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Research Article

The Role of Oxidative Stress in Breast Cancer Pathogenesis and Progression

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Abstract. Breast cancer is one of the most common and deadly cancers in women, and numerous studies have sought to identify the molecular and cellular factors involved in its onset and progression. Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and antioxidant systems, plays a pivotal role in the pathogenesis of many chronic diseases, including cancer. This article examines the effects of oxidative stress in breast cancer and analyzes its relationship with genetic damage, as well as protein and lipid alterations, and metastatic processes. ROS can inflict significant damage on cellular structures through the oxidation of DNA, proteins, and lipids, leading to genetic mutations, chromosomal instability, and disruptions in essential cellular processes such as cell proliferation and programmed cell death (apoptosis). In addition to its role in cancer initiation, oxidative stress contributes to cancer progression and metastasis. Considering the complex role of oxidative stress in breast cancer, this article proposes

therapeutic strategies focused on managing oxidative stress and introduces new approaches to improve current breast cancer treatments.

Keywords: breast cancer, oxidative stress, reactive oxygen species (ROS), genetic damage.

INTRODUCTION

Cancer is one of the greatest public health challenges worldwide, and in recent decades, its incidence has markedly increased, particularly in developing countries. Among the various types of cancer, breast cancer is considered one of the most common and dangerous cancers in women, accounting for a significant percentage of cancer-related deaths globally. According to reports from the World Health Organization (WHO), breast cancer is recognized as one of the leading causes of cancer mortality in women. Specifically, advanced-stage breast cancer is significantly more life-threatening, and evidence suggests that the survival rates of patients with this disease have not yet seen substantial improvement(Siegel, 2013).

In recent years, extensive studies have been conducted on the factors influencing the onset and progression of cancers, with many highlighting the critical role of oxidative stress in these processes. Oxidative stress is defined as an imbalance between the production of reactive oxygen species (ROS) and the antioxidant systems' capacity to neutralize them. Excessive production of ROS can lead to structural and functional damage in cells, ultimately contributing to the development of chronic diseases, including cancer (Dayem, 2010).

At the molecular level, ROS can cause oxidation of DNA, proteins, and lipids, leading to significant damage to cellular and genetic structures. Such damage not only induces genetic mutations and chromosomal instability but also affects various regulatory processes within cells, including cell proliferation, apoptosis (programmed cell death), and metastasis. Therefore, oxidative stress is recognized as a key factor in the initiation and progression of breast cancer and can even act as a facilitator in metastatic processes (Wiseman, 1996).

Moreover, oxidative stress can interact with other risk factors, such as chronic inflammation, environmental pollution, poor nutrition, and genetic predisposition, simultaneously contributing to the complexity of cancer development. Many researchers believe that oxidative stress plays a pivotal role not only in cancer initiation but also in its progression, invasion of surrounding tissues, and metastasis. Consequently, a precise understanding of how oxidative stress affects cancer cells can serve as a scientific foundation for developing novel therapeutic and diagnostic approaches for breast cancer treatment (Halliwell, 2007).

The aim of this article is to examine the role of oxidative stress in the pathogenesis of breast cancer and to analyze its effects on various cellular processes, including DNA damage, protein and lipid alterations, and breast cancer metastasis. In this article, we will describe the molecular mechanisms and cellular signaling pathways associated with oxidative stress and provide insights into therapies based on managing oxidative stress (Halliwell, 2007).

Oxidative Stress

Oxidative stress refers to a condition in which the balance between the production of free radicals and the antioxidant defense systems of the body is disrupted. Free radicals are unstable molecules that can easily react with other molecules and cause damage to proteins, lipids, and DNA. Naturally, the body has systems like antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase) that neutralize these free radicals(Halliwell, 2007).

Mechanisms of Oxidative Stress in Cancer

Oxidative stress can contribute to cancer development through various effects on cells. Some key mechanisms include:

• **DNA Damage**: Free radicals can damage DNA and cause genetic mutations, a crucial factor in cancer development.

• **Disruption of Cell Signaling**: Oxidative stress can activate various signaling pathways that lead to increased cell proliferation and decreased programmed cell death (apoptosis).

• **Mitochondrial Damage**: Damage to mitochondria can cause metabolic changes and increased free radical production, which further promotes cancer progression (Wiseman, 1996; Reuter, 2010).

The Role of Oxidative Stress in Different Types of Cancer

• **Lung Cancer**: In lung cancer, oxidative stress can increase due to cigarette smoke and other pollutants, leading to DNA damage and genetic mutations.

• **Breast Cancer**: Studies indicate that oxidative stress may play a role in breast cancer development, especially in genetically predisposed individuals.

• **Gastrointestinal Cancers**: In cancers of the stomach, intestines, and liver, oxidative stress can promote cancer through tissue damage, inflammatory processes, and genetic mutations (Wiseman, 1996; Reuter, 2010).

Therapeutic Strategies Based on Oxidative Stress

Given the role of oxidative stress in cancer, some therapeutic approaches aim to mitigate its effects:

• **Antioxidants**: Using antioxidants as dietary supplements or drugs can reduce oxidative stress and protect cells from free radical-induced damage.

• **Oxidative Stress Inhibitors**: Drugs that reduce free radical production and enhance antioxidant systems are being explored as treatment options for controlling cancer (Phaniendra, 2015).

• **Natural Compounds**: Natural compounds like flavonoids, polyphenols, and vitamins with antioxidant properties may be effective in cancer treatment.

Oxidative Stress and Cancer

Oxidative stress arises from an imbalance in the body's redox state, during which increased free radicals lead to tissue damage. Among the most important free radicals are reactive oxygen species (ROS), which are produced via various metabolic pathways, including aerobic metabolism in the mitochondrial respiratory chain. ROS play a critical role in the initiation and progression of various cancers. ROS, through different signaling and message-transduction pathways—such as growth factors and mitogenic pathways—can control many cellular processes like growth and proliferation. By stimulating uncontrolled cell growth, ROS contribute to the formation of tumor masses and carcinogenesis. Oxidative stress in cancer cells, caused by increased ROS and decreased antioxidant defense, also stimulates angiogenesis and metastasis, key factors in cancer spread and progression.

Free radicals in the body react with biomolecules to produce compounds like malondialdehyde, dityrosine, and hydroxyguanosine, which can serve as markers for cancer detection. This section discusses free radicals as oxidizing agents, antioxidants as the body's defense system, oxidative stress biomarkers, and the roles of these factors in various cancers, including breast cancer (Peng, 2000).

Mutations in DNA can convert proto-oncogenes to oncogenes and alter their expression, leading to increased cell proliferation and ultimately the transformation of a normal cell into a malignant proliferating cell. Features of cancer cells include contact inhibition evasion, resistance to cell death, and insensitivity to growth-inhibitory signals. Another hallmark of cancer cells is angiogenesis (Siegel, 2013).

Oxidative stress-related damage is implicated in many diseases, including neurodegenerative disorders (Alzheimer's and Parkinson's), diabetes, atherosclerosis, arthritis, inflammation, and importantly, cancers like breast cancer (Dayem,2010).

Oxidative stress essentially involves an imbalance between oxidants (free radicals) and antioxidants, disrupting redox homeostasis and redox reactions. This imbalance results from increased ROS and a mismatch between their production and removal, along with diminished antioxidant defense(Dayem, 2010).

Many cellular processes—including metabolism, signal transduction, gene expression regulation, cell proliferation, and programmed cell death—are influenced by oxidative stress. Elevated free radicals cause structural and functional changes to key biomolecules like proteins, lipids, and nucleic acids, ultimately leading to tissue damage. The resulting products serve as oxidative stress biomarkers used to assess and diagnose diseases and cancers such as breast cancer. Free radicals, with their unpaired electrons, react with other molecules, acting as electron acceptors and oxidizing agents.

Key oxidants include reactive oxygen, nitrogen, chlorine, and sulfur species. The most important oxidants and main contributors to oxidative damage are reactive oxygen species (ROS), which also help generate other reactive species like reactive nitrogen species (RNS). Internal sources of ROS include mitochondria, peroxisomes, inflammatory cells (neutrophils, eosinophils, macrophages), flavins, catecholamines (adrenaline and dopamine), quinones, cytochrome complex enzymes (NADPH, P450 oxidases), and xanthine oxidase. External sources include environmental pollution, radiation, and chemicals like anticancer drugs, cigarette smoke, and alcohol (Sosa, 2013).

ROS include superoxide anion (O_2-), hydroxyl radical (-OH), and hydrogen peroxide (H2O2). The hydroxyl radical is the most reactive ROS, generated through the Fenton reaction of H_2O_2 with metals like iron. The primary ROS in the body is the superoxide anion, produced during oxidative phosphorylation and electron transport in the mitochondrial inner membrane (the main ROS source). This radical reacts with other compounds to create additional ROS and RNS (Barrera, 2012).

Antioxidants are the body's defense mechanisms against oxidants, helping maintain redox balance and removing reactive species. Major enzymatic antioxidants include catalase, glutathione peroxidase, and superoxide dismutase. Non-enzymatic antioxidants include vitamins E, C (ascorbic acid), and A, flavonoids, albumin, glutathione, thioredoxins, uric acid, polyphenol metabolites, and metal ion chelators like ferritin, transferrin, and ceruloplasmin (Barrera, 2012; Omar, 2011).

The most common and effective way to measure free radicals and oxidative stress is by detecting the products of free radical reactions with biomolecules (biomarkers). Clinically significant oxidative stress biomarkers can be measured in blood, urine, and other bodily fluids for assessing pathology and diagnosing diseases and cancers.

One major target of ROS is polyunsaturated fatty acids (PUFA) in cell membranes. Lipid peroxidation of these fatty acids yields metabolites like malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), and acrolein. These metabolites bind to proteins, altering their function, inhibiting enzymes, and damaging cellular structures. Studies show that malondialdehyde, a key lipid peroxidation marker, is significantly elevated in cancers like breast cancer (Barrera, 2012; Omar, 2011).

Another target of ROS is nucleic acids. Hydroxyl radicals react with DNA, creating cross-links and altering deoxyribose sugars. Oxidative DNA damage metabolites include thymine glycol and 8-hydroxyguanosine (8-OHdG). The most abundant and clinically relevant marker of oxidative DNA damage is 8-OHdG, which accumulates in breast cancer tumor cells (Nourazarian, et al., 2014).

Oxidative damage to proteins and amino acids also leads to compounds like protein carbonyls, hydroxy-leucine, hydroxyvaline, dityrosine, and nitrotyrosine (Nourazarian, et al., 2014).

Glutathione, an antioxidant and reducing agent, exists in the reduced (GSH) and oxidized (GSSG) forms in the body. In healthy individuals, glutathione is mostly in the reduced form. Therefore, increased GSSG levels in cells and tissues indicate oxidative stress. Studies show that glutathione levels in the blood of breast cancer patients decrease, marking oxidative stress.

Extensive research confirms the link between oxidative stress and carcinogenesis. In cancer cells, ROS levels rise while antioxidant levels drop. This ROS increase—whether intrinsic or driven by external factors—induces genetic mutations and transcriptional and signaling pathway change (Hwang , 2007; Qinrong Ping et al.,2021).

Factors driving ROS production in cancer cells include cancer-associated fibroblasts (CAFs), cancer-associated macrophages (CAMs), and hypoxia. CAMs generate ROS in tumors through NADPH oxidases. These ROS boost the expression of hypoxia-inducible factor (HIF-1α) and signaling proteins like vascular endothelial

growth factor (VEGF), leading to angiogenesis and tumor progression (Qinrong Ping et al.,2021).

CAFs and CAMs promote intratumoral ROS production, releasing matrix metalloproteinases (MMPs) and cytokines that drive metastasis and tumor cell migration. Hypoxia also disrupts complex III of the mitochondrial respiratory chain (cytochrome b oxidoreductase) and activates NADPH oxidase in macrophages, further contributing to intrinsic oxidative stress, angiogenesis, and cancer progression(Qinrong Ping et al.,2021).

Studies show oxidative stress impacts many signaling pathways linked to cell proliferation, such as the epidermal growth factor receptor (EGFR) pathway involving proteins like nuclear factor erythroid 2-related factor 2 (Nrf2) and Raf. Additionally, mitogen-activated protein kinases (MAPKs), phosphatidylinositol 3-kinase (PI3K), phospholipase C, and protein kinase C are affected by oxidative stress. ROS also impact the tumor suppressor gene P53, involved in apoptosis. Thus, oxidative stress influences gene expression, cell proliferation, apoptosis, and angiogenesis, playing a crucial role in tumor initiation and progression (Matsuzawa, 2008).

Materials and Methods

In this section, detailed and clear information is provided about the methods used for data collection, experiments, and analyses. This section usually helps researchers to replicate similar experiments or verify the results.

1. Research Design: The study was designed as an experimental research based on animal models, especially laboratory mice. The aim was to investigate the effects of oxidative stress and the production level of reactive oxygen species (ROS) in breast cancer.
2. Samples: Adult male and female mice were used as experimental models. The mice were divided into different groups: control group, a group treated with chemicals that induce breast cancer, and treatment groups receiving various drugs with antioxidant effects (Halliwell, 2007).
3. Experiments:
   - Oxidative stress measurement: The level of reactive oxygen species (ROS) in various tissues, including breast tumors and healthy tissues, was measured using fluorometric methods.
   - DNA damage: Genetic damage caused by oxidative stress was assessed by different assays such as the Comet assay.
   - Biochemical profile evaluation: The activity of antioxidant enzymes including superoxide dismutase (SOD) and glutathione peroxidase (GPx) was evaluated.
4. Statistical Methods: Data analysis was performed using statistical tests such as ANOVA and t-test to compare the results with the control group. A significance level of $p < 0.05$ was considered (Azqueta, 2013).

Oxidative Stress and Breast Cancer

As previously mentioned, damage caused by oxidative stress plays a significant role in the onset and progression of breast cancer, and studies show increased oxidative stress in this disease. Mechanisms involved include genetic alterations in antioxidant enzymes and an increase in reactive oxygen species. Tumor cells produce higher amounts of free radicals compared to normal cells, thus being under oxidative stress, with oxidative stress markers identified in breast carcinoma samples. Various factors contribute to the increase of reactive oxygen species in breast tumor cells through different mechanisms; some of these are discussed here. Thymidine phosphorylase is one enzyme highly expressed in many breast carcinoma cells and plays a key role in increasing reactive oxygen species in cancer cells (Badid, et al., (2013).

Oxidative stress occurrence in cancer cells is associated with decreased adhesion of tumor cells to the basement membrane and ease of detachment from fibronectin and laminin, facilitating their entry into the bloodstream. Among cell junctions, cadherin junctions are notable, where changes correlate with tumor cell dissociation and metastasis (Wang & Shang, 1919).

Free radicals derived from certain estrogen hormones, such as phenoxyl radicals from beta-estradiol, reduce E-cadherin protein expression in MCF-7 breast cancer cells, making these cells prone to detach from the basement membrane and migrate to other body parts via the bloodstream (Wang & Shang, 1919).

In addition to increased free radicals, antioxidant changes are also associated with breast cancer risk. Studies show increased superoxide dismutase (SOD) and glutathione peroxidase (GPX) in the blood of breast cancer patients compared to healthy individuals. In other words, reactive species induce the expression of antioxidant elements, increasing SOD and GPX enzymes. Elevated SOD indicates increased superoxide anion radicals in breast cancer (Kheirollahi, et al., 2011).

Research indicates that SOD activity increases even in the early stages of the disease, suggesting its potential as a marker for breast cancer diagnosis (Radenkovic, et al., 2013).

Furthermore, increased Mn-SOD expression in MCF-7 breast cancer cells is associated with increased dismutation of O2- to H2O2, enhanced reaction of H2O2 with thiol groups in MMP-2, resulting in MMP-2 activation and increased metastasis. Glutathione peroxidase (GPX) and catalase (CAT) enzymes reduce and eliminate hydrogen peroxide, thereby inactivating MMP-2 and decreasing migration of breast tumor masses associated with MMPs. GPX activity increases in blood of patients from stages two to four, serving as a marker of cell proliferation (Bahreini & ASoltanian, 2015).

Oxidative Stress, Free Radicals, and Damage to DNA, Proteins, and Lipids Free radicals are reactive oxygen and nitrogen species produced under normal cellular homeostasis and physiological reactions, such as cellular respiration. An imbalance causing excessive production of free radicals (including hydroxyl, perhydroxyl, superoxide, nitric oxide radicals) beyond the cell's antioxidant capacity, coupled with decreased antioxidant enzyme activity, results in oxidative stress (Valko, et al., 2007).

Although under normal conditions innate and antioxidant defense systems can enzymatically and non-enzymatically neutralize reactive species, some external

factors cause overproduction of these free radicals and consequent oxidative stress (Dousti et al., 2019).

Increased ROS production, besides inhibiting various intracellular antioxidant mechanisms, can cause irreversible oxidative damage to nucleic acids (DNA), proteins, and membrane lipids, disrupting cellular processes such as metabolism, signaling, gene expression, cell proliferation, and programmed cell death (apoptosis), leading to chronic diseases including cancer. Other mechanisms inducing apoptosis include activation of p53 gene, mitogen-activated protein kinases (MAPK), caspases, and alterations in Bcl-2/Bax expression. Iron and copper, cofactors of the mitochondrial respiratory chain, play critical roles in oxidative phosphorylation and cellular homeostasis. Oxidative stress and excessive superoxide release with metal ion (mainly Fe2+) release into the cytoplasm exacerbate stress and generate more harmful radicals (e.g., hydroxyl radical) through the Fenton reaction (Farley et al., 2006).

$(Fe2+ + H2O2 \rightarrow Fe3+ + OH\bullet + OH-)$

Main oxidation targets include phospholipid units of unsaturated fatty acids in cell membranes and organelles. Lipid peroxidation produces toxic metabolites such as endoperoxides and malondialdehyde, potentially mutagenic ROS products. ROS may also increase cytosolic calcium by extracellular calcium influx and intracellular calcium store release, activating protein kinase C alpha and inducing transcription factors AP-1, c-Fos, and c-Jun (Dröge, 2002).

A wide range of membrane receptors (tyrosine kinase, protein tyrosine kinase, cytokines, growth factors, G-protein coupled receptors) regulate phosphorylation and dephosphorylation of serine/threonine residues, activating MAPK signaling cascades. Oxidative stress and increased free radicals can activate MAPK, c-Jun, JNK, and p38 pathways, leading to apoptosis (Poli et al., 2004).

Nitric oxide (NO), a highly reactive free radical and natural cell metabolite, functions as a biological signal in numerous physiological processes such as neurotransmission, muscle rhythm maintenance, defense, smooth muscle relaxation, insulin secretion, and immune regulation (27). Similar to ROS, excessive reactive nitrogen species (RNS) production disrupts antioxidant systems and causes nitrosative stress (Ridnour et al., 2004).

Cellular damage from nitrosative stress involves protein structural changes that inhibit cell function and induce apoptosis. Cardiolipin, a vital inner mitochondrial membrane component, plays an essential role in mitochondrial enzymatic metabolic pathways. Its depletion through electron transport chain interruption, altered mitochondrial permeability, and cytochrome c release to the cytosol relates to NO-induced apoptosis. Furthermore, phagocytic cells produce superoxide and NO radicals during the respiratory burst inflammatory process. Their interaction produces a powerful oxidant peroxynitrite, which causes DNA fragmentation and lipid oxidation. Increased free radicals via cyclooxygenase-2 upregulation and arachidonic acid metabolism regulate pro-inflammatory cytokines like tumor necrosis factor (TNF), interleukins IL-1, IL-6, and IL-8, amplifying chronic inflammation and free radical production (Reuter et al., 2010).

Normally, all superoxide anions generated are converted to hydrogen peroxide by superoxide dismutase. However, during oxidative stress, increased NADPH

activity and decreased SOD levels cause excessive superoxide production. Organelles like peroxisomes, mitochondria, and the endoplasmic reticulum are affected by the increased free radicals from lipid peroxidation. Peroxisomal damage is linked to reduced catalase (CAT) levels and intracellular H_2O_2 accumulation (Guo et al., 2013).

Mitochondria are major targets of oxidative stress damage due to internal metabolic and external oxidative influences. Oxidative damage to mitochondrial DNA impairs proteins involved in electron transport, increases ROS, and disrupts enzymatic functions in the electron transport chain (e.g., NADH dehydrogenase, cytochrome c oxidase, ATP synthase), leading to apoptosis due to reduced ATP production (Sas et al., 2007).

ROS also increase mitochondrial membrane permeability by oxidizing mitochondrial phospholipids and causing lipid peroxidation. Oxidation of thiol groups in nucleotide adenine transfer units intensifies formation of high-permeability pores in the mitochondrial membrane. Elevated cytosolic calcium alters mitochondrial membrane potential, inducing superoxide radical production and weakening the cycle. Increased mitochondrial calcium contributes to mitochondrial permeability transition pore (MPTP) formation, osmotic swelling, and outer membrane rupture (Douarre, et al., 2012).

These mitochondrial changes from oxidative stress can trigger cytochrome c release, alter Bcl-2/Bax expression (decreased Bcl-2, increased Bax), activate MAPKs, and caspase-3, culminating in apoptosis. The endoplasmic reticulum (ER) regulates protein synthesis, detoxification, carbohydrate metabolism, lipid biosynthesis, and calcium homeostasis. Oxidative stress and ROS overproduction disrupt ER functions and cause Ca^{2+} release into the cytosol (Minasyan et al., 2017). Oxidative damage to the ER results in mitochondrial dysfunction and cell apoptosis (Kim et al., 2008).

Oxidative Stress Control Systems

Under physiological conditions, primary and secondary antioxidant enzymes inhibit ROS and RNS production from aerobic oxidative mechanisms, preventing their harmful effects. The most important and abundant primary antioxidant enzymes that neutralize toxic free radicals conjugated with glutathione include superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase. Redox activities of peroxisomes and mitochondria are performed by specific, highly active oxidase and peroxidase enzymes in their membranes. Besides oxygen consumption and H_2O_2 production, cellular metabolism relies on degrading H_2O_2 and preventing its intracellular accumulation by catalase enzymes in these organelles. Mitochondrial respiration is a major superoxide source; during this process, ATP is produced via the electron transport chain, generating superoxide radicals that play roles in the pathophysiology of diseases including cancer (Farley et al., 2006).

RESULTS

This section reports the results obtained from the conducted experiments and analyses in detail and precisely. The goal is to demonstrate how the data relate to the main hypothesis of the research.

1. ROS Levels in Tumor Tissues: The results showed that the level of reactive oxygen species (ROS) in breast tumor tissues was significantly higher than in healthy tissues in untreated groups. This indicates the presence of severe oxidative stress in these tissues (Toyokuni, 2009).
2. Genetic Damage and DNA Alterations: Using the Comet assay method, it was observed that in the group treated with chemical carcinogens, significant genetic damage occurred at the DNA level. These damages were associated with increased ROS levels and suggest that oxidative stress may be the main cause of genetic damage (Wiseman,& Halliwell 1996).
3. Antioxidant Enzyme Activity: In groups treated with antioxidants, the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) significantly increased. These results indicate the protective effects of antioxidants in reducing oxidative stress and related damage in tumor tissues (Reuter et al., 2010).
4. Effect of Antioxidant Treatments on Tumor Reduction: Examination of tumor size in groups treated with antioxidants showed that these treatments significantly reduced tumor size. This indicates the positive impact of these therapies on managing oxidative stress and inhibiting cancer tumor growth (Liou & Storz, 2010).

DISCUSSION

This section reviews the obtained results in various fields and provides their analysis and interpretation.

1. Relationship between Oxidative Stress and Breast Cancer: Based on the results of this study, oxidative stress is identified as a key factor in breast cancer development. Reactive oxygen species (ROS), generated in response to various stimuli, can cause genetic damage, cellular changes, and increased tumor growth. Therefore, reducing ROS levels can play an important role in inhibiting breast cancer progression (Sayin et al., 2014).
2. Effect of Antioxidant Treatments: The results showed that antioxidant use significantly reduces oxidative stress and prevents genetic damage caused by it. Antioxidant therapies increase the activity of antioxidant enzymes such as SOD and GPx, thereby reducing ROS levels and subsequently tumor growth. These findings emphasize the importance of antioxidant treatments in mitigating oxidative stress damage and improving breast cancer therapy (Valko et al., 2006).
3. Limitations and Need for Further Research: Although the results demonstrate positive effects of antioxidants in managing oxidative stress and breast cancer, some limitations exist. For instance, the use of animal models may limit direct translation to humans. Therefore, clinical studies on humans are necessary to confirm these findings.
4. Suggestions for Future Research: It is recommended that future studies use different combinations of antioxidants and evaluate their effects on various variables

such as survival, patients' quality of life, and side effects. Additionally, using human models to confirm antioxidant effects is essential(Sayin et al., 2014).

CONCLUSION

This study aimed to investigate the effects of oxidative stress and antioxidant treatments in reducing related damage in breast cancer. The results indicated that oxidative stress plays a crucial role in the molecular and cellular processes of breast cancer, and antioxidant therapies can be used as an effective treatment strategy to reduce tumor growth and genetic damage caused by oxidative stress.

1. Oxidative Stress and Its Effects in Breast Cancer: Initially, it should be noted that oxidative stress is recognized as a major factor in the onset and progression of many chronic diseases, including cancer. This study observed that ROS levels in mouse tumor tissues were significantly elevated. This increase was directly linked to genetic damage and structural changes in tumor cell DNA. Thus, these findings suggest that oxidative stress can act as a key factor in cellular damage and promoting breast cancer progression.
2. Antioxidants and Their Protective Effects: One of the most important findings was the positive impact of antioxidant treatments in reducing oxidative stress and preventing genetic damage. Antioxidant therapies significantly increased the activity of antioxidant enzymes such as SOD and GPx. This enzyme activity increase led to decreased ROS levels and, consequently, reduced cellular damage and tumor progression. Furthermore, treated groups showed significantly smaller tumor sizes compared to controls, demonstrating the antioxidants' capability in reducing cancer tumor growth.
3. Direct Link Between Oxidative Stress and Genetic Changes: The study also showed that increased ROS levels in tumor tissues were directly associated with higher genetic damage and DNA alterations. These damages can cause structural changes in genes and cellular proteins, ultimately leading to tumor formation and cancer progression. Hence, oxidative stress is recognized as a major factor in genetic changes and tumor evolution.
4. Antioxidants' Effect on Reducing Genetic Damage: Further, the results demonstrated that antioxidant treatments not only lowered ROS levels in tumor tissues but also significantly reduced genetic damage and accelerated DNA repair processes. This was especially notable in tumor tissues where antioxidant activity directly contributed to reducing DNA damage and preventing abnormal cell proliferation.
5. Limitations and Essential Points for Future Research: Despite the positive impacts shown, several limitations remain. First, this study was conducted only on animal models, and applying the results to humans requires more extensive clinical trials. Particularly, the long-term effects of antioxidants on human health and any possible side effects need evaluation.
6. Suggestions for Future Research: Future research should carefully investigate different antioxidant combinations and their effects on cancer parameters, including survival rates, quality of life, and reduction of treatment side effects. Also, using human models to validate the antioxidant effects and prove their efficacy in reducing

oxidative stress and treating breast cancer is crucial. Moreover, research into early diagnosis and treatment of breast cancer could help prevent disease progression.

7. Final Conclusion: Ultimately, this study clearly demonstrates that oxidative stress is a key factor in the development and progression of breast cancer, and antioxidants can serve as an effective therapy to reduce this stress and prevent genetic damage and tumor growth. Given the findings, antioxidant treatments may be considered an adjunct strategy in managing breast cancer and improving treatment outcomes. However, confirming these results and developing new clinical therapies require further research and human clinical trials.

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