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Review Article

Exploring the Molecular Mechanism of Phytoconstituents in Breast Cancer

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I N F O

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A B S T R A C T

Cancer is a disease caused by many biological abnormalities that result in uncontrolled cell division. Breast cancer is considered the most prevalent cancer among women worldwide. A tumor in the chest, a change in breast size, discomfort in the breast, and fluid leakage from the nipple are all indicators of breast cancer. Cyclin-dependent kinases (CDKs) are commonly overexpressed, and the tumor suppressor protein p53 is under-expressed in breast cancer tissues. In addition, many cell cycle control proteins, including the cyclin-dependent kinases inhibitors, p27, p21, and p57 are downregulated simultaneously. Using natural compounds to target these molecules may provide valuable treatment for breast cancer as natural compounds have a great potential for advancement and cause fewer side effects. Since ancient times, people have used plants as a source of medicine since they are so abundant. Many medications used to treat human illnesses today are derived from plants. Testing natural extracts for potential anti-cancer biological activity is the first step in developing an effective and side-effect-free anti-cancerous therapy based on phytochemicals. Using natural compounds and their derivatives as anti-cancer agents offers a potential source for novel cancer treatments.

Keywords: Breast Cancer, Phytoconstituents, Inhibitors, Anti-Cancerous

Introduction

Breast cancer is currently the most common life-threatening malignancy identified and the primary cause of mortality among women. The risk of dying from breast cancer is significant, and it is one of the most prevalent cancers in women. A tumor in the chest, a change in breast size, discomfort in the breast, and fluid leakage from the nipple are all indicators of breast cancer.[1] Breast Cancer is caused by many reasons such as obesity, alcohol consumption, ionizing radiation, early menarche, late menopause, lack of physical exercise, nulliparity, etc. Another risk factor that influences 5 percent to 10 percent of the patients is the inheritance of genes like BRCA1 and BRCA2.[2,3] According to data from the International Agency for Research on Cancer (IARC) and Globocan, 2.08 million new cases and 0.62 million fatalities from breast cancer were reported in 2018.[4] A terrifying peak of 6.99 million mortality trolls will have been reached by 2040 if present trends continue.[5] Possible treatments that are available mainly are chemotherapy, surgery, radiation therapy, immunotherapy, targeted therapy, hormonal therapy, etc. Unfortunately, since there is no viable treatment for advanced illness circumstances, chemotherapy can still not cure breast cancer effectively.[6]

Any plant with one or more organs that contain chemicals used for therapeutic purposes or are precursors to effective pharmaceuticals is referred to as a medicinal plant. The phrase "medicinal plant" may be used to refer to any plant.[7] Plant-based preparations are a vital component of all available therapies, mainly in rural areas, because they are convenient, low-cost, and have fewer side effects.[8] In drug development, medicinal plants have long been considered a rich source of bioactive ingredients. These can be used to develop pharmacopoeial, non-pharmacopoeial, and synthetic drugs. Besides that, these plants are integral to the development of human cultures around the globe. Plant phytochemicals are bioactive plant components that do not nourish plants but guard against infections, infestations, or predation by microbes, pests, pathogens, or predators.[9] There is a lot of evidence to suggest that increasing one's intake of fruits and vegetables that are green and yellow may lower one's chance of developing cancer.[10, 11] It has been shown that an extensive range of naturally occurring chemicals has significant chemo-preventive capabilities against cancer.[12, 13] Compounds that occur naturally are abundantly distributed across the natural world and may be obtained by people by consuming foods, including fruits, vegetables, and drinks. These modest dietary components that don't include nutrients have a significant chemo-preventive effect on experimental carcinogenesis by various agents. This review will concentrate on organic substances that target several signaling pathways that contribute to breast cancer development and can potentially be effective anti-breast cancerous drugs.

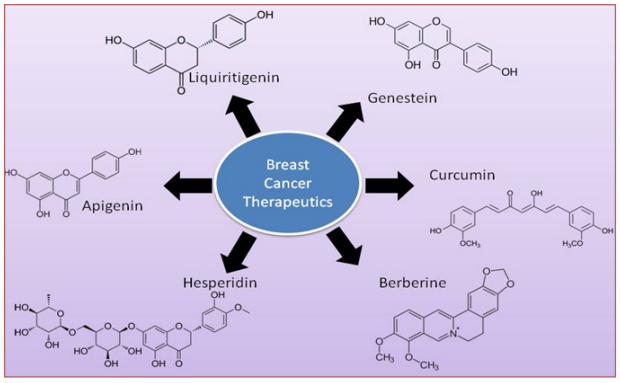

Figure 1.Role of Different Phytochemicals in Breast Cancer Prevention

Therapeutic Potential of Phytoconstituents in Breast Cancer

Liquiritigenin

Liquiritigenin is a naturally occurring flavonoid that has been isolated from the Glycyrrhizae radix. It has been shown to possess various pharmacological properties, including anti-inflammatory, anti-oxidative, estrogenic, and anti-tumor activity.[14] In vitro, liquiritigenin has been shown to protect glomerular mesangial cells, i.e., HBZY-1, against high glucose-induced extracellular matrix buildup, inflammatory response, and oxidative stress by lowering the production of interleukin 6 (IL-6), interleukin 1 (IL-1), and nuclear factor-kappa B activation (NF-kB).[15]

Liquiritigenin has anti-cancerous properties in triple-negative breast cancer by decreasing proliferation, inducing apoptosis, and lowering triple-negative breast cancer cell invasion and migration. In addition, Liquiritigenin has been shown to influence BRCA1 expression by altering DNA methyltransferase activity and BRCA1 promoter methylation.[17] Multiple ER regulatory elements were activated by liquiritigenin, as were native target genes with ERβ.[16] The ERβ ligand liquiritigenin substantially improved the reduction of breast cancer cell survival and tumor-xenograft development by RO 48-8071, a small-molecule oxidosqualene cyclase inhibitor.[17] Liquiritigenin may suppress the production of connective tissue growth factor by increasing the level of the miR-383-5p gene, which in turn inhibits breast cancer cells' proliferative, migratory, and invasive capabilities and promote apoptosis.[18] In MCF-7 breast cancer cells, it has been shown that liquiritigenin's methylation boosted its antiproliferative and cytotoxic effects.[19]

Apigenin

Apigenin is a flavonoid component in plants like garlic, onion, parsley, tea, and chamomile. Numerous biological processes carried out by Apigenin include its ability to fight cancer, act as an antioxidant, and reduce inflammation.[20] Apigenin has been shown to have antimetastatic properties in various malignancies, including breast, prostate, skin, lung, and ovarian cancer. Apigenin's anti-cancer or antimetastatic properties are thought to be mediated by targeting vascular endothelial growth factor (VEGF), phosphorylated Janus kinase 1 (pJAK1)/STAT3 signaling, and mitogen-activated protein kinase (MAPK).[21]

Apigenin inhibited triple-negative breast cancer cell migration and cancer stem cell characteristics at least partially inhibiting the action of YAP/TAZ-TEADs. As a result, Apigenin appeared to be a potential drug for treating triple negative breast cancer patients with high YAP/TAZ activity.[22] In MCF-7 and MDA MB-231 breast cancer cell lines, Apigenin promotes apoptosis and significantly damages DNA and lipids, contributing to its overall cytotoxic capacity.[23] Apigenin causes apoptosis and cell cycle arrest in the G2/M phase, which reduces the proliferative action of E2. It is significant to note that Apigenin blocks the Akt/FOXM1 signaling pathway by reducing the production of FOXM1, a crucial transcription factor involved in the cell cycle. Additionally, Apigenin modifies the expression of genes controlled by FOXM1, including those associated with the cell cycle, especially in the MCF-7/Akt clone.[24] A recent study

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shows that the inhibition of tumor growth and the EMT (Epithelial to Mesenchymal Transition) process in the MDA-MB-231 human breast cell line is positively correlated with the blocking of IL-6 (Interleukin-6) associated inflammation. Apigenin's anti-invasive and anti-cancerous properties inhibit the downstream signaling pathways connected to IL-6 when taken orally.[8]

Hesperidin

Species including grapefruits, lemons, and oranges contain large amounts of the flavonoids hesperidin.[25] The modulation of signaling pathways, cell cycle regulatory proteins, glucose uptake, enzymes, oxidative status, miRNA expression, plasma and liver lipid profiles, tumor suppressor p53, along with DNA repair mechanisms have all been linked to the chemotherapeutic and chemo sensitizing effects of hesperidin.[26]

Hesperidin can minimize the occurrence of cell apoptosis by downregulating the activity of inducible nitric oxide (NO) synthase, which has a suppressive impact on the expression and activity of NO synthase.[27] The P53 gene was also discovered to be a crucial protein in the suppression of breast cancer stem cells.[28] Hesperidin has recently been found to reduce PD-L1 expression in the MDA-MB231 human breast cancer cell line by inhibiting the PI3K/Akt and NF-B pathways, so constraining the growth of breast cancer and lessening these cells' ability to migrate, thereby attenuating aggressiveness of the cells.[29] In MCF-7 doxorubicin cells, hesperidin acts as a preventative resistance agent, has cytotoxic effects, and promotes apoptosis.[30]

Berberine

Many medicinal plants, including Phellodendron amurense and Coptis japonica, contain the isoquinoline quaternary alkaloid known as Berberine. There is mounting evidence that Berberine has anti-cancer properties. Berberine acts as a DNA intercalator and influences gene regulation, specifically the production of oncogenic and tumor suppressor proteins. P53, MAPK, PI3K/Akt, and NF-B are among the signaling pathways that Berberine uses to exert its anti-cancer effects.[31]

Evidence suggests that Berberine causes apoptosis by upregulation in the expression of Bax, cleaved caspase3, and cleaved caspase9, while downregulation in the face of Bcl2; these processes occur not only in MCF7 cells but also in T47D luminal A cells.[32] Berberine targets EGFR and AKT kinase domains. Berberine modulates the PI3K signaling pathway by targeting AKT. According to recent in vitro and in silico investigations, Berberine has modest action against additional targets (p38 and ERK1/2).[33] Berberine inhibits TNBC cell proliferation and metastases in an orthotopic animal model. Berberine dramatically lowers TGF-1 expression in TNBC (triple negative breast cancer cells). Berberine therapy reduces the basal levels of smad3 phosphorylation and MMP-2 expression in HCC1806 triple-negative breast cancer cells.[34] Another research suggests that exercise and Berberine may have anti-cancer effects via regulating intestinal microbial metabolites, enhancing the immune system, activating the mitochondrial apoptosis pathway, and activating the Fas death receptor apoptosis route.[35]

Curcumin

A non-toxic, incredibly promising natural antioxidant, curcumin is a polyphenolic chemical produced from the culinary spice turmeric. It works to inhibit the growth of cancer cells by interacting with a variety of molecules and metabolic processes. Curcumin controls a number of hallmarks of cancer, including cancer signaling pathways, cell proliferation, tumor angiogenesis, and transcription factors, via influencing several targets.

Curcumin might activate Slug and revive the production of E-cadherin, as well as prevent β-catenin's nuclear translocation. As a result, the migration of breast cancer stem cells is finally inhibited. These actions eventually promote the production of E-cadherin/β-catenin complexes and the intracellular retention of β-catenin.[36] For the first time, curcumin's ability to target mammospheres by preventing stem-like traits and controlling the EMT process has been shown. The results of the same study suggest that curcumin may act as a specific sort of anti-metastasis therapy for breast cancer.[37] According to studies, curcumin administration induces p53-independent apoptosis in MDA-MB-231, SKBR3, and EMT6 cells by lowering p53 expression levels and phosphorylated p53 (S392, S15, and S392) levels.[38] According to research, curcumin can also suppress MDA-MB-435 cells from proliferating by downregulating the expression of EZH2.[39]

Genistein

The isoflavone genistein, a native of Southeast Asia and a natural phytoestrogen, is found in soybeans.[40] Genistein produces cell cycle arrest and antimetastatic characteristics and eventually impacts breast cancerous cell development via several pathways. Higher doses of genistein are often required to notice its antiproliferative or anti-growth effects. The tumor suppressor p21 is increased, whereas NF-KB, HIF-1, and VEGF are all on the decline in this signaling pathways.[41]

Genistein may operate as an inhibitor by inhibiting HIF-1 from activating its VEGF and other downstream effectors. In breast cancer cells, genistein can bind to HIF-1α and inhibit its activity. Genistein binds to elements in the FIH-1 binding domain of HIF-1α, according to further docking experiments.[42] Genes associated with inflammation can be modulated by genistein with the aid of ER, according to

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research on the impact of genistein on the inflammation of malignant cells with various distinct receptors α and β ratio, i.e., ERα and ERβ ratio.[43] ERβ-1 altered the cell cycle transition in MCF-7 cells, increasing the anti-cancer effectiveness of genistein.[44] In BRCA1-impaired breast cells and overcoming drug resistance, as well as radio sensitization and radioprotection. These phytochemicals offer appropriate nourishment while minimizing the negative effects of traditional cancer treatment since they are strong antioxidants.

Table 1.Phytoconstituents and their Molecular Inhibitor

Phytoconstituents	Source	Molecular Inhibitor	References
Liquiritigenin	Glycyrrhiza glabra (Licorice)	DNA Methylation, ER regulation	17, 19
Apigenin	Garlic, Onion, Tea	TNBC cells and Cancer Stem cells, by inhibiting the action of YAP/TAZ-TEADs, Blocks Akt/FOXM1 signaling pathway	25, 27
Hesperidin	Grapefruit, lemon, orange	Inhibiting NO synthase, PI3K/Akt, and NF-B pathways	30, 32
Berberine	Phellodendron amurense and Coptis japonica	modulates the PI3K signaling pathway, targeting EGFR and AKT kinase	36
Curcumin	Curcuma longa	Inhibited breast cancer stem cells by promoting the activity of E-cadherin/β-catenin complexes	39
Genistein	Soybeans	Inhibit the activity of HIF-1α, suppresses Akt phosphorylation and GPR30 activation	48, 45

cancer cells, genistein suppresses Akt phosphorylation and GPR30 activation, which results in G2/M phase arrest via down regulating the production of cyclin B1.[45] Thus, genistein could be a potential therapeutic alternative for the delivery of the anti-breast cancerous drug.

Conclusion and Future Perspective

There are a large proportion of deaths due to breast cancer among women worldwide, which is among the most commonly diagnosed cancers. It remains a major challenge to treat and diagnose breast cancer despite the advancement in therapeutic techniques and diagnostic procedures. A variety of chemotherapeutic components are presently used in breast cancer treatment, including paclitaxel, docetaxel, doxorubicin, carboplatin, bevacizumab, and cyclophosphamide. Phytochemicals offer a practical method to get around other negative side effects by improving the bioavailability, cytotoxicity, stability, and prolonged release of traditional chemotherapeutic drugs.

Fruits, vegetables, whole grains, and other plant foods contain phytochemicals, which have been linked to significant health benefits. Phytochemicals exert anti-tumor effects via distinct mechanisms. Many of these phytochemicals affect cancer growth and progression by regulating molecular pathways. Phytochemicals destroy rapidly proliferating cells by targeting improperly expressed molecular factors, removing oxidative stress, regulating cell growth factors, preventing malignant tissue from forming new blood vessels, and inducing apoptosis. In addition, they are capable of targeting breast cancer stem

Conflicts of Interest: None

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