such as fewer side effects and the capacity to activate a variety of signaling mechanisms involved in cancer development. Additionally, during the preceding 10 years, synthetic compounds with natural pharmacological agents that mimic the actions of natural chemicals have been approved as anticancer medications (41).

In the realm of oncology, the use of herbal remedies has been extensively accepted as a supplemental or alternative treatment (42, 43). Numerous new cytotoxic chemicals have been discovered from plants each year, opening up fresh avenues for the treatment of cancer. The study of naturally occurring molecular entities which could be helpful to the pharmaceutical business is a focus for many academics (44). When substances are found to have anticancer effects in preclinical research, researchers are often looking for a way to confirm their clinical efficacy. This review has a specific focus on breast cancer and describes the research on herbal remedies with considerable and active anticancer activities as well as the anticancer ingredients discovered in such herbal treatments.

Breast cancer treatment with plant-derived anticancer compounds

Nature provides various medicinal plants for humans to combat different diseases and improve public health. Since ancient times, people have used plants and their bioactive substances as medicines. It is reported that numerous types of medicinal plants and their phytochemicals avoid the spread and development of cancer (39). There are over 250 000 plant species in the plant kingdom, but only about 10% of those have been studied for potential treatments of different diseases. Plant elements such as the flower, flower stigmas, pericarp, sprouts, fruits, seeds, roots, rhizomes, stem, leaf, embryo, and bark contain phytochemicals and

their derived counterparts, which have a variety of therapeutic uses. Several primary and secondary metabolites play important roles in hindering cancer cell activating proteins, enzymes, and signaling systems or in activating DNA repair processes, promoting the formation of protective enzymes, and triggering antioxidant activity, resulting in potent anticancer effects, including Lignans, flavonoids, alkaloids, vitamins, terpenes, taxanes, saponins, mineral substances, oily substances, gums, glycosides, biological molecules (45, 46) . Table 2 provides detailed information on some medicinal plants on cell lines of breast cancer. Additionally, Figure 2 shows the generalized concept of carcinogenesis, immune responses, and the efficiency of natural phytochemicals against cancer.

Different strategies for the development of plant-derived anticancer substances

The potency of medicinal plants as therapeutic agents depends on the type and quantity of their active compounds, which vary from species to species depending on latitude, longitude, altitude, age, climate, and season. Different parts of the plant may have various pharmaceutical effects, which propose them as bioactive compounds in anticancer treatments. Several techniques are used to purify active compounds including combinatorial chemistry, isolation tests, and bioassay-guided fractionation. The purification of these compounds are carried out in several steps. Firstly, natural extracts (from dry or wet plant materials) with known biological activities are evaluated. Appropriate matrices, such as Superdex, Sephadex, and Silica, are then employed for the fractionation of natural extracts. The fractionated extracts are tested for bioactivity, and then the active fractions are separated using a variety of analytical techniques such as thin layer chromatography (TLC), high performance liquid chromatography (HPLC), fourier-transform infrared spectroscopy (FTIR), mass spectroscopy (MS), and nuclear magnetic resonance (NMR). Although these steps are flexible, it is important that the bioactive chemicals have the highest purity, quality, and quantity. This can be achieved by utilizing high-quality solvents and matrices as well as careful handling. The extracted compounds must be purified before evaluating *in vitro* or *in vivo* anticancer effects. Furthermore, it is necessary that more studies are performed on some characteristics of the extracted bioactive compounds such as pharmacokinetics, pharmacodynamics, immunogenicity, metabolic fate, biosafety and side effects, drug interactions, and dose concentration. Figure. 3 depicts a thorough planning for the synthesis, characterization, testing, and prospective use of a bioactive chemical as a cancer treatment agent.

Current challenges of plant-derived anticancer compounds

Although bioactive compounds have potent anticancer properties, they also have drawbacks that need to be resolved before their application in clinical trials and improved for the approved drugs. The main concerns in regard to the use of these compounds are their poor aqueous solubility, poor penetration into tumors, absorption by normal cells, limited therapeutic activities, and harmful side effects (47, 48). Today, the uses of colchicine, camptothecin, and derivatives of podophyllotoxin side are limited due to their adverse events. In addition, some anticancer compounds like vinca alkaloids have a limited impact and are usually employed in conjunction with other medications (49). Further challenges in the discovery and development of new anticancer agents are associated with their extraction, synthesis, optimization, and characterization. New developments in analytical technology and computational methodologies are anticipated to facilitate the identification of new compounds, improve their extraction, and/or decide on their chemical synthesis or modifications.

Conclusions

In addition to the role of herbal products in treatment of a variety of human diseases, natural chemicals are still considered as an inexhaustible source for the development of new active chemotherapeutic agents. Although a great number of natural substances demonstrate therapeutic value in preclinical investigations, their quantity dramatically decreases when they enter the clinical trial stage. It is still difficult for researchers to choose the best *in vitro* and *in vivo* models demonstrating the efficacy of natural substances and confirming their inclusion in clinical trials. Alternative in silico and in vitro methods that can considerably reduce the time and expense needed for *in vivo* studies should be proposed to address these liabilities. The low bioavailability of natural substances usually limits their efficacy. As a result, in addition to the compound's

effectiveness, which should be of great interest, researchers must focus on drug delivery systems that can resolve the compound's pharmacokinetic problems and the investigation of suitable derivatives offering a number of advantages in terms of biological availability and efficacy.

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Table 1. List of the anticancer drug classes and active compounds in each class and common side effects.

Drug Classes	Active Compounds	Common side effects*
Antimetabolites	5'-triphosphate, 5-Fluorouracil, Deoxyadenosine, 1-β-D-arabinofuranoside, Mercaptopurine, Gemcitabine diphosphate and triphosphate, 5-Fluorouracil, 9-beta-D-arabinosyl-2-fluoroadenine, 6-Mercaptopurine, Methotrexate, 6-Thioguanosine, 5-Fluorouracil, Methyl-tetrahydrofolate Leucovorin	Bleeding and Bruising (Thrombocytopenia), Anemia, Delirium loss, Constipation, Appetite, Diarrhea, Fatigue (Swelling), Edema
Alkylating agents	Busulfan, Carmustine, Acrolein and phosphoramide mustard, 5-aminoimidazole-4-carboxamide, Lomustine, Mechlorethamine, Melphalan, Azo-Procarbazine, Triethylenethio-phosphoramide, Semustine	Nausea and vomiting

Drug Classes	Active Compounds	Common side effects*
Anthracyclines	Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitoxantrone	Severe cough allergic, Photosensitivity, Hoarseness of voice, Skin and nail hyperpigmentation, Flushing of the face, Allergic reactions (anaphylaxis), Fatigue, Joint pain
Antitumor antibiotic	Bleomycin, Dactinomicyn, Mitomycin, Plicamycin	Feeling of unwellness (malaise) rash, Fatigue, Fever and chills, Hair loss, Diarrhea, Nausea or vomiting, Loss of appetite
Epipodophyllotoxins	Etoposide, Teniposide	Nausea, Unusual tiredness or weakness, Constipation, Stomach pain, Diarrhea, Sores in the mouth and throat, Loss of appetite or weight, Vomiting
Taxanes	Cabazitaxel, Docetaxel, Paclitaxel	Fatigue at the IV site, Muscle aches and pains, Called myalgia, which can be extreme. Redness or swelling, Skin rashes, Nausea and vomiting, Hair loss, Mouth sores. Joint or bone pain
Vinca alkaloids	Vinblastine, Vincristine, Vinorelbine	Nausea, Diarrhea, Constipation, Tiredness/weakness, Abdominal pain, Headache, Mouth sores, Vomiting
Campotothecins	SN-38 (7-ethyl-10-hydroxycamptothecin), Topotecan	Diarrhea, Constipation, Back pain, Tiredness/weakness, Headache, Nausea, Vomiting, Abdominal pain
Platinum analogs	Carboplatin, Cisplatin, Oxaliplatin	Headache, Vomiting, Constipation, Nausea, Mouth sores, Altered taste sensation, Abdominal pain, Diarrhea.
Monoclonal antibody	Bevacizumab, Cetuximab, Rituximab, Trastuzumab	Nausea, Allergic reactions such as hives or itching, Diarrhea, including chills, Fatigue, Fever, Muscle aches and pains, Allergic reactions, Vomiting, Low blood pressure, Skin rashes, Flu-like signs and symptoms
Growth inhibitor	Axitinib, Bortezomib, Sunitinib, Crizotinib, Lapatinib, Dasatinib, Imatinib, Dabrafenib, Nilotinib, Bosutinib, Sorafenib, Pazopanib, Trametinib, Vandetanib, Vemurafenib	Coughing up blood, Depressed mood, Chest tightness. Clay colored stools, Cloudy urine, Bleeding gums, Decreased urination, Bloody nose

*https://www.drugs.com/professionals.html

Table 2. plant-derived anticancer compounds in cell lines of breast cancer.

Natural compounds	Source extractions	Cell lines	Active concentrations	Findings	Ref
Nobiletin	Citrus depressa	MCF-7	500 ml	Reduces ERK1/2, cyclin-D1, p21 upregulation, mTOR and AKT inhibition	(50)
Resveratrol	Vitis vinifera	4T1	IC50 = 93 μM (72 h)	S-phase slowdown Cell cycle suppression, higher levels of apoptosis	(51)
Resveratrol	Vitis vinifera	SUM159/MCF10A/ MCF-7	100 mg/ kg/d)	Through inhibition of Wnt β -catenin pathway	(52)
Resveratrol	Vitis vinifera	/ MDA-MB-231/ MCF-7	10, 25, and 50 μM	Decrease in MMP-9, MMP-2, c-Myc, and Cyclin D1 expression, decrease in Sox2 translation and stimulation of STAT3 and Akt	(53)
Curcumin	Curcuma longa	BT-474/ MDA-MB-231	1–25 μg/mL (72 h)	Akt phospho-rylation and MAPK stimulation, Decrease HER-2 oncoprotein, and Decrease NF-B	(54)
Curcumin	Curcuma longa	MDA-MB- 231	10, 20 and 30 μm/ml	Expression of EGFR and Induction of cell death	(55)
Curcumin	Curcuma longa	MCF-7	1, 5, 10, 30 and 50 M	By suppressing NF-B/ AP-1, MAPK, and PKC signaling, TPA causes MMP-9 overexpression	(56)

Natural compounds	Source extractions	Cell lines	Active concentrations	Findings	Ref
Curcumin	Curcuma longa	MDA-MB-231/MCF-10F/ Tumor2	30 μM	Reduced expression of EMT-associated, Fibronectin, Slug, N-cadherin, Twist1, Vimentin, AXL, and. E-cadherin/ proteins -catenin	(57)
EGCG	Epigallocatechin gallate	MDA-MB-231	[?] 75 μM (24 h)	Reduce expression of -catenin, p-Akt, and cyclin D1, inactivate the catenin signaling mechanism, Reduced proliferation of cells and disruption of adhesion junction formation	(58)
Eugenol	Syzygium aromaticum	, 0.25, 0.50, 0.75, 1.0 and 1.5 μM,	BT-20/ MDA-MB-231/ MDA-MB- 468	Inhibits NF-B signaling, thereby decreasing IL-8 and IL-6 production.	(59)
Baicalin	Scutellaria baicalensis	MCF-7/ MDA-MB-231	0, 20 or 30 μM	Reduces NF-B-p65 protein synthesis and NF-B- elicited upregulation of BCL2, BIRC3, BIRC2, and CCND1 expression	(60)

Natural compounds	Source extractions	Cell lines	Active concentrations	Findings	Ref
Artemisinin (Artesunate)	Artemisia annua	MDA-MB-231	25, 50 and 100 μM (48 h)	Reduce Bcl-2, enhance Bax, G2/M-phase arrest Reduce Cyclin-B1 and Cyclin-D1, heterochromatin agglutination, degeneration of mitochondrial vacuoles; nuclear enlargement, Reduce the amount of organelles within cells	(61)
Ellagic acid	Juglans regia	MCF-7 cells;	0, 10, 20 and 30 μg/mL	Reduces signaling of TGF-/Smads	(62)
Ginseng extract	Ginseng	MCF-7	100–400 μM (24 h)	Reduce Bcl-2, augment Bax, cytochrome c, and activated caspase-3,augment ROS production	(63)
Oleuropein	Olea europaea	1.7 mg/day	MCF-7	Blocking the growth and proliferation of MCF-7 cell xenografts	(64)
Eupatorin	Eupatorium semiserratum	MCF-7/MDA-MB-231	20 μg/ml	By inhibiting the p-Akt pathway, and boosting the production of SMAC/Diablo, cytochrome c, Bax, Bak1, Bad, and HIF1A	(65)
Emodin	Aloe vera	-	IC50 = 8.6 μM	Unique energy-dependent pathway of drug uptake inducing apoptosis	(66)

Natural compounds	Source extractions	Cell lines	Active concentrations	Findings	Ref
Genistein	Glycine max	MCF-7	10 nM–10 μM	Through the downregulation of the Hedgehog-Gli1 Signaling	(67)
Genistein	Glycine max	MCF-7/MDA-MB 231/ MCF10a	18.5 μM	Elevated levels of BRCA2 and BRCA1 protein	(68)
Artesunate	Artemisia annua	-	IC50 = 2.3 μM	VEGF expression reduction	(69)
Kaempferol	Moringa oleifera	MDA-MB231	50 μM	Increase the production of NRF2 and its enzyme NQO1 in MCF-7 cells, thereby preventing oncogenesis	(70)
Kaempferol	Moringa oleifera	MCF-7	10 μM	halts cell cycle progression at the G2/M phase by inhibiting CDK1	(71)
Betulinic acid	Betula sp.	-	IC50 = 13.5 μM	Induction of the extrinsic apoptosis mechanism through increased levels of DR4, DR5, and PARP cleavage	(72)
Icariin	Epimedium sagitatum	MDA-MB-231 /4 T1	10 or 20 μM	Reduces the signaling cascade of NF-B and SIRT6	(73)
Betulin	Betula sp.	-	IC50 = 30.7 μM	Induction of the extrinsic apoptosis cascade through increased levels of DR4, DR5, and PARP cleavage	(74)

Natural compounds	Source extractions	Cell lines	Active concentrations	Findings	Ref
Isoliquiritigenin	Spatholobus suberectus	MCF-7/ MDA-MB-231 /BT-549	10 μg/ml	By blocking β-catenin/ ABCG2 signaling.	(75)
Berberine	Berberis vulgaris	-	IC50 = 25 μM	Activation of cell cycle arrest, a combined effect with drugs/dose-dependent decrease in tumor volume and angiogenesis	(76)
Epicatechin gallate	Camellia sinensis	-	IC50 = 350 μM	Promote apoptosis in various types of cells of cancer	(77)
Morusin	Ramulus mori	MCF-10A/ MDA-MB-231/4 T1 /EMT6 and MCF-7	1, 2, 4, 6 and 8 μg/ml	Lipoapoptosis and adipogenic transformation are mediated by PPAR and C/EBP	(78)
Epigallocatechin	Camellia sinensis	-	IC50 = 22 μM	Growth restriction	(79)
D Rhamnose β-ηεδεριν	Clematis ganpiniana	MCF-7/ SUM1315/ MDA-MB-231/ BT474	5, 10, 20, 40 and 80 μg/ml	via inhibiting the pathway of PI3K and AKT and enhancing the ERK pathway	(80)
Myricetin	Camellia sinensis	MDA-Mb-231	50 mg/kg	By suppressing the expression of MMP2/9 as well as ST6GALNAC5 proteins	(81)
Ingenol mebutate	Euphorbia peplus	-	IC50 = 23.9 μM	Necrotic mechanism	(82)
β-Ελεμενε	Rhizoma Zedoariae	MDA-MB-231 / MCF-7	0–320 μmol/L	inhibiting the aerobic glycolysis triggered by dimer formation of PKM2 and nuclear transfer	(83)

Natural compounds	Source extractions	Cell lines	Active concentrations	Findings	Ref
Dehydrocorydaline	Corydali syanhusuo	MDA-MB-231	20,30, 40, 50 or 100 μM	By reducing BCL 2, CCND 1, BCL 3, and CDK1 and enhancing the generation of pro-apoptotic proteins caspase9/3/8	(84)
Theacrine	Theobroma grandiflorum	MDA-MB-231	10–100 μM	EMT induced by TGF is inhibited	(85)
Bilobetin	Ginkgo biloba		IC50 = 57.6 μM	Stopping the cell cycle at the G2/M phase	(86)
Harmine	Peganum harmala	MDA-MB-231 and MCF-7	50, 100 or 150 μM	By decreasing pErk, Bcl2, pAkt, and TAZ expression	(87)
Isoginkgetin	Ginkgo biloba	-	IC50 = 92.1 μM	Stopping the cell cycle at the G2/M phase	(86)
α-σανταλολ	Santalum album	20, 40 μM	MDA-MB 231/ MCF-7	via suppressing the Wnt/-catenin signaling pathway	(88)
Licoagrochalcone	Glycyrrhiza glabra	-	IC50 = 28.6 μM	Promotion of apoptosis and suppression of cell division	(89)
Astragaloside IV	Astragalus membranaceus	MCF-7/MDA-MB- 231/ / MDA-MB-468	40 and 80 μg/ml	prevent BC cell proliferation and metastasis via inducing expression of TRHDE-AS1	(90)
Apigenin	Matricaria chamomilla	-	IC50 = 100 μM	augmentation of the DR5 mechanism	(91)

Natural compounds	Source extractions	Cell lines	Active concentrations	Findings	Ref
Betulinic acid	Castanopsis acuminatissima	MCF-7	50 μM	via reducing topoisomerase or cyclin, suppressing VEGF signaling, decreasing SP and NF-B stimulation, and downregulating matrix metalloprotease production	(92)
Chamomillol	Matricaria chamomilla	-	IC50 = 300 μM	Repress angiogenesis by repressing expression proteins.	(93)
Cucurbitacin B	Cucurbeta pepo	MDA-MB-231	0.5 and 1 mg/kg	Reduce NF-B and STAT3	(94)
Lycorine	Narcissus pseudonarcissus	MCF-7/T47D/ MDA-MB- 231	5 or 10 mg/kg	via interfering with the Src/FAK pathway	(95)
Ginsenoside	Panax ginseng	-	IC50 = 30 μM	Activation of apoptosis and suppression of cell division	(96)
Citral	Cymbopogon citratus	MDA-MB-231	2.5, 5.0 and 10.0 μg/ml	Reducing the expression of aldehyde dehydrogenase 1A3	(97)
Borbonol	Persea americana	-	IC50 = 20.5 μM	Inhibition of proliferation	(98)
Matrine	Sophora flavescens	MCF-7	2, 4, 8 and 10 mM	through the aggregation of light chain 3 II and reduced levels of p62, phosphorylation of mTOR and AKT was suppressed	(99)
Germacrone	Rhizoma curcumae	MCF-7	100 or 200 μM	via inhibiting ER-driven gene expression	(100)

Natural compounds	Source extractions	Cell lines	Active concentrations	Findings	Ref
Salvicine	Salvia prionitis		IC50 = 1.4 μM	Breaks two strands of DNA through increasing TOP2 activity; prevents re-ligation	(101)
Noscapine	Papaver somniferum	MCF-10/ MCF-7/ MDA-MB-231	20, 40, 60, 80 and 100 μM	A decrease in the expression of the NF-B gene and protein, along with an increase in the expression of the IB gene	(102)
Cepharanthine	Stephania cepharantha	MDA-MB-231 and MCF-7	5 μM for MCF-7,4 μM for MDA-MB-231	By disrupting AKT/mTOR signaling system	(103)
Ursolic acid	Ocimum tenuiflorum	MDA-MB-231	10.0 μg/ ml	Reduced EGFR, PI3K/Akt/mTOR, and ERK activity	(104)
Protocatechu aldehyde	Salvia miltiorrhiza	MCF-7 and MDA-MB-231	0, 5,10, 25, 50, or 100 lM	inhibits the expression of -catenin and cyclin D1	(105)
Silibinin	Silybum marianum	-	IC50 = 24 μM	Apoptosis induction and cell cycle arrest	(106)
Piperlongumine	Piper longum	MCF-7/MDA-MB-231/MDA-MB-453 And BT-549	6.25,12.5, 25, 50 and 100 lM	Through decreasing Bcl-2, cyclin D1, p-Akt, p53, p70S6K1, and 4E-BP1 expression and increasing cytochrome c and Bax expression; by inhibiting the PI3K/Akt/mTOR signaling axis.	(107)
Gossypol	Gossypium hirsutum	MDA-MB-231 / MDA-MB-468 MM-231 / MM-468	0–100 μM 0–50 μM	Increases the expression of BNIP3, TNFRSF9, and GADD45A	(108)

Natural compounds	Source extractions	Cell lines	Active concentrations	Findings	Ref
Silymarin	Silybum marianum	-	IC50 = 75 μM	Interaction with the production of cell cycle regulators and apoptotic proteins; activation of cell cycle arrest	(109)
Pterostilbene	Cyanococcus	MDA-MB-468	Dose:50 μM	Reduces phosphorylation of mTOR and AKT and decreases cyclin D1 expression	(110)
Paradol	Zingiber officinale	-	IC50 = 20.4μM	Reduced cellular viability	(111)
Colchicine	Colchicum autumnale	MCF-7	0.3125, 0.625, 1.25, 2.5, 5, 10, 20 and 40 μg/ml	through cells unable to exit the G2/M phase.	(112)
Tanshinone-IIA	Salvia miltiorrhiza	MDA-MB-231	0, 3 and 6 μM	Through inducing S-phase cell cycle arrest and boosting GSK3 expression, MMP expression is inhibited.	(113)
Shogaol	Zingiber officinale	-	IC50 = 24.4 μM	Inhibitory activity	(114)
β-caryophyllene oxide	Myrica rubra	MDA-MB-231 and MCF7	5–500 μM	Inhibition of NF-B	(115)

Table 3. plant-derived anticancer compounds in animal model of breast cancer

Natural compounds	Source extractions	Animal models	Dose/administration	Therapeutic effects	Ref
EGCG	Epigallocatechin gallate	CB-17 rodents with severe combined immunodeficiency	100 mg/kg of EGCG dissolved into 100 L of water is administered orally every two days.	Reduce tumor proliferation; reduce miR-25 expression; reduce Ki-67; and enhance pro-apoptotic PARP expression	(50)
Artemisinin (Artesunate)	Artemisia annua	Xenograft model of 4T1 cells in female BALB/c mice	Every day intraperitoneal injection of 100 mg/kg artemisinin dissolved in 0.2% DMSO for twenty days	Reduced splenic and tumor Treg and MDSC growth; enhanced percentages of CD4 + IFN- + T cells; elevated FN- and TNF-	
Ginseng	Ginseng	Xenograft model of MCF-7 cells in female BALB/c athymic nude mice	Ginseng extract (50 or 100 mg/kg) was given intravenously once a day for four weeks	Increase Bax, activated caspase-3, and activated PARP; reduced Bcl-2; reduced tumor weight	(51)
Resveratrol	skin of grapes, blueberries, raspberries, mulberries, and peanuts	Xenograft model of MDA-MB-231 cells in female athymic mice	resveratrol (ethanolic solution) 25 mg/kg/day intraperitoneally for three weeks	reduce tumor size, boost apoptotic index, and stop angiogenesis	(52)
Curcumin	Turmeric or Curcuma longa	Female athymic nude mice with BT-474 xenograft mod-el overexpressing HER-2	Curcumin was administered intraperi-toneally twice weekly for a period of four weeks at a dose of 45 mg/kg, dissolved in 0.1% DMSO	Tumor volume reduction	(53)

Natural compounds	Source extractions	Animal models	Dose/administration	Therapeutic effects	Ref
Berberine	Berberis vulgaris	-	IC50 = 25 μM	Cell cycle arrest induction, drug-drug interactions, dose-dependent tumor volume decrease, and angiogenesis	(54)
Combretastatin	Combretum caffrum	mice	IC50 = 80-190 μM	Tubulin binding results in the microtubules being less stable	(55)
Ginkgetin	Ginkgo biloba	mouse	IC50 = 10 μM	Autolysosome production and redox environment are mediated by p62/SQSTM1, and the signaling transducer and activator of transcription 3 activity is inhibited	(56)
Noscapine	Papaver somniferum	mice	IC50 = 45 μM	Triggering several signaling cascades, such as apoptosis	(57)
Cryptotanshinone	Salvia prionitis	mice	IC50 = 1.1 μM	Multifaceted mechanisms of action include apoptosis, G2/M arrest, and cellular movement inhibition. All these pathways are orchestrated by NFB inhibition	(58)

Table 4. Clinical studies of plant-derived anticancer substances for breast cancer

Natural Compounds	Identifiers	Titles	Observations
Resveratrol	NCT04266353	Effect of Resveratrol on Serum IGF2 in African American Women	Participants will be given 150 mg of resveratrol per day for six weeks
Ginseng	NCT00631852	A Phase II Biomarker Trial of Gelatin Encapsulated Extract of American Ginseng Root (LEAG) in Breast Cancer	American ginseng extract from the roots was administered as follows: four 250 mg tablets were taken daily for five to fourteen days prior to surgery
Artemisimin (Artesunate)	NCT00764036	Patients with metastatic or locally advanced breast cancer are being studied in a prospective open uncontrolled phase I study to determine the compatibility, safety, and pharmacokinetics of the semi-synthetic artemisinin derivative artesunate from the Chinese herb artemisia annua	The medication was given orally once day for four weeks in dosages of 100, 150, or 200 mg of artesunate.
EGCG	NCT00917735	Study of the Green Tea Extract's Efficacy on Breast Cancer Risk Biomarkers in High-Risk Women With Different Catechol-O-Methyl Transferase (COMT) Genotypes under Placebo Control	Two green tea extract capsules containing 51.7% EGCG should be taken orally twice day, after breakfast and supper, for a period of one year.
Curcumin	NCT03980509	Curcumin, the active ingredient in turmeric, in a "Window Trial" for primary invasive breast cancer tumors	From the time surgical resection is scheduled until the night before surgical resection, 500 mg of curcumin will be given orally twice daily, after each meal

Figure legends:

Figure. 1) Main agents involved in the development of cancer.

Figure. 2) Anticancer mechanisms of some plant-derived compounds .

Figure. 3) Extraction, characterization, testing, and prospective use of a bioactive chemical as a cancer treatment agent.

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