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Review Article

The Potential Effect of Plant Based Antioxidants in Breast Cancer Prevention and Treatment

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ABSTRACT

Breast cancer is the most common cause of death among women worldwide. According to the 2024 Cancer Statistics report, it has surpassed lung cancer as the most frequently diagnosed cancer around the world. Oxidative stress is one of the most common risk factors for breast cancer. Oxidative stress can cause mutations in breast tissue that can ultimately lead to breast cancer. Antioxidants are molecules that nullify the effects of oxidative damage and can be used as chemopreventive and chemotherapeutic agents for breast cancer. The present review examines natural antioxidants, such as vitamins, curcumin and quercetin and their roles as chemopreventive and anticancer agents for breast cancer. Many *in vitro* and *in vivo* studies support their effects as chemopreventive or chemotherapeutic agents. Although many additional studies are required to support their use as drugs, in the future, these molecules are potential candidates for chemopreventive and chemotherapeutic drugs against breast cancer.

Keywords: Antioxidants, Breast cancer, Oxidative stress, Free radicals, Chemoprevention, Chemotherapy.

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INTRODUCTION

Female breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related death in women worldwide, surpassing lung cancer with an estimated 2.3 million new cases (11.7%) in 2020.[1] Breast cancer has many risk factors, such as family history, alcohol consumption, mutations, obesity, hormonal therapy and oxidative stress.[2] There is a homeostasis between oxidative stress and antioxidation in eukaryotic cells. Any imbalance in this homeostasis can cause damage to the cell. Excessive formation of free radicals can cause severe damage to the cell membrane, enzymes and DNA, which can lead to various kinds of diseases, mutation and carcinogenesis.[3] Many factors are involved in the occurrence of breast cancer and many reports indicate that the imbalance between oxidation and antioxidation plays a significant role.[4] Evidence suggests direct roles of oxidative stress and lipid peroxidation in breast cancer. The level of malondialdehyde significantly increases in the serum of breast cancer patients,[5] which is one of the major end products of the peroxidative degradation of polyunsaturated fatty acids.[6] Many reports suggest that an important reason for impaired mitochondrial metabolism can be the generation of Reactive Oxygen Species (ROSs). Reactive Oxygen Species (ROSs) can cause DNA damage and genomic instability, which can lead to cancer progression.[7] Oxidative stress plays important roles in the initiation and pathogenesis of breast cancer.[8] The DNA of breast cancer cells consists of high concentrations of modified bases such as 8-hydroxy-2′-deoxyguanosine (8-OHdG). A 3.35-fold increased level of 8-OHdG was observed in ER-positive malignant cells. In an *in vitro* study, the 8-OHdG levels in the ER-positive MCF-7 cell line were significantly higher (9.3-fold) than those in ER-negative cell lines.[9] Another study also identified increased levels of 8-OHdG in the DNA of early-stage cancer tissue rather than late cancer tissue, which indicates an important role of ROSs in the early stage of breast carcinogenesis.[10] Alterations in breast cell genes are likely to be due to the oxidative stress that is generated by oestrogen in combination with receptor-mediated proliferation of damaged cells. Both synthetic and natural oestrogens can cause chromosomal aberrations and damage to DNA and breast tissues *in vitro* and/or *in vivo*.[11] Superoxide dismutase 2 is an antioxidant enzyme that is considered to be

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a tumour suppressor. The SOD2 gene is frequently found to be downregulated in various human cancers, including breast cancer.[12] According to several studies, superoxide dismutase 2 expressions in MDAMB-435 and UACC-893 cells were lower than that in the normal epithelial cell line MCF-10A, which directly indicated that the low level of superoxide dismutase 2 is related to the presence of excessive ROSs, which cause damage to mitochondrial DNA in these breast cancer cell lines.[13,14] In many breast cancer cases, overexpression and altered location of superoxide dismutase 1 have been reported. In normal cells, SOD1 is located in the cytosol, but in the case of breast cancer, SOD1 is also present in mitochondria and protects cancer cells from ROSs that are present in superoxide that is generated in this organelle. Not only SODs but also other antioxidative enzymes are downregulated or absent in breast cancer. The enzyme methionine sulfoxide reductase A prevents protein oxidation and is reported to be downregulated in breast cancer cell line MDA-MB231.[15] Although excessive ROS production leads to programmed cell death, continuous production at sublethal levels can cause adaptive responses and resistance to apoptosis. Protein kinase B (Akt), which is an antiapoptic factor, is activated by the presence of H_2O_2.[16]

Preventive effects of antioxidants in breast cancer

Antioxidants are considered to be scavengers of free radicals. They reduce the harmful effect of ROSs in cells and prevent them from inducing oxidative damage; oxidative damage can cause many diseases, including cancer. Antioxidants can reduce cancer risk by preventing DNA damage by ROSs or free radicals. Many studies have indicated the presence of oxidative stress and decreased catalase in breast cancer.[17] Although breast cancer is easily treatable if diagnosed at early stages, approximately 30% of early diagnosed cases can still lead to metastasis; hence, advancements in treatment and preventive measures are needed to reduce the risk of breast cancer-related mortality.[18] Vitamin C (ascorbate) is an important nutrient. It exhibits many significant properties, including immune stimulation, inhibition of nitrosamine synthesis and inhibition of metabolic carcinogen activation, but its main function is associated with the protection of cells from oxidative damage. Its cancer-preventive effects may be associated mainly with its protective effects against oxidative stress. Recent studies suggest the importance of vitamin C in breast cancer prevention. Vitamin C is considered to reduce the risk of breast cancer post-menopause.[19] The chemopreventive effect of vitamin C is due to its role in enhancing the immune system and preventing metastasis. Vitamin E (tocopherol) is a water-insoluble vitamin that is present mainly in fat and oils. Vitamin E prevents cancer by enhancing the immune system and preventing free radical-induced damage to breast cells. Tocopherol acts as a poor antioxidant outside the plasma membrane but functions as a potent antioxidant inside the cell membrane, where it stabilizes the membrane and removes free radicals.[20] 2 recent epidemiological studies in human and rat respectively, suggest a role of vitamin E in breast cancer prevention. The results of the studies indicate that dietary sources of vitamin E can provide females with modest protection from breast cancer.[21,22] The role of tocopherol in breast cancer is investigated by using various approaches in animal models. Tocopherol reduces the progression of daunorubicin-induced mammary tumours in rat models. It is assumed that tocopherol prevents free radical-associated DNA damage in mammary cells.[23] According to a study; tocopherol along with selenium inhibits DMBA-induced mammary cancers in rats (on a high polyunsaturated diet). It is hypothesized that tocopherol inhibits DMBA-induced mammary tumours due to the dependence of rats on dietary fat composition.[24]

Curative effects of antioxidants in breast cancer

Antioxidants are considered to be good sources of drugs of various kinds of diseases, including microbial infection, inflammation and cancer. Secondary metabolites of plants are potent antioxidants and have been used as chemotherapeutic agents for a long time. This part of the review focuses on the most potent antioxidants and their role as anti-breast cancer agents. Some of the important antioxidants with anti-breast cancer properties are discussed below.

Epigallocatechin Gallate (EGCG)

Epigallocatechin gallate, which is a polyphenol, is abundantly present in tea plants (*Camellia sinensis*). Many studies confirm the role of epigallocatechin gallate as an anti-breast cancer agent. One study reported that Epigallocatechin Gallate (EGCG) had antiproliferative effects on the growth of MDA-MB-231 human breast cancer cells. EGCG-treated cells showed cell cycle arrest at the G1 phase and Downregulation of Cyclins (D and E), Cyclin-Dependent Kinases (CDK 4 and CDK 1) and PCNA under both *in vitro* and *in vivo* conditions.[25] Another study confirmed the antiproliferative effects of epigallocatechin gallate along with Suberoylanilide Hydroxamic Acid (SAHA), which is a Histone Deacetylase (HDAC) inhibitor and the combination of downregulated p27, PTEN and oestrogen Receptor alpha (ERα).[26]

Resveratrol

Resveratrol is a common phenolic compound that has been found to be present in various fruits, such as berries and grapes and in beans. Resveratrol is a proven antioxidant that prevents lipid peroxidation and has chemotherapeutic effects on various types of cancers.[27] The anticancer activity of resveratrol occurs through the inhibition of various signalling pathways, including Hippo/YAP. Resveratrol controls breast cancer cell proliferation by inducing apoptosis in 4T1 TNBC cells[28] and regulating p53 and ERα protein expression.[29] It has also been reported that in MCF-7 and MDA-MB-231 breast cancer cells, resveratrol causes the upregulation of ATP2A3, which is responsible for triggering apoptosis and changes in intracellular Ca2+ regulation.[30]

Tocopherol

Tocopherol is a common but important oxidant that is used to scavenge free radicals that are responsible for DNA damage and the regulation of lipid peroxidation in various organs, including the breast and prostate.[31] Tocopherol is considered to be a bioenhancer for many anticancer agents. Tocopherol succinate functions as a bioenhancer of pterostilbene activity against breast cancer cells.[32] According to one report, the administration of δ- and γ-tocopherol can inhibit tumour formation in an animal model of oestrogen receptor-positive breast cancer. Tocopherol treatment causes the modulation of c-Casp-9, c-PARP, ER-α, p27, CDK6 and Nrf-2 pathway genes.[33]

Curcumin

Curcumin is isolated from the rhizomes of *Curcuma longa* (*Curcuma* spp.). The plant *Curcuma longa* is commonly known as turmeric and belongs to the ginger family. It has been well established as a therapeutic since ancient times.[34] Curcumin is a potent antioxidant and protects cells from many diseases, including cancer. Various studies have indicated that curcumin treatment increases the levels of p53 and Bax in breast cancer cell line MCF-7.[35] Curcumin targets various molecular signalling pathways that are directly or indirectly involved in cell proliferation, including MAP3K1, MAPK1, SERPINE1, TGF-α, TGFβ1 and PGAP3. Experimental evidence indicates that the molecule also controls breast cancer cell proliferation by inducing apoptosis by decreasing CDC25 and CDC2.[36] Curcumin also causes the activation of mitochondrial-associated apoptosis in breast cancer cells.[37] Additionally, curcumin acts as a bioenhancer and causes increased apoptosis along with paclitaxel.[38]

Quercetin

Quercetin is commonly present in various plant parts, including vegetables, fruits and seeds. It is a naturally occurring antioxidant and has several therapeutic properties. It is a proven anticancer agent both *in vitro* and *in vivo*.[39] Quercetin induces apoptosis in MCF-7 cell lines by suppressing cyclin D and P21 expression and reducing the phosphorylation of P38MAPK, which is a hallmark of cell proliferation. Anticancer activity of quercetin in HER2-overexpressing BT-474 BC cells was reported through the activation of the extrinsic apoptotic pathway. Quercetin also inhibits cell growth by modulating PI3k, EGFR and Her2/neu factors.[40]

Lycopene

Lycopene is one of the main carotenoids in vegetables and fruits, especially in tomato. It is considered to be the most effective free radical quenching agent among known carotenoids.[41] It is known for its anticancer properties against various cancer types, including breast cancer. Lycopene exerts its anticancer properties by regulating signalling pathways and inducing apoptosis. In addition, it inhibits tumour invasion, angiogenesis and metastasis.[42] Lycopene regulates the ERK and Akt/mTOR pathways in breast cancer.[43] According to reports, lycopene can inhibit the proliferation, invasion and metastasis of two aggressive breast cancer cell lines, namely, H-Ras-transformed MCF10A and MDA-MB-23. It increases the expression of Bax and caspase-9 in MCF-7 human breast cancer cells. Lycopene also shows anticancer activity against triple-negative breast cancer cells by activating the Bax protein and inhibiting the phosphorylation of Akt.[44] In ER/HER2-negative breast cancers, lycopene reduces cell growth by downregulation of Skp2.[45]

Capsaicin

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is a capsaicinoid that is present in peppers and is used mainly as a spice worldwide. In addition to antioxidant properties, it has other pharmaceutical properties, including antimutagenic and anticarcinogenic properties.[46,47] Capsaicin interacts with microsomal P450-dependent monooxygenases and prevents cells from xenobiotic-related toxicity.[48] Capsaicin induces the generation of ROSs and inhibits Rac1 activity in aggressive breast cancer cells, including H-Ras MCF10A cells.[49] It induces apoptosis in breast cancer stem cells (MCF-7) by regulating Notch signalling and activating caspase-3. Capsaicin reduces the size and migration of MDA-MB 231 breast cancer cells.[50] In association with the EGFR/HER-2 pathway, it also exerts antiproliferative effects by Notch signalling.[51]

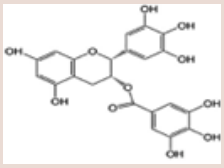
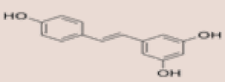
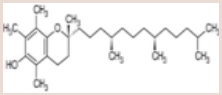
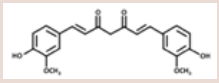
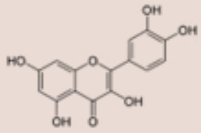
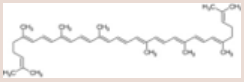
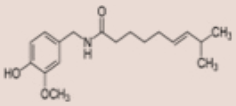
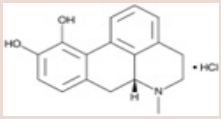
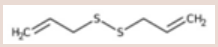
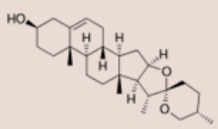
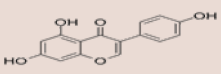
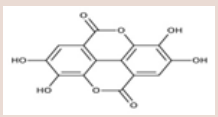
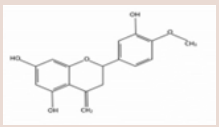
Apomorphine

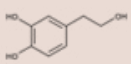
Apomorphine (a quinoline alkaloid) is derived from morphine and can be isolated from water lily plants. Apomorphine is considered to be an effective antioxidative agent. Apomorphine uses cytochrome c for its potential iron ion-reducing properties and scavenges OH radicals in aqueous media.[52] Apomorphine is considered to have antiproliferative activity against many cancer cell lines. According to one study, apomorphine acts as an inhibitor of TNF-α-induced Matrix Metalloprotease-9 (MMP-9) cell invasion in MCF-7 cell lines. Further studies suggested that it inhibits Activator Protein-1 (AP-1) because the TNF-α-induced transcription of MMP-9 is suppressed by Extracellular signal-Regulated Kinases 1 and 2 (ERK1/2).[53] In another study, apomorphine, dopamine and phenylethylamine were able to inhibit the proliferation of foetal calf serum-stimulated human breast cancer (MCF)-7 cells. Apomorphine also inhibited human oestrogen receptor-negative Breast cancer (MDA-MB-231) cell line proliferation.[54]

Diallyl sulfide

Garlic (*Allium sativum* L.), its extract and the molecules that are present in garlic are known to have many medicinal properties and have beneficial effects on human health. Garlic is specified as a remedy for a variety of diseases in Egyptian records.[55] It is considered to have many potential antimicrobial, antithrombotic

Table 1: Antioxidants and their breast cancer targets.

Antioxidant	Chemical structure	Main plant source	Breast cancer target
Epigallocatechin gallate		Camellia sinensis	Downregulation of cyclins (D and E), cyclin-dependent kinases (CDK 4 and CDK 1) and PCNA, p27.
Resveratrol		Vitis vinifera	Expression regulation of p53 and ERα protein and upregulation of ATP2A3.
Tocopherol		Auropus androgynus	Modulation of c-Casp-9, c-PARP, ER-α, p27, CDK6 and the Nrf-2 pathway genes.
Curcumin		Curcuma longa	p53 and Bax activation and CDC25- and CDC2-related apoptosis.
Quercetin		Curcuma domestica	Cyclin D and P21 expression downregulation and reduced phosphorylation of P38MAPK.
Lycopene		Lycopersicon esculentum	Bax protein activation and inhibition of phosphorylation of Akt.
Capsaicin		↱ Capsicum annuum	EGFR/HER-2 pathway regulation, regulation of Notch signalling and activation of caspase-3.
Apomorphine		Nymphaea nouchali	Upregulation of Bax and downregulation of Bcl-2 genes.
Diallyl sulfide		*Allium sativum* L	TNF-α-induced transcription of MMP-9 suppresses by Extracellular signal-Regulated Kinases 1 and 2 (ERK1/2), prosurvival signalling pathways Akt, Raf/MEK and NF-κB and inducing apoptosis; inhibition of Skp2.
Diosgenin		Dioscorea alata	Inhibition of EGF-receptor PTK activity and cell cycle arrest at the G2M phase.
Genistein		Genista trictoria	Disruption of the Mitochondrial Membrane Potential (MMP).
Ellagic acid		Myriophyllum spicatum	TGF-β/Smads pathway regulation, downregulation of CDK6 and disruption of the Mitochondrial Membrane Potential (MMP).
Hesperidin		Citrus sinensis	Cyclin D1 and p53 expression regulation.

Antioxidant	Chemical structure	Main plant source	Breast cancer target
Carotenoids		Tagetes erecta	p53 signalling pathway and HSP60.
Hydroxytyrosol		Olea europaea	Blocking the G1 to S phase transition.

and anticancer effects.[56,57] Many studies confirm its effectiveness as a chemopreventive agent for breast cancer.[58] Diallyl Disulfide (DADS), which is an oil-soluble compound, acts as an antioxidant by regulating Nuclear factor erythroid 2-related factor 2 (Nrf2) during oxidative stress and is also considered to be effective reducing breast tumours that are induced by many carcinogens. It also reduces the proliferation of 2-amino-1-methyl-6-Phenylimidazo-4-5-b-pyridine (PhIP)-induced mammary tumours.[59] DADS significantly inhibit the growth of human breast cancer cells (KPL-1, MCF-7, MKL-F and MDA-MB-231) *in vitro* and *in vivo* without any effect on normal cells.[60,61] The mechanism involves the induction of apoptosis through the upregulation of Bax and downregulation of Bcl-2 genes.[62]

Diosgenin

Diosgenin is a well-known steroid that is present abundantly in plants such as Dioscorea alata, *Smilax China* and *Trigonella foenum graecum*. Diosgenin exhibits antioxidant properties by increasing the levels of the antioxidant enzymes SOD and GPx and minimizing the level of lipid peroxidation.[63] In addition to its antioxidant properties, diosgenin possesses various other medicinal properties, including antidiabetic, immunomodulatory and anticancer properties. In MCF-7 (ER+), MDA 231 (ER-) and MCF-10A (normal breast epithelial cells), diosgenin is a potent anticancer agent that inhibits prosurvival signalling pathways Akt, Raf/MEK and NF-κB and induces apoptosis in both ER+ and ER- BCa. Diosgenin causes G0/G1 cell cycle arrest in BCa cells and inhibits *in vivo* tumour growth in xenograft models.[64] Diosgenin suppresses FAS expression and modulates Akt, mTOR and JNK phosphorylation in HER2-overexpressing cancer cells.[65] Diosgenin significantly inhibits actin polymerization, Vav2 phosphorylation and Cdc42 activation, which might be, at least in part, the source of the antimetastatic potential of diosgenin.[66] Furthermore, diosgenin inhibits the expression of Skp2 in breast cancer cells. Notably, diosgenin reduces cell viability and motility and induces apoptosis via suppression of Skp2 in breast cancer cells. According to a finding diosgenin could be a potential inhibitor of Skp2 for treating human MCF7 and MDA-MB-231 breast cancers.[67]

Genistein

Genistein (4′,5,7-trihydroxyisoflavone)) is a phytoestrogen that is structurally classified as an isoflavone and is considered the simplest isoflavonoid in Leguminosae. *Genista trictoria* is the plant from which it was first isolated in 1899.[68] Genistein is a well-known antioxidant that exhibits a wide range of therapeutic effects and has a wide range of potential health benefits. It shows chemopreventive effects against various types of cancer, including breast cancer and prostate cancer.[69] According to a study by Coral *et al.*, Lamartiniere genistein suppresses the development of Dimethylbenz[a]Anthracene (DMBA)-induced mammary cancer in rats and the researchers hypothesized that genistein promotes cell differentiation, which results in the downregulation of EGF Signalling pathway genes.[70] According to one study, the antiproliferative activity of genistein does not depend on the inhibition of EGF receptor PTK activity or oestrogen receptor signalling pathways.[71] Genistein shows potent oestrogen agonist and antiproliferative effects on ER(+) and ER(-) human breast cancer cells under *in vitro* conditions in a very low concentration range (10 nM-20 μM).[72] Another study by Choi *et al.*, indicated a time-dependent induction of p21WAF and inhibition of cyclin B1 in breast cell lines MCF-7 and MDAMB-231, which finally led to the arrest of cells at the G2M phase.[73,74]

Ellagic acid

Ellagic acid, which is a phenolic lactone, is a naturally occurring antioxidant that is present in various plant species, mainly in the fruit part of the plant. Ellagic acid is present in berries such as grapes, strawberries, cranberries and raspberries.[75] Ellagic acid possesses a variety of therapeutic properties, including anti-inflammatory, antimutagenic and anticancer properties.[76]

Several studies have confirmed the anti-breast cancer activity of ellagic acid *in vitro* and *in vivo*. According to one study, ellagic acid at a nontoxic dose causes antiangiogenesis by specifically targeting the VEGFR-2 signalling pathway in breast cancer.[77] According to a study by Chen *et al.*, ellagic acid inhibits the proliferation of MCF-7 cells *in vitro* by regulating the TGF-β/Smad signalling pathway, which results in the arrest of the cell cycle at the G0/G1 phase; Therefore, TGF-β/Smad pathway regulation in breast cancer cells could be a novel target for breast cancer chemotherapy, although further studies are needed to confirm the regulation of the TGF-β/Smad signalling pathway by ellagic acid.[78] Another study identified 1 more novel target of ellagic acid. Youssef and colleagues showed the downregulation of CDK6, which was found to be overexpressed in breast cancer.[79] Another study showed that ellagic acid treatment causes a significant enhancement of radiation-induced cytotoxicity in breast tumour cells. Ellagic acid disrupts the Mitochondrial

Membrane Potential (MMP), which makes breast tumour cells sensitive to radiation *in vitro*.[80] Interestingly, the same ellagic acid treatment helps normal cells overcome the free radical-induced damage that is caused by radiation.[81] Another finding suggests that ellagic acid can inhibit cancer cell growth via the regulation of matrix metalloproteinases, vascular endothelial growth factor expression and apoptosis induction.[82]

Hesperidin

Hesperidin is a flavonoid that is found abundantly in citrus fruit. Sweet orange (*Citrus sinensis*) is one of the richest sources of hesperidin. The peel and the membrane parts have higher concentrations of hesperidin than the other parts.[82] Hesperidin has significant antioxidant properties, as it scavenges free radicals and protects the RBC cellular membrane from H_2O_2-induced peroxidative damage and reduces the DNA strand break formation that is caused by free radicals.[83]

In addition to its potent antioxidant properties, hesperidin also has various other pharmaceutical properties; including anticancer properties.[84] Several reports have confirmed the chemopreventive and chemotherapeutic properties of hesperidin, especially for breast cancer. Hesperidin shows cytotoxic effects on the human breast cancer cell line MCF-7 at very low concentrations. When these cells were treated with hesperidin along with doxorubicin, the results indicated that hesperidin showed a synergistic effect by inhibiting Pgp expression.[85] Another *in vitro* study indicated that hesperidin inhibited the proliferation and migration of MCF-7 3D cells. It reduced p21 expression but increases cyclin D1 and p53 expression in the mammosphere, which resulted in the induction of G0/G1 cell cycle arrest and apoptosis in MCF-7 cells. Studies have confirmed that it does not affect the microtubule machinery in MCF-7 breast cancer cells, as it shows antimitotic effects in other types of cancer cells.[86]

Carotenoids

Carotenoids are among the most common naturally occurring pigments. More than 600 carotenoid compounds have been identified to date and among them, β-carotene is the most common.[87] Carotenoids protect plants from photooxidative damage and scavenge singlet molecular oxygen and peroxyl radicals. They also play protective roles in humans, where they synergistically interact with other antioxidants and improve the antioxidant defence system. Evidence suggests that carotenoids have a protective effect on human skin against photooxidative damage.[88] Carotenoids not only act as powerful antioxidants but also have various other therapeutic properties, including antiproliferative properties. These compounds can also reduce the adverse effects of anticancer drugs on normal cells by scavenging free radicals that are generated during chemotherapy and affecting the cytotoxicity of anticancer drugs on cancer cells.[89] The effect of carotenoids on breast cancer has been controversial: many studies have indicated a high risk of breast cancer due to carotenoid consumption,[90] whereas many other studies have confirmed the chemotherapeutic effects of some carotenoids on human breast cancer.[91] One of these studies indicated that several carotenoids significantly inhibited breast cancer cell proliferation via caspase-independent apoptosis and cell cycle arrest. Lutein, which is a potent carotenoid, inhibits breast cancer cell growth, with an effect that is quantitatively similar to the effects of taxanes, paclitaxel and docetaxel. It causes an increase in intracellular Reactive Oxygen Species (ROSs), specifically in Triple-Negative Breast Cancer (TNBC) cells; at the same time, it does not show any side effects on normal cells. Additionally, lutein can activate the p53 signalling pathway and affect HSP60 levels in TNBC cells.[92]

Hydroxytyrosol

Hydroxytyrosol is a common phenolic compound that is found abundantly in olive oil phenolics. Hydroxytyrosol is a potent antioxidant that scavenges free radicals and the peroxidation chain reaction prevents cells from lipid peroxidation. It is a common component in skin protection products.[93] In addition to antioxidative properties; hydroxytyrosol has many other pharmaceutical properties, including antidiabetic and anticancer properties. It shows different effects under normal oxygen levels and hypoxic conditions. Under hypoxic conditions, it can downregulate proapoptotic proteins BCL-2 and COX-2 and cause the death of cancer cells. According to Han *et al*., hydroxytyrosol causes cell cycle arrest in MCF-7 human breast cancer cells by significantly blocking the G1 to S phase transition. It also suppresses the migration and invasion of ER-positive breast cancer cells.[94] In *in vivo* studies, hydroxytyrosol reduced tumour growth and cell proliferation in mammary tumour-bearing rats. HT regulates the Wnt signalling pathway, which promotes an increase in Secreted Frizzled-Related Protein 4 (SFRP4).[95] Additionally, hydroxytyrosol reduces the oxidative stress that is caused by Taxol in breast cancer patients.[96]

CONCLUSION

Breast cancer is one of the most common causes of cancer-related death in women worldwide. Oxidative stress is one of the most common risk factors for breast cancer. Imbalanced homeostasis between free radicals and antioxidants in mammary cells can lead to breast cancer. Eukaryotic cells have an inbuilt mechanism for reducing oxidative damage in the cell membrane and DNA, but many factors, including smoking and alcohol consumption, can suppress this effect because they cause cells to undergo oxidative damage. Oxidative damage can be significantly reduced by the consumption of antioxidants that are present in fruits, vegetables and many other food items. These antioxidants prevent the DNA damage that is caused by reactive oxygen species. Not only do antioxidants function as cancer preventive agents but also many antioxidants have been proven to be excellent anticancer agents, especially for breast cancer (Table 1). There are many

antioxidants that work as bioenhancers of approved anti-breast cancer drugs. One of these antioxidants, namely, ellagic acid, has more than one novel anticancer target and has very little effect on normal cells; hence, it could be a significant candidate for breast cancer chemotherapy. Many antioxidants have already proven to be good candidates as chemopreventive and chemotherapeutic agents, but the present review covers only some of the most studied antioxidants.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ROS: Reactive oxygen species; **DNA:** Deoxyribonucleic acid; **8-OHdG:** 8-hydroxy-2′-deoxyguanosine; **SOD:** Superoxide dismutase; **H_2O_2:** Hydrogen per Oxide; **DMBA:** 7,12-Dimethylbenz[a]anthracene; **EGCG:** Epigallocatechin gallate; **SAHA:** Suberoylanilide hydroxamic acid; **CDK:** Cyclin-dependent kinases; **HDAC:** Histone deacetylase; **ERα:** Oestrogen receptor alpha; **MMP-9:** Metalloprotease-9; **Nrf2:** Nuclear factor erythroid 2-related factor 2; **TNBC:** Triple-negative breast cancer; **SFRP4:** Secreted frizzled-related protein 4.

SUMMARY

- Breast cancer is considered to be one of the most common causes of death among women worldwide.
- Cancer Statistics report 2020 reported that the breast cancer is number one diagnosed cancer all over the world.
- There many factors responsible for breast related malignancies, ROS is one of the risk factors for breast cancer.
- The oxidative stress can be reduced by the treatment of cells with antioxidants, which protect the cells from oxidative damage.
- In present review article, the authors tried to collect and summarized the data, which showed that the effect of oxidative stress can be reduced or prevented by using antioxidants isolated from natural sources.

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