

Review

Targeting Oxidative Stress Biomarkers in Breast Cancer Development and the Potential Protective Effect of Phytochemicals

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Abstract: Breast cancer continues to represent one of the most widespread and lethal health afflictions on a global scale. The advancement of this malignancy is predominantly influenced by genetic mutations that precipitate unregulated cellular growth and proliferation, with oxidative stress being a crucial factor in all phases of carcinogenic development. Oxidative stress emerges from a disruption in the equilibrium between reactive oxygen species (ROS) and antioxidants, which inflicts damage on cellular components and facilitates the onset of cancer. Although numerous studies have advocated the notion that augmenting antioxidant levels may confer protection against cancer, other investigations have yielded contradictory results. Nevertheless, the effectiveness of antioxidants in cancer prophylaxis remains contentious, with research exhibiting variable outcomes. Certain studies have indicated that a high consumption of fruits and vegetables abundant in antioxidants may lower cancer risk. However, the irrefutable evidence is currently absent. Furthermore, the chemotherapeutic agents, such as taxanes and cisplatin, utilized in breast cancer management are reported to produce ROS as an integral aspect of their therapeutic mechanisms, thereby highlighting the intricate interplay between redox equilibrium and oncological treatment. This review emphasizes the pro-oxidant hypothesis, which asserts that heightened levels of ROS may selectively annihilate cancer cells, given that normal cells generally sustain low levels of ROS. Some recent reports have indicated that the application of plant-based molecules as a therapeutic supplement may help treat breast cancer effectively. However, a comprehensive understanding of the role of oxidative stress in breast cancer and use of antioxidants could pave the way for more precisely targeted therapeutic strategies aimed at the modulation of redox homeostasis.

Keywords: oxidative stress; breast cancer; phytochemicals; Reactive Oxygen Species; redox homeostasis

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1. Introduction

Currently, the occurrence of cancer is counted as one of the deadliest diseases in the world. Mutations in DNA lead to uncontrolled cell growth and cell proliferation, resulting in cancer. The most common form of cancer prevalent among women is breast cancer. It also has the highest mortality rate globally [1]. Among females, breast cancer is reported to be the leading cause of cancer deaths. In India, many new emerging cases and deaths have been observed compared to other countries, which could be due to late diagnosis, social stigma, and less access to health facilities.

An imbalance between free radical species and antioxidants results in oxidative stress. One of the most important species of free radical is Reactive Oxygen Species (ROS), which

constitutes both radical and non-radical species. The overproduction of ROS or non-functioning of antioxidants leads to a pro-oxidant environment characterized as oxidative stress. ROS interacts with cellular constituents like lipids, proteins, and nucleic acids, affecting the structures and functions of these biomolecules. These observations relate ROS to disease and aging [2]. Different signaling pathways and various cellular processes, including cell proliferation, are affected by alterations in ROS levels in cells. Thus, any imbalance or increase in the ROS results in uncontrolled cell growth, ultimately leading to the development of a tumor. Whenever the homeostasis of ROS is disturbed, oxidative stress is generated, even if it is reversible or not widespread [3].

Oxidative stress is responsible for the occurrence of various types of diseases like neurological degenerative disease, atherosclerosis, and many types of cancers, including breast cancer [4,5].

Biomarkers that are indicative of oxidative stress have been rigorously examined for their correlation with the onset and advancement of various malignancies, particularly breast cancer, as the mechanisms underlying oxidative stress may play a significant role in several established risk factors for breast cancer, which include obesity, habitual alcohol consumption, and circulating estrogen concentrations [6–8]. Breast cancer cells exhibit a heightened vulnerability to oxidative insult and are characterized by elevated levels of oxidative stress, manifesting as protein damage, DNA damage, and lipid peroxidation [9]. Moreover, numerous factors associated with breast cancer risk may influence the levels of endogenous oxidative stress [10]. Consequently, this review focuses on a systematic literature review aimed at identifying and summarizing all published epidemiological studies that examine the relationship between oxidative stress biomarkers [11], the risk of developing breast cancer, and the prognosis following breast cancer diagnosis, while also delineating prospective avenues for future research.

In the past decade, significant advancements have been made in the development of chemotherapeutic agents; nevertheless, there persists a pressing need to address the challenge of drug resistance. A multitude of studies has concentrated on the exploration of phytochemicals, which are non-nutritive botanical compounds possessing disease-protective or -preventive characteristics. These compounds are classified as non-essential nutrients, as they are not requisite for the maintenance of human life. Compounds derived from these botanical sources have been shown to effectively target specific molecular subtypes of breast cancer and breast cancer stem cells. Phytochemicals are recognized for their non-toxic nature, and they exhibit a diverse array of biological activities, including anti-inflammatory, anti-proliferative, antioxidant, and anticancer effects.

This review also aims to highlight the role of oxidative stress in breast cancer pathogenesis, focusing on how an imbalance in Reactive Oxygen Species (ROS) can drive tumor progression and affect cellular processes like proliferation, DNA damage, and lipid peroxidation. Moreover, it seeks to address the potential of phytochemicals as a promising avenue for breast cancer prevention and treatment, emphasizing their non-toxic nature and diverse biological activities, such as antioxidant, anti-inflammatory, anti-proliferative, and anticancer effects.

This review aims to identify existing gaps in the literature, particularly the need for further research into the precise mechanisms by which oxidative stress influences breast cancer risk and progression, and the potential for phytochemicals to overcome current therapeutic challenges like drug resistance. By summarizing these studies, this review also suggests directions for future research aimed at integrating oxidative stress biomarkers and phytochemicals into the prevention and management of breast cancer.

2. Oxidative Stress and Cancer

2.1. Oxidative Stress

A free radical contains unpaired electrons, which make them highly reactive and capable of accepting electrons, thus acting as an oxidizing agent. The ROS and reactive nitrogen species (RNS) are some of the main oxidants responsible for oxidative stress [12]. Both enzymatic and non-enzymatic reactions are responsible for ROS production. The respiratory chain of mitochondria is one of the main non-enzymatic sources of ROS [6]. NADPH oxidases (NOX), xanthine oxidase, uncoupled endothelial nitric oxide synthase (eNOS), arachidonic acid, and other enzymes, such as the cytochrome P450 enzymes, lipoxygenase, and cyclooxygenase, are responsible for the generation of ROS [13–16]. All of these are internal sources of ROS production. However, exposure to some external factors such as radiation, environmental pollution, and various chemical compounds can also lead to their production [14–17]. The most important ROS in the body is superoxide anion, which is generated during electron transport chains and oxidative phosphorylation in mitochondria. Its effect, however, is of short duration as it is localized and is unable to cross the biological membrane. Its dismutation results in the production of hydrogen peroxide, which is more stable and can easily cross the membrane [18].

The overproduction of these free radicals, as well as the non-functioning of antioxidants, can disturb the homeostasis of the body, leading to oxidative damage. A number of antioxidant enzymes including catalase, superoxide dismutase (SOD), glutathione peroxidases (GPXs), peroxiredoxins (PRXs) [19] and glutathione reductases (Gr), along with various non-enzymatic antioxidants like vitamin A, vitamin C, vitamin E, glutathione, polyphenol metabolites, etc., play an important role in maintaining redox homeostasis of the body [20–22].

The dismutation of superoxide into hydrogen peroxide and oxygen is catalyzed by SOD. Three isoforms of SOD are known. Both SOD1 and SOD3 are copper zinc enzymes present in cytosol, whereas SOD2 is in the extracellular matrix. SOD2 occurs in the mitochondrial matrix with a manganese enzyme in its catalytic center. Catalase located in the peroxisomes detoxifies hydrogen peroxide by degrading it to water and molecular oxygen. Glutathione peroxidase (GPX) consists of eight isoforms of enzymes with different localizations and functions. Glutathione (GSH), a natural antioxidant, reduces hydrogen peroxides and lipid hydroperoxides by becoming oxidized itself to glutathione disulfide (GSSG), using H_2O_2 as an electron donor. The reduced form of glutathione is regained by the action of the glutathione reductase enzyme [23,24].

2.2. Influence of Oxidative Stress on Breast Cancer

Carcinogenesis is a process of the transformation of normal cells into cancerous cells by initiating a change in sequence of molecular and cellular events. During the process of carcinogenesis, the level of ROS increases while the level of antioxidants has been reported to decrease. Some of the specific features acquired by cancerous cells are uncontrolled division, cell death resistance, genetic instability, angiogenesis, metastasis, and metabolic deregulation [25–27]. Irreversible changes in DNA that occur due to point mutation or chromosomal aberrations lead to tumor initiation [28]. Chemical carcinogens and ionizing radiations are the most common reasons of loss of genome integrity, and both factors are concerned with the production of a high level of ROS. Carcinogens and radiation are often the biggest sources of loss of genomic integrity. They are also potential sources of ROS and mediate part of their detrimental roles on DNA damage. ROS in these cells can determine the level of the oxidative damage about to take place. It is still not clear whether ROS level increases as a result of cancer or if the increased ROS level results in the initiation of cancer [29]. The carcinogenesis process can be divided into three steps, which are initiation,

promotion, and progression. In the initiation stage, mutation occurs, resulting in the damage of stable DNA, and this process is not reversible. In the promotional stage, a clonal expansion of the mutated cells occurs, and various physiological processes are disturbed related to apoptosis, angiogenesis, etc. Some signal pathways are also affected [30]. The final progression stage is involved in the conversion of benign lesions into cancerous lesions, causing metastasis [31–34]. ROS plays a potent role in both the initiation and promotional stages of carcinogenesis.

ROS can cause oxidative damage to DNA via the oxidation of bases or sugar moiety of different purines and pyrimidines. The most common target is 2'-deoxyribose, which results in strand breaks and the release of unaltered DNA bases. A well-known oxidative DNA damage marker is 8-hydroxy-2'-deoxyguanosine (8-OH-dG), the presence of which was detected in breast cancer patients, while it was found to be absent in the normal tissue of the same patient [35]. Interestingly, the levels of 8-OH-dG decline in advanced stages of breast cancer [36]. This results in the indication that ROS is responsible for DNA damage, which in turn leads to the induction and progression of cancer.

Many of the risk factors associated with breast cancer are directly or indirectly linked to ROS. Genetic predisposition, for example, is a condition where mutation occurs in BRCA1 and BRCA2 genes. The BRCA1 gene is involved in controlling the levels of ROS in the cells, thus providing protection [37]; hence, mutation in this gene would lead to a disturbance in the homeostasis of the redox status of the body. BRCA1 also increases the expression of various genes involved in antioxidant response, like GST, oxidoreductases, and glutathione peroxidases. It also induces the expression of Nrf1 and Nrf2-nuclear factor, erythroid 2 related factor, two antioxidant transcription factors. The function of these two response factors is to induce an antioxidant effect and detoxification enzymes in response to oxidative stress [38]. Among these two, Nrf2 is the main transcription factor. Keap1 is the repressor of the Nrf2 signaling pathway and is induced by oxidative stress [39]. Although, a new contradiction seems to have arisen, which indicates that Nrf2 shows some oncogenic properties and might be involved in resistance to chemotherapy [40,41]. However, extensive research is required to clarify the actual role it might play in the prevention or induction of cancer.

A rise in the level of free radicals in tumor cells leads to the assumption that oxidative stress greatly influences carcinogenesis. The presence of oxidative stress markers in breast carcinoma samples also supports this notion. Thymidine phosphorylase enzyme causes the degradation of thymidine to thymine and 2-deoxy-D-ribose phosphate. In breast cancer expression, this enzyme is highly upregulated, which could be the main cause of oxidative stress in tumor tissues [42].

Inflammation is also very common in all cancers, including breast cancer. Both neutrophils and macrophages are involved, resulting in macrophage penetration in breast tumors, which further leads to an increase in the level of ROS through NADPH oxidase. NADPH oxidase is regulated by G-protein RAC1, which in turn is encoded by RAS protooncogene. It causes excess production of the superoxide anions and finally the distortion of cells [43].

Hypoxia and glucose deficiency are another common feature of tumor cells. Oxidative stress and the increased production of ROS also lead to this. Several signaling pathways are also affected by these factors.

2.3. Effect of ROS on Different Subtypes of Breast Cancer

Effect of ROS on Hormone-Dependent Cancer: During the progression of breast cancer, estrogens serve as ligands to activate estrogen receptors (ER) through both genomic and nongenomic mechanisms. Estrogen facilitates the production of reactive oxygen species

(ROS) via mitochondrial metabolic processes. It is noteworthy that the phenomenon of estrogen-induced ROS production and the resultant DNA strand breaks have been extensively documented in estrogen-responsive cells for several decades. Investigations conducted by Shaolong Zhang and associates elucidated the kinetics of estrogen-mediated ROS generation and the formation of double-strand breaks (DSBs), categorizing them into two distinct types. DSBs that are associated with oxidative DNA damage predominantly manifest in the most fragile and transcriptionally active chromatin domains. Conversely, additional DSBs emerge from the enzymatic activities of factors such as apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like 3b (APOBEC3B) and topoisomerase I/II, which facilitate chromatin restructuring and enhance estrogen signaling by alleviating torsional stress [44]. Intriguingly, a limited production of ROS can sufficiently mitigate DNA damage and postpone tumorigenesis in a BRCA1-deficient murine model of breast cancer. In this experimental model, substantial quantities of endogenous estrogen oxidative metabolites induce the formation of DNA adducts and generate apyrimidinic/apyrimidine sites associated with DSBs and genomic instability within the mammary gland. Antioxidant therapeutic interventions that inhibit estrogen oxidation have demonstrated efficacy in reducing oxidative DNA damage and delaying the onset of breast tumors. Moreover, the ablation of ER α can initiate autophagic processes and suppress the activation of the unfolded protein response (UPR) triggered by antiestrogen treatments, thereby augmenting ROS-mediated cell death in breast cancer [45].

Beyond the influence of estrogen, a multitude of hormones exert significant effects on the proliferation and metastasis of breast cancer. For example, progesterone receptors (PRs) have been demonstrated to facilitate STAT signaling pathways that are intricately associated with inflammatory and immune responses, thereby modulating the behavior of breast cancer cells [46]. Furthermore, glucocorticoid receptors are pivotal in the mediation of oxidative stress and inflammatory processes, with substantial evidence suggesting that these receptors exhibit heightened activity in breast cancer and its metastatic environments. Clinically, synthetic derivatives of glucocorticoids are frequently administered as anti-inflammatory therapeutics and immunosuppressive agents [47]. Such findings underscore the intricate interplay between hormonal regulation, reactive oxygen species (ROS) production, and the dynamics of breast cancer.

Effect of ROS on Triple-Negative Breast Cancer: Triple-negative breast cancers (TNBCs) are correlated with poor patient survival outcomes due to their highly aggressive biological properties and the lack of effective targeted therapeutic interventions. An increasing body of evidence suggests that oxidative stress-related cellular signals (OSCS) play a significant role in the initiation, advancement, and metastasis of breast cancer [48]. In a study focusing on TNBC, Malik et al. (2021) reported elevated ROS levels across all TNBC cell lines when compared to both normal cells and estrogen receptor-positive (ER+) breast cancer cell lines [49], while the role of ROS in the pathophysiology of TNBC remains inadequately elucidated. Despite the elevated recurrence rates and dismal prognostic outcomes among TNBC patients, certain subsets of this population exhibit prognoses comparable to other breast cancer subtypes [50], underscoring the notion that TNBC represents a highly heterogeneous neoplasm, necessitating individualized gene expression profiling prior to risk-stratified therapeutic approaches.

Fortunately, advancements in sequencing technologies have ushered in novel platforms and opportunities to analyze the disease at a molecular level [51]. In another study, investigation revealed the identification of two distinct molecular subtypes through the consistent cluster analysis of TNBC datasets based on prognosis-associated OS genes, thereby indicating divergent prognostic outcomes and tumor microenvironment (TME) characteristics, further emphasizing the heterogeneity present among TNBC patients [52]. Although

ROS can facilitate the reprogramming of the extracellular matrix, cancer-associated fibroblasts, and endothelial cells within the breast TME [53], no discernible differences between the two molecular subtypes was observed. Variability in TNBC datasets and differences in cellular composition ratios within the breast TME may account for this finding, which does not necessarily imply a contrary role of ROS in stromal cell functions.

In relation to the influence of aging on TNBC, a primary emphasis is placed on recognizing cellular senescence as a critical factor contributing to treatment resistance in TNBC [54]. Nonetheless, the precise mechanisms by which cellular senescence contributes to the etiology and progression of TNBC remain inadequately understood

3. Signaling Pathways in Breast Cancer Induction

3.1. Mitogen Activated Protein Kinase (MAPKs) Pathway

As a result of this, several cellular processes are also affected. The MAPK family consists of many kinases like extracellular regulated kinases, p38 α , and c-jun N terminal kinases. All of them play a significant role in controlling cellular messages by the phosphorylation of various proteins [55]. These proteins are also known as stress-activated protein kinases (SAPKs) [56]. Under stress conditions in cancer cells, the Activating Protein1 (AP1) is activated. It is a transcription factor, which plays a vital role in cell proliferation and transcription. This transcription factor consists of two subunits, i.e., Jun and Fos. In cancerous cells under a high oxidative stress state, the activation of the MAPK pathway (p38 and JNK) leads to the hyperphosphorylation of Jun and Fos subunits of cancerous cells, resulting in the activation of the AP-1 protein. In many of these cells, cell proliferation is activated by the AP-1 protein. The combined effects of the MAPK pathway and AP-1 participate in the proliferation of cells and induce cancer under the condition of oxidative stress [57].

3.2. Estrogen Receptor Pathway

Many of the studies conducted previously in areas of breast carcinoma have shown that an elevated level of estrogen for a long period of time is related to high breast cancer risk. Two types of pathways are involved in this process, e.g., the ER (estrogen receptor)-dependent pathway and the ER-independent pathway. In the ER-independent pathway, the genotoxic metabolites are formed by the oxidative metabolism of estradiol. These genotoxic metabolites lead to DNA damage directly. In a study where cross-bred mice between estrogen receptor α knockout mice and Wnt-1 overexpressing mice was used, the cross-bred mice still showed mammary tumor formation and DNA damage, which must have occurred by following the ER-independent pathway [58].

In the ER-dependent pathway, the formation of catechol quinone metabolites activates endogenous estrogen, estradiol, and other benzene ring-containing compounds to weak carcinogens [59]. A specific cytochrome P450 (CYP) enzyme causes the hydroxylation of estrogen at C2 or C4 position to catechol estrogens [60]. Catechol methyltransferase (COMT) causes further metabolism and the detoxification of catechol metabolites of estrogen. This can also occur by phase 2 conjugation reactions. Glucuronosyl-transferases and sulfotransferases are the enzymes that are responsible for the catalyzation of these reactions [61].

CYP1A1 hydroxylates E2 at the C2 position, while CYP1B1 metabolizes estradiol to 4-OH estradiol and is further converted by CYP peroxidases to estradiol-3,4-quinone. Studies have shown that 4-OH estrogen is more carcinogenic than 2-OH estrogen. Higher catalytic COMT activity towards 2-OH might be responsible for this [62]. The metabolites formed bind covalently to adenine or guanine on DNA. 4-OH-estradiol-1-N7-guanine and 4-OH-estradiol-1-N3-adenine are the adducts formed. These adducts are released, creating basic sites on DNA, making them more prone to the mutation process by interrupting

the DNA repair process. These mutations can induce certain types of cancer, including breast cancer. In breast cancer cases, higher amounts of quinone metabolites are found as compared to normal controls, indicating that these quinones play a major role in the process of carcinogenesis [63]. The reactive quinones and semiquinones are formed via the redox recycling of catechol estrogen, especially 4-OH estradiol. Semiquinones are oxidized to quinones by molecular oxygen. The cycle is completed by the reduction of semiquinone to quinone by CYP reductase. This process is accompanied by the reduction of molecular oxygen to superoxide anion and its further conversion to hydrogen peroxide. Both superoxide anions and semiquinones are mutagenic. NADPH quinone oxidoreductase reduces quinone to hydroquinone by the transfer of two electrons and without the formation of reactive semiquinone production. Fe^{3+} and Cu^{2+} ions are reduced to Fe^{2+} and Cu^{+} ions by catechol estrogen. These transition metals catalyze the Fenton reaction, resulting in the formation of hydroxyl radical from hydrogen peroxide and superoxide anion [64]. The hydroxyl radical takes part in the addition and transfer of electrons as well as in the abstraction of hydrogen. It initiates lipid peroxidation by abstracting hydrogen from lipids in membranes. However, its reaction with DNA bases proceeds with the process of addition, like its addition with guanine ends up with the formation of 8-hydroxyguanine radical, leading to DNA damage [65–67]. The mechanism of action of the estrogen receptor pathway is shown in Figure 1.

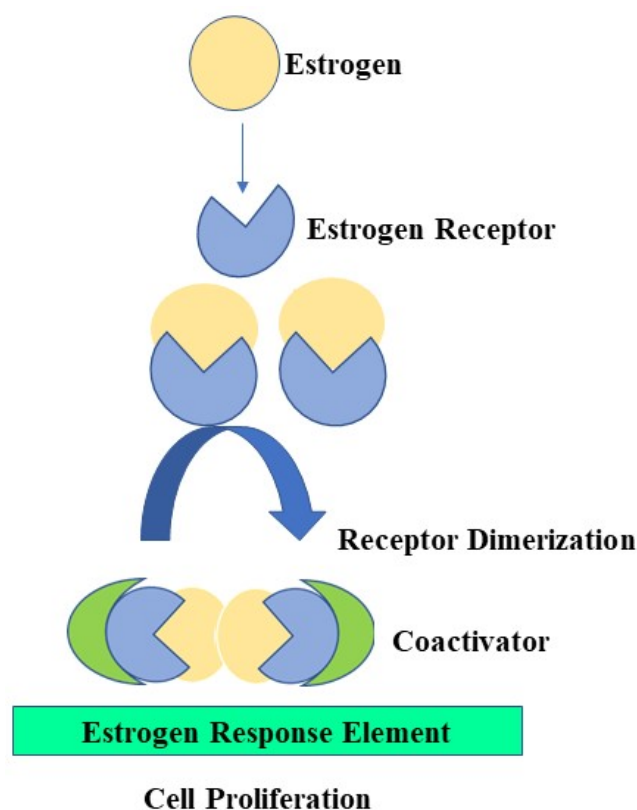


Figure 1. Mechanism of action of the estrogen receptor pathway.

3.3. Beta Catenin Signalling Pathway

The Wnt pathway is divided into β catenin-dependent and β catenin-independent pathways, which are also known as canonical and non-canonical signaling pathways, respectively. In about half of breast cancer patients, Wnt signaling is found to be activated. It has been linked to an overall reduced survival rate [68]. In the triple-negative breast cancer role of Wnt, canonical signaling has been studied deeply, although the level of nuclear β catenin has been found to be raised in other subtypes of breast cancer as well [69–71].

Overexpression of canonical Wnt signaling, ligands, and receptors is often found in breast cancer [72,73]. In mice models, continuous Wnt signaling was required for the induction of MMTV-Wnt tumors [74]. In some mouse models, the initiation of the mammary tumor was seen by the overexpression of R-spondin 2 alone [75]. Two tumor cell lineages have been identified in MMTV-Wnt mice models. These lineages are of luminal and basal descent [76]. The secretion of canonical Wnt signaling characterizes luminal subclone, which is also an essential requirement for tumor growth of the basal-like recipient cells [77].

3.4. HER2 Receptor Pathway

HER receptors are present on cell surfaces as monomers. Intracellular domains of HER proteins undergo dimerization and transphosphorylation by binding ligands to the extracellular domain. However, HER2 has no known activating ligands. It is either already in the active state, or it becomes active by dimerizing with either HER1 or HER3. This dimerization results in the autophosphorylation of tyrosine residues in the cytoplasmic domain, initiating several signaling pathways, such as the MAPK pathway, PIK3 pathway, and PKC; all of these result in cell proliferation, differentiation, invasion, and angiogenesis. Heterodimers are more potent than homodimers. In many invasive breast cancers, HER2 is overexpressed. About 25–50 copies of HER2 receptors have been determined in breast cancer cases, and a 40–100-fold increase has been observed in the HER2 protein expressing about 2 million receptors on the tumor cell surface [78]. In another study of 189 cases of breast cancer, the amplification of the HER2 gene was observed, establishing the prognostic significance of HER2 [79,80]. HER2 amplification has also been related to the stage of diseases, absence of estrogen and progesterone receptors, number of axillary nodes, and histological type. Studies suggest that HER2 amplification occurs in the early stages of tumorigenesis. In half of the ductal carcinoma, HER2 is amplified, and it is maintained during its progression to invasive disease and metastasis [81]. HER2 amplification is also associated with resistance to hormonal agents and creates a higher chance of the cancer metastasizing to the brain [82].

4. Potential for Therapy

4.1. Redox Homeostasis and Phytochemicals

In all stages of carcinogenesis, oxidative stress is involved; thus, enhancing the level of antioxidants can be a potential source for the therapy or prevention of cancers. Although, some studies have supported this view, while others have proven against it. In a study of MCF-7 cells, tamoxifen-induced toxicity was found to be reduced by intracellular vitamin C. The cause of this was the scavenging of ROS, which in turn provides protection against lipid peroxidation [83]. The same results were also seen in another case, where Paclitaxel-induced cancer cell death was reduced significantly by glutathione, N-acetyl cysteine, and H₂O₂ scavengers [84]. The presence of resveratrol also yielded similar results in other cancer cell lines [85]. When the effect of vitamin E was studied in breast cancer cell lines, such as MCF-7 and T47-D, tamoxifen-induced cytotoxicity was found to be reduced [86].

A lot of inconsistency has also been reported in the effect of antioxidants in cancer prevention or treatment. A high intake of fruits and vegetables containing active compounds like carotenoids, phenols, etc., has been known to reduce cancer risk [87,88], but no solid evidence has been found to support this. Another study by Misotti and Gnagnarella presented a review on the association of breast cancer risk with the supplementation of vitamins [89]. They categorized the number of studies and type of vitamins used for supplementation. Although some results did support the fact that vitamin supplementation reduced the cancer risk, the overall results were not that convincing. In another study known as the Rotterdam study, 3000 post-menopausal Dutch women of 55 years or older

were recruited as subjects, and their ferric reducing antioxidant potential was determined, which gave their overall dietary antioxidant capacity. The study revealed that a higher dietary antioxidant capacity was associated with lower cancer risk. However, individually, this was more beneficial in smokers and elderly people [90].

Normal cells have low levels of ROS, which are necessary for survival, but as the levels increase, as is usually seen in cancer cells, the response of antioxidants also increases to a certain extent, where it ultimately results in the destruction of the cancerous cell. This forms the basis of the pro-oxidant theory that increasing the level of ROS might help in the destruction of cancerous cells by oxidative damage, sparing the normal cells as the normal cells contain low levels of ROS [91]. This theory corroborates the fact that the use of vitamin C could be beneficial in the therapeutic treatment of cancer, as it also shows pro-oxidant effects.

Although pro-oxidant theory is reasonable enough, solid evidence supporting the theory is still lacking. However, a number of drugs, which are being used in the treatment of breast cancer, also help in maintaining redox homeostasis. Taxanes and Cisplatin generate superoxide anion and other ROS, respectively [92]. Although, this is a coincidence, but until recently, the generation of ROS by these therapeutically used drugs is only connected with a number of side effects shown by these drugs [93]. A list of anti-cancer drugs and their mechanism of action is depicted in Table 1 below.

Table 1. List of anticancer drugs and their effects on intracellular ROS.

Drug Name	Type of Cancer	Mechanism
Doxorubicin	Breast cancer, sarcoma	Fenton's reaction, electron leakage [94]
Arsenic trioxide	Lung cancer	Electron leakage [95]
5-florouracil	Colon cancer	P53-dependent ROS [96]
Platinum drugs (synergistically used with PARP inhibitors)	Breast cancer	ROS-dependent DNA damage [97]
NOV-002	HER-2 negative breast cancer	GSSG Mimetic [98]

4.2. Role of Phytochemicals as Anticancer Agents

(i) Resveratrol

Commonly found in grapes, berries, and soy beans, resveratrol is a natural polyphenolic compound known to show radical scavenging properties. In Sprague Dawley rat models, where cancer was induced through DMBA, resveratrol not only induced apoptosis but also reduced lipid peroxidation and DNA damage. Another study reported the same findings when they performed a review on various breast cancer cells, which showed that resveratrol induces apoptosis and reduces invasiveness and migration [99].

(ii) Tocopherols

These fat-soluble phenolic compounds are strong antioxidants, which make them anticarcinogenic agents. In N-nitrosourea-induced breast carcinogenesis in rats, the administration of γ - and δ -tocopherol inhibited tumor formation. However, the same effect was not observed in HER2-dependent tumors [100]. However, the administration of γ -, δ -tocopherol, and γ -TmT in an estrogen-induced xenograft model in MCF-7 line inhibited tumor growth [101].

(iii) Carotenoids

Carotenoids are natural lipid-soluble pigments found in fruits and vegetables. They can scavenge ROS effectively and, hence, have proven to be highly beneficial. In a case-controlled study performed in Chinese women, it was found that the consumption of

carotenoids reduces the risk of breast cancer [102]. Another study conducted among postmenopausal women revealed that α and β carotenes may reduce breast cancer risk. However, the use of γ tocopherol may increase the risk [103]. In another study, E3N, which was a French component of EPIC, the protective effects of serum levels of carotenoids, tocopherols, and retinols were correlated with breast cancer risk. It was observed that no direct association between the two could exist [104].

(iv) Eugenol

Eugenol (4-allyl(-2-methoxyphenol)), a phenolic natural compound available in honey and in the essential oils of different spices, such as *Syzygium aromaticum* (clove), *Pimenta racemosa* (bay leaves), and *Cinnamomum verum* (cinnamon leaf), has been exploited for various medicinal applications. For a very long time, the pharmacological properties of eugenol have been exploited in various Asian countries as antiseptic, analgesic, and antibacterial agents. Apart from these, eugenol has also been demonstrated to have antioxidant, antiviral, and anti-inflammatory properties [105,106]. However, no trace of carcinogenic or mutagenic properties has been inferred from the use of eugenol. In several cancer cell lines, like mast cells, melanoma cells, and HL-60 leukemia cells, the application of eugenol has shown anti-proliferative effects and the initiation of apoptosis in these cell lines. Eugenol has also shown to be potentially effective in the treatment of breast cancer. In another study, the treatment of breast cancer cell lines, e.g., MDA-MB-231 and SK-BR-3, with eugenol inhibited 76.4% of cell proliferation in MDA-MB-231 and about 68.1% of inhibition in SK-BR-3 [107]. The expression of MMP2 and MMP9 showed a significant decrease and increase, respectively, in the expression of Caspase-3, Caspase-7, and Caspase-9 [108].

(v) Rutin

Rutin (3,3',4',5,7-pentahydroxyflavone-3-rhamnoglucoside) is a type of bioflavonoid glycoside with beneficial pharmacological properties. The anti-cancer property of rutin in different types of cancers has been studied. The anti-cancer property of rutin is attributed to its property of showing the inhibition of malignant cell growth, the induction of cell cycle arrest and apoptosis, and the modulation of angiogenesis, inflammation, and oxidative stress. Several signaling pathways have been reported to be regulated by Rutin. In the case of ER- α positive-breast cancer MCF-7 cells, rutin interferes with the p53- and p21-dependent pathways and causes the arrest of the cell cycle at the G2/M phase [109]. The enhancement of p53 by rutin also induces apoptosis in breast cancer. Rutin has also shown synergistic effects with tamoxifen in ER- α positive breast cancer and has shown to increase the efficacy of anti-proliferation [110].

(vi) Curcumin

Curcumin (1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene3, 5-dione) is obtained from the plant *Curcuma longa*. It has antioxidant as well as antiproliferative and apoptotic effects. In Her2-positive cell lines, such as SKBR3 and BT474, curcumin is more potent than in the triple-negative cell lines. This might be due to the expression of ER rather than that of Her2. Curcumin could induce changes in cell membrane potential and could induce apoptosis [111]. Curcumin also causes the release of cytochrome C and the upregulation of caspase-9 and caspase-3, which may induce the mitochondrial-dependent apoptotic pathway. Then, PARP causes DNA fragmentation and apoptosis [112]. The mechanism of action of different phytochemicals in cancerous cells is presented in Figure 2. The effects of some phytochemicals on several breast cancer cell lines are summarized in Table 2.

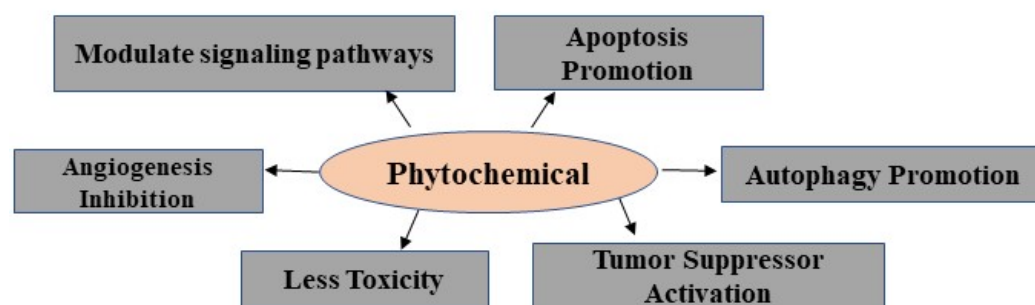


Figure 2. Mechanism of action of phytochemicals in cancerous cells.

Table 2. The effects of several phytochemicals on different breast cancer cell lines.

Phytochemical	Type of Cancer Cells	Dose	Results
Resveratrol	MDA-231	12.5–50 μ M	Cisplatin treatment when combined with resveratrol shows an inhibition in the viability of MDA231 cells [112]
Tocopherols	MCF-7	1 μ M	Inhibited the estrogen-induced expansion of the breast cancer stem population [113]
Carotenoids	MDA-MB-231	IC50 51.8 μ g/mL	Significant impairment of cell adhesion [114]
Eugenol	SK-BR-3	5–20 μ M	Anti-proliferative and anti-apoptotic effect [115]
Rutin	MDA-MB-231	200–400 μ M	Causes invasion and migration of cancer cells [110]
Curcumin	T47D	IC50 2.07 μ M	G2/M cell cycle arrest [112]

5. Conflicting Role of Antioxidants in Breast Cancer Treatment

It has been established that antioxidants may exert opposing effects on breast cancer; while certain antioxidants appear to confer beneficial outcomes in cancer therapy, others have been shown to promote tumor initiation and persistence. Melatonin has the potential to induce cancer regression by enhancing the efficacy of chemotherapy and restoring breast tumor sensitivity to this therapeutic approach, while also alleviating adverse effects associated with chemotherapy (e.g., cognitive impairment, sleep disturbances, and depressive symptoms) [116]. Clinical trials involving resveratrol provide support for the chemo-preventive properties of its supplementation through the modulation of estrogen metabolism. In conjunction with chemotherapy or radiotherapy, curcumin has also been found to mitigate their adverse effects, such as dermatitis and pain, alongside significant progress made in determining the dose-limiting toxicity (DLT) of curcumin in combination with chemotherapeutic agents, which has been shown to effectively reduce angiogenesis [117]. Remarkable progress has been achieved concerning antioxidant vitamins such as vitamin E, which is recognized as a chemo-preventive agent for breast cancer, in addition to it being an effective inhibitor of fibrosis induced by radiotherapy. Vitamin C has been observed to enhance immune function, potentially decreasing breast cancer patient mortality post-diagnosis and ameliorating chemotherapy side effects through the restoration of the antioxidant status in breast cancer patients. Significant strides have been made regarding the pro-oxidant function of high doses of vitamin C, as well as its role as a modulator of the antioxidant response in tumor cells, serving as an adjunctive treatment for breast cancer. Recent developments in research concerning vitamin D have revealed lower rates of advanced disease and/or mortality among the normal-weight populace, underscoring the necessity for patient stratification based on weight to mitigate the volumetric dilution of administered compounds. Importantly, it is recognized that calcitriol enhances thioredoxin reductase 1, a system integral to antioxidant status and the resistance

of tumor-infiltrating natural killer (NK) cells. This correlation warrants further exploration to elucidate the prospective role of calcitriol in adoptive cell immunotherapy. Vitamin D has also demonstrated the capacity to alleviate musculoskeletal symptoms and arthralgia in breast cancer patients undergoing treatment with aromatase inhibitors [118–120]. Additional antioxidants, such as carotenoids, have been linked to a reduced risk of breast cancer and recurrence among survivors, while hydroxytyrosol has exhibited significant potential in enhancing breast cancer treatments in conjunction with chemotherapy, as well as in alleviating associated side effects [121]. Ultimately, epigallocatechin gallate has been identified as capable of reducing mammographic density, providing protection against breast cancer and radiation-induced adverse effects, while selenium has been recognized as a safeguard against treatment-related side effects, albeit its potential as an adjunctive agent in breast cancer treatment remains largely unexplored [122]. Breast cancer is a heterogeneous disease in which distinct subtypes may exhibit varying REDOX statuses. Therefore, to thoroughly comprehend the potential role of antioxidants in cancer therapy and prevention, it is imperative to enhance the characterization of REDOX status across each subtype, patient demographic, and cellular category (e.g., triple-negative breast cancer versus estrogen receptor-positive, normal weight versus overweight/obese patients, or cancer stem cells versus non-cancer stem cells) [123]. For an in-depth understanding of the potential role of antioxidants in treating breast cancer, it is essential to understand the REDOX status, function, and interrelationship of the different components of the balance (e.g., enzymes, oxidative stress, antioxidants) and their interaction with other molecules (e.g., DNA, proteins, lipids) that regulate cell fate in an individual. Table 3 highlights the List of clinical trials utilizing phytochemicals treatment in breast cancer.

Table 3. List of clinical trials utilizing phytochemicals synergistically with conventional breast cancer therapy.

Phytochemical	Year of Study	Mechanism
EGCG	2016	EGCG along with standard drugs exhibited significant reduction in pain, itching, and burning feeling [122]
Silymarin	2025	Helps in reducing severity of radiotherapy [123]
Curcumin (with Paclitaxel)	2020	Synergistic use proved to be more effective than paclitaxel-placebo group [124]
Mistletoe extract	2020	Improved pain management and reduced appetite loss in patients undergoing surgery and chemotherapy [125]
Ginger	2016	Effective in relieving chemotherapy-induced nausea and vomiting [126]

6. Future Perspectives

Oxidative stress is recognized as a pivotal factor in the therapeutic landscape of oncology, wherein cytotoxic modalities augment oxidative damage as a mechanism to eradicate neoplastic cells. In addition to its implications in oncological therapies, oxidative stress arising from both endogenous factors (such as metabolic processes and immune responses) and exogenous influences (including ionizing radiation, tobacco use, and various chemicals) may induce modifications in the metabolic pathways of tumor cells, the architecture of tumor vascular networks, and the infiltration of macrophages within tumors [127]. These modifications can significantly affect not only the advancement of tumors but also the adaptability of cancer cells to oxidative stress, potentially resulting in heightened therapeutic resistance, angiogenesis, and an increased propensity for metastasis. Given the essential function of oxidative stress mechanisms in both oncological treatment and the possible

escalation of cancer metastasis, it has been posited that oxidative stress may hold particular significance in the prognostic assessment of cancer.

In general, investigations pertaining to oxidative stress biomarkers and breast cancer prognosis have been constrained by limited sample sizes (ranging from 30 to 363 cases) and/or the absence of standardized analytic methodologies (such as multivariable survival analyses). A variety of biomarkers have been employed, with certain studies quantifying DNA damage, lipid peroxidation, and/or protein damage across diverse biological specimens (including blood, tissue, and urine). Moreover, the timing of biomarker assessments varied, with certain investigations evaluating markers prior to surgical intervention, subsequent to surgery, during chemotherapy, and following any cancer treatments. The most extensive and earliest investigation identified a positive correlation between a biomarker indicative of lipid damage and prognostic outcomes; however, this study utilized a lipid peroxidation marker characterized by its non-specificity [128]. A significant limitation in the existing literature is the paucity of studies conducted within minority populations, encompassing African American and Hispanic women, who may present with distinct risk factor profiles for breast cancer and divergent levels of oxidative stress biomarkers [129]. Additionally, another notable limitation is the absence of studies that examined associations by breast cancer molecular subtype, which could provide valuable insights into the mechanisms of oxidative stress both in the etiology and prognosis of breast cancer. Further constraints were evident, as the majority of studies did not investigate multiple valid biomarkers across various biological samples (e.g., urine and blood or blood and tumor tissue), which may assist in mitigating the limitations associated with utilizing a singular biomarker. Lastly, there remains an inadequacy of data to facilitate a meta-analysis at this juncture; however, such an endeavor may be feasible following future research. Prospective large-scale studies that incorporate multiple sample types (such as tissue and urine) and utilize valid biomarkers assessed at various time points post-diagnosis (both pre and post-cancer treatments) may yield particularly insightful findings and contribute to addressing the methodological limitations of prior prognostic studies.

7. Conclusions

It is undeniable that oxidative stress is induced in cancerous cells, including breast cancer, by a sudden increase in ROS. ROS is involved in all stages, including the development as well as the progression of cancer. This obviously makes treating oxidative stress a potential therapeutic target in controlling cancer. However, different researchers have presented the contradictory results. Various theories have been given in defining the role of ROS, and the use of antioxidants might have a significant impact on ongoing treatments. The pro-oxidant compounds may increase ROS levels in cancerous cells, leading to their destruction, but the increased ROS levels would also leave a hazardous impact on the normal (noncancerous) tissues in the body. Since breast cancer is a complicated disease, these treatments might have different effects on different subtypes of cancer. Some researchers have also suggested the use of an antioxidant inhibitor as therapy for cancer. All these contradictory explanations do not offer a clear clinical support to state whether oxidative stress plays a direct or indirect role in the induction of breast cancer. However, extensive research is needed to generate enough experimental or clinical data to ascertain the safe application of antioxidants in breast cancer therapy.

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