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Breast Cancer Is Globally Emerging Challenging: Epidemiology, Pathogensis and Therapeutic Approach (Enzymatic and Non-Enzymatic Antioxidant) –A Review

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Abstract

Breast cancer (BC) stands as the most predominant neoplastic growth worldwide, representing a significant global health challenge. With 7.8 million women diagnosed by the end of 2020 and 2.29 million new cases reported in 2022, breast cancer accounts for approximately 11.5% of all cancer diagnoses globally. While developed countries report higher incidence rates, low- and middle-income countries, including Pakistan, face disproportionately high mortality rates due to delayed diagnosis, limited access to effective therapies, and inadequate healthcare facilities. This review comprehensively examines the epidemiology, pathogenesis, risk factors, and therapeutic approaches for breast cancer, with particular emphasis on the role of oxidative stress and antioxidant systems. The pathogenesis of breast cancer involves complex mechanisms including genetic alterations (BRCA1/2 mutations, PIK3CA, TP53), hormonal homeostasis disturbances, and immune interference within the tumor microenvironment. Oxidative stress, generated from endogenous and exogenous sources, plays a dual role in carcinogenesis—promoting tumor development when antioxidant systems are insufficient while potentially inducing apoptosis at controlled levels. The cellular antioxidant defense system

comprises enzymatic antioxidants (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, thioredoxin reductase, and peroxiredoxin) and non-enzymatic antioxidants (glutathione, thioredoxin, vitamins A, C, D, and E, along with micronutrients including zinc, magnesium, and selenium). Emerging evidence suggests that these antioxidants exhibit potential anticancer properties through various molecular mechanisms. Furthermore, nanotechnology-based drug delivery systems, including lipid-based nanocarriers and polymeric nanoparticles, offer promising strategies for targeted antioxidant delivery, enhancing bioavailability and therapeutic efficacy. This review highlights the critical value of developing preventive, protective, and treatment strategies against breast cancer, particularly in resource-limited settings, while exploring the therapeutic potential of antioxidant-based approaches in breast cancer management.

Introduction

Cancer has emerged as one of the most pressing health challenges in recent times. Due to its high incidence and mortality rates, cancer was the fourth leading cause of death in the 1970s; however, it now ranks second, following cardiovascular diseases. Among women, breast cancer (BC) is the second most common cancer worldwide after lung cancer and represents the primary cause of cancer-related death [1]. The incidence and mortality rates of BC vary across geographic regions. Although developed countries report higher absolute numbers, the most significant increases in BC incidence are observed in low- and middle-income countries (LMCs), including Turkey [2].

Globally, breast cancer is the most prevalent malignant disease. By the end of 2020, approximately 7.8 million women were living with a diagnosis of breast cancer [3]. In Pakistan, the lifetime risk for a woman to develop breast cancer is one in nine [4]. Among all Asian nations, Pakistan has the highest incidence and mortality rates [5]. Compared to neighboring countries such as India and Iran, Pakistan's BC incidence rate is 2.5 times higher [6,7]. A major obstacle in Pakistan is the lack of a national cancer registry, leading to poor data quality. Based on hospital-based estimates, new cases range from 34,000 to 90,000 annually, with around 16,232 deaths [8].

Each year, one million women worldwide are diagnosed with breast cancer [9,10]. Cancer is a major contributor to mortality in both developed and developing nations, including Pakistan. In 2020 alone, there were 19.3 million new cancer cases and approximately 10 million deaths globally [11]. In Pakistan, it is estimated that one out of every nine women may be affected [12, 13]. In regions such as the Americas, Europe, and Australia, improved awareness, widespread mammographic screening, accurate diagnosis, and increased access to effective treatments have contributed to declining mortality rates [14]. Nevertheless, cancer cases continue to rise [15]. The growing death toll, particularly in developing countries, is largely attributable to delayed diagnosis, limited healthcare access, and insufficient availability of effective therapies. While treatment options like radiation, targeted therapy, chemotherapy, and immunotherapy exist, their timely use is often hindered by low public awareness and late detection [16, 17].

Cancer remains a leading global cause of death and significantly reduces life expectancy. In 2022, there were 19.96 million new cancer cases and nearly 10 million deaths [18]. The World Health Organization (WHO) currently identifies breast cancer as the most common cancer type worldwide [19]. According to United Nations data from 2022, BC had the highest incidence among all cancers, with 2.29 million new cases, accounting for 11.5% of all cancer diagnoses globally [20, 21]. Several risk factors associated with breast cancer exert their effects by modulating the cellular oxidative stress state [22, 23]. Oxidative stress can lead to genetic mutations or altered cell growth (**Figure 1**), thereby promoting neoplastic development. Reactive oxygen species (ROS) contributing to this process arise from endogenous sources (e.g., peroxisomes, mitochondria, cytochrome P450, and inflammatory cells) and exogenous

sources (e.g., xenobiotics, metals, pathogens, drugs, and radiation) [24–26].
Increased oxidative stress can initiate tumor formation and drive tumor progression, either through direct oxidative damage to macromolecules or via aberrant redox signaling caused by oxidative stress [27]. When antioxidant defenses are insufficient to protect cells, high ROS levels may raise cancer risk. Given the established role of oxidative stress in carcinogenesis and cancer progression [27-29], antioxidant-based cancer therapy has attracted considerable interest. Over recent decades, numerous antioxidants have been developed. These can be categorized into non-enzymatic antioxidants (e.g., glutathione, thioredoxin, vitamins C and E) and enzymatic antioxidants (e.g., superoxide dismutase, catalase, NADPH oxidase, peroxiredoxin, etc.). Some have shown potential anticancer effects, and various antioxidant therapeutic strategies have been explored in preclinical and clinical research.
Overall, breast cancer mortality has declined due to increased awareness and advances in pathogenesis, detection, prevention, and treatment. However, BC treatment remains expensive and resource-intensive, placing a substantial burden not only on patients but also on healthcare systems and governments. Therefore, developing effective strategies for BC prevention, protection, and treatment is of critical importance.

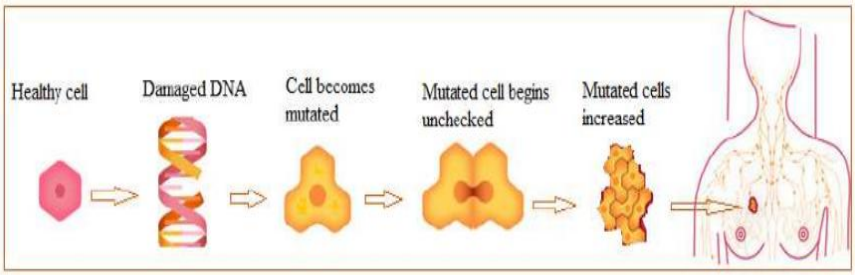

Figure 1: Breast cancer development [30].

Epidemiology
Globally, breast cancer accounts for approximately one-third of all female cancers, and its mortality rate represents about 15% of diagnosed cases. It is the most common malignancy among women worldwide, with breast cancer patients comprising up to 36% of all oncology cases. In 2018, an estimated 2.089 million women received a breast cancer diagnosis [31, 32]. The incidence of this tumor is rising across all global regions, with the highest rates observed in industrialized nations. Nearly half of all cases worldwide occur in developed countries [32, 33]. This pattern is largely attributed to the so-called Western lifestyle, which includes poor dietary habits, smoking, chronic stress, and low physical activity [34].
Mammography has become the recognized screening tool for breast cancer, showing the greatest benefit in women aged 50–69 years [31, 33]. Conventional mammography has a sensitivity of 75–95% and a specificity of 80–95% [34]. For women at risk of hereditary breast cancer, magnetic resonance mammography is used as a screening method. When a suspicious lesion is identified on mammography, an ultrasound is performed, followed, if needed, by a core needle biopsy and histopathological analysis.
In 2018, the number of breast cancer cases (crude rate per 105) was 234,087 (85) in the United States, 55,439 (94) in the United Kingdom, 56,162 (99) in France, 71,888 (85.4) in Germany, and 66,101 (58) in Japan [32]. Belgium has the world's highest incidence rate (crude rate: 113/105), while Australia leads among continents (94/105) [32]. In Poland, breast cancer is also the most frequently diagnosed female malignancy, with a steady rise in cases (8,000 new cases in 1990; 20,203 in 2018) [32]. Europe's average incidence rate is 84/105 [32]. The lowest rates are seen in Southeast Asia and Africa, where the standardized incidence rate remains below 25/105 [32]. In 2018, the lowest rates were recorded in Bhutan (crude rate: 5/105) and The Gambia (6.5/105) [32].
Despite advances in early diagnosis and pharmacotherapy in recent years, breast cancer remains the leading cause of cancer-related death among women globally. In 2018,

626,679 deaths were attributed to breast cancer. Unlike incidence, the highest mortality rates are found in developing countries [32] (e.g., Fiji, crude rate 36/105; Somalia, 29/105; Ethiopia, 23/105; Egypt, 21/105; Indonesia, 17/105; Papua New Guinea, 25/105) [32], which account for as much as 60% of all breast cancer deaths. This trend is primarily due to limited screening programs, poorer access to diagnostics, and fewer modern treatment options compared to developed nations [35]. By contrast, the standardized crude death rates are 16.3/105 in Belgium, 13/105 in the United States, and 9.3/105 in Japan [32].

In Poland, breast cancer incidence is much lower than in EU countries (in 2013, standardized incidence rate: Poland 51.8 vs. EU 106.6) [36]. Over the past 30 years, cases among premenopausal women aged 20–49 have nearly doubled. Unfortunately, Polish women remain relatively unaware of preventive measures, often neglecting breast self-care and underestimating the importance of regular check-ups. Compared to other European nations, Poland has low participation in preventive care for example, 80% of women in the Netherlands attend free mammography screening programs, 71% in England, but only 44% in Poland [36]. The 5-year survival rate for breast cancer in Poland is 78.5%, significantly lower than the 90% achieved in the United States [37].

Breast cancer

Breast cancer is a type of malignant tumor that develops from cells in the breast tissue. A malignant tumor refers to a mass of cancerous cells that have the ability to invade nearby tissues or spread to distant organs in the body through a process known as metastasis. Although breast cancer occurs almost exclusively in women, men can also develop it, though such cases are rare.

The human body is made up of trillions of living cells. Under healthy conditions, cells grow, divide, and die in a controlled and predictable manner. During early development, normal cells divide more rapidly to support growth. Once adulthood is reached, most cells divide only to replace old or damaged cells or to repair injuries. Cancer arises when cells in a specific part of the body begin to multiply uncontrollably. While there are many different forms of cancer, they all originate from the uncontrolled growth of abnormal cells [38].

The formation of cancerous cells is caused by damage to DNA. Every cell contains DNA, which directs all of its activities. When a normal cell suffers DNA damage, one of two things typically happens: the cell either repairs the damage or undergoes cell death. In contrast, cancer cells fail to repair their damaged DNA, and they do not die as expected. Instead, these damaged cells continue to produce new cells that the body does not need. All subsequent cells derived from them inherit the same DNA damage. Although some DNA damage can be inherited across generations, most DNA damage is caused by environmental factors or errors occurring during normal cell division (**Figure 2**) [38].

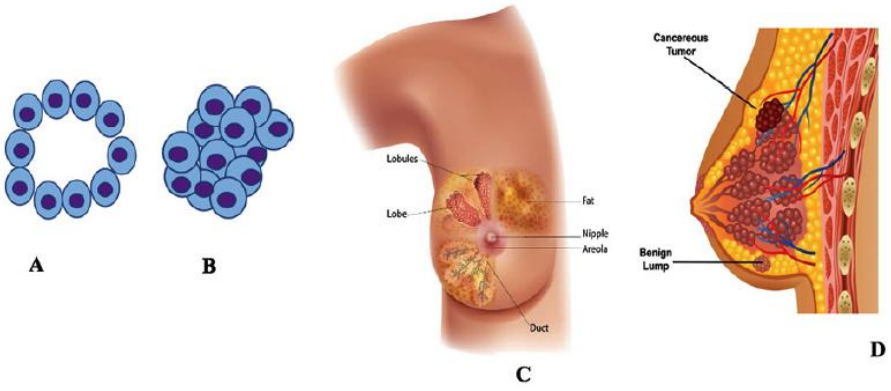

Figure 2: Comparison of breast cells pre and post toumr infection, (A) normal breast cells in women, (B) cancer breast cells (abnormal in growth and division), (C) structure of breast in normal woman, (D) Formation of tumour (malignant), (Created in BioRender.com).

Breast cancer-related genes: Several genes have been linked to the emergence and progression of breast cancer. Both oncogenes and tumor suppressor genes (anti-oncogenes) play critical roles in tumor initiation and development. Therefore, any mutations or abnormal amplifications of these genes can result in the development of breast cancer [39].

Anti-oncogenes: BRCA1 and BRCA2 are two well-known tumor suppressor genes associated with an increased risk of breast and ovarian cancer are BRCA1 and BRCA2. The BRCA1 gene is located on chromosome 17q21 and consists of 24 exons. It encodes a protein of 1,863 amino acids, corresponding to a transcript size of 5.6 kb [44]. In contrast, BRCA2 is situated on chromosome 13q12 and comprises 27 exons, with exon 11 being the largest at 4.9 kb. The BRCA2 protein is made up of 3,418 amino acids (10.2 kb). Ovarian cancer development has been linked to mutations specifically in exon 13 of BRCA1 and exon 11 of BRCA2 [43]. Both BRCA1 and BRCA2 function primarily as tumor suppressors, as they produce proteins involved in DNA damage response. Additionally, they belong to the group of DNA repair genes that help regulate the cell cycle [40].

Significance of the BRCA genes: BRCA genes encode protein groups essential for the transcriptional regulation of DNA synthesis and act as tumor suppressors. Their role includes detecting specific DNA lesions, particularly double-strand breaks, and facilitating their repair. Mutations in these genes can take various forms, including point mutations or insertions and deletions [41]. The recombinase enzyme RAD51 works together with BRCA2 to repair double-strand DNA breaks and enable homologous recombination. Notably, exon 11 encodes a structural domain containing eight repeating units known as “BRC” repeats, through which BRCA2 modulates RAD51 activity. Consequently, RAD51 and the protein products of the BRCA1 and BRCA2 tumor suppressor genes collaborate in DNA break repair, thereby maintaining genomic stability [42].

RISK FACTORS

The main contributing factors identified for breast cancer include radiation exposure to the chest before age 30, family history, genetics, physical inactivity, race, being overweight, pregnancy history, hormone replacement therapy use, alcohol intake, age, high breast density, and smoking [45]. Current statistics emphasize that benign breast pathology with or without atypia is also a recognized risk factor for developing breast cancer. Additional factors associated with the disease are early onset of menstruation, late first childbirth, and absence of breastfeeding. These characteristics are commonly observed in low- and middle-income nations such as Pakistan, Bangladesh, and India.

Sex: Approximately 99% of breast cancer cases occur in women, while men account for only 1%. In Poland, the standardized incidence rate for male breast cancer is 0.4 per 100,000, with no more than 100 new cases reported annually [46]. Nevertheless, the incidence among men is steadily rising, similar to the trend in women, likely due to rising obesity rates and increased life expectancy [47].

Age: Age is a critical risk factor for breast cancer. Globally, incidence rates are rising across all age brackets, with the highest rates observed in women under 50 [47].

Although breast cancer remains uncommon in younger women, it presents a notable clinical and social challenge because it tends to follow a more aggressive course. Studies indicate that in young women, breast cancer is often associated with higher histological grade, reduced expression of steroid receptors, frequent HER-2 overexpression, or a "basal-like" (triple-negative) molecular subtype [48]. Moreover, incidence among premenopausal women has nearly doubled over the past 30 years [46].

Hormonal Status: A woman's hormonal profile significantly influences breast cancer risk. Research suggests that risk increases with longer lifetime exposure to estrogen, which can result from early menarche, late menopause, delayed first childbirth, and a lower number of children [47, 49–52].

Genetic Factors: Only a small fraction (5–10%) of breast cancer cases are hereditary. The most well-known genetic mutations linked to the disease are in the BRCA1 and BRCA2 genes [53]. BRCA1, located on chromosome 17, is a tumor suppressor gene encoding a nuclear protein essential for genomic stability. Along with products from other suppressor genes, signal transduction genes, and DNA damage detection genes, this protein forms a complex that binds RNA polymerase II and interacts with histone deacetylase, influencing transcription, DNA repair, and recombination. The BRCA1 protein and the product of BRCA2 (a suppressor gene on chromosome 13) are particularly involved in repairing double-strand DNA breaks via homologous recombination [54].

Ionizing Radiation: Early exposure to ionizing radiation is a well-established risk factor. In 2007, John and colleagues analyzed data from the Breast Cancer Family Registry to examine the link between diagnostic or therapeutic radiation exposure and breast cancer risk [55]. They found an elevated risk among women previously treated with radiotherapy for cancer and among those who underwent chest X-rays for tuberculosis or pneumonia monitoring [56]. The highest risk was seen in patients who received multiple exposures at a very young age [57].

Alcohol Consumption: Numerous studies have linked alcohol intake to increased breast cancer risk [58]. This association arises from multiple mechanisms: alcohol raises blood estrogen levels by reducing liver metabolism and enhancing the conversion of androgens to estrogens. It also suppresses immune function and DNA repair, promotes cell proliferation and migration, and its own metabolites are carcinogenic [59]. It is estimated that each daily intake of 10 grams of pure alcohol raises breast cancer risk by approximately 9% [60].

Pathogenesis

The primary pathogenic mechanisms involve genetic alterations, changes in hormonal homeostasis, and immune interference, which are described below.

Genetic alterations: Genetic mutations form the foundation of carcinogenesis. Individuals carrying heterozygous mutations in BRCA1/2 may undergo malignant transformation following a significant external secondary event, leading to genomic instability and cellular dysfunction. This instability subsequently causes acquired genetic changes in cells, including non-inherited somatic mutations such as those in PIK3CA and TP53 [61]. Furthermore, chromosomal instability a recognized hallmark of cancer drives somatic copy number variations and intratumoral heterogeneity among subclones as tumors progress [62]. During tumor evolution, mechanisms such as DNA copy number loss, transcriptional repression, epigenetic silencing, and whole-genome doubling enable potentially malignant cells to evade immune responses and enhance their adaptive capacity under various pressures [63, 64]. Through these complex

genomic disruptions, cells irreversibly accumulate harmful alterations that allow them to survive purifying selection in human germline evolution, ultimately gaining fitness, reducing tumor cell loss, and progressing toward malignancy [65].

Changes in hormonal homeostasis: Hormonal exposure—including menopausal hormone therapy, excessive estrogen intake through diet, and endocrine imbalances from various causes represents a major contributing factor in sporadic breast cancer. Specifically, estrogen binding to nuclear estrogen receptors (encoded by ESR1) acts as a trigger for breast cancer. An imbalance between estrogen and progesterone can stimulate cell proliferation and may lead to DNA damage accumulation. Under these conditions, excess estrogen fosters the expansion of malignant cells and increases supportive stromal tissue, thereby accelerating cancer progression [66]. Upon ligand binding, estrogen receptors regulate gene transcription by attaching to estrogen response elements in promoter regions, thus controlling gene expression [67]. Additionally, estrogen receptors can directly interact with other proteins, including those involved in growth signaling pathways, which further enhances the transcription of genes critical for cell growth and resistance to apoptosis [68]. In summary, disruptions in estrogen balance within breast tissue can promote breast cancer progression and metastasis.

Immune interference: Breast cancer cells develop within a complex microenvironment containing various benign cell types and extracellular matrix components. Cancer-associated fibroblasts (CAFs) are the most abundant cell type; however, the breast cancer microenvironment also includes lymphocytes, macrophages, myeloid lineage cells, and others that mainly participate in immune responses [69, 70]. In early tumor development, the immune microenvironment primarily suppresses tumor growth through cytokine activity from activated CD8+ and CD4+ T cells. Yet, once tumors become aggressive, cancer cells express immune checkpoint modulators such as CTLA-4 and PD-L1 to dampen immune responses. The composition of microenvironmental cells, including CAFs, and cytokine profiles is influenced by breast cancer cell invasion, thereby promoting tumor progression [71]. Breast cancer employs distinct immune evasion mechanisms that drive its progression and resistance to immunotherapy. Over time, breast cancer can evolve, increasing genomic complexity and heterogeneity, which imposes selective pressures and leads to variable treatment responses [72]. Specifically, breast cancer cells mimic the anti-inflammatory mechanisms of the central nervous system to evade antitumor immunity, a process dependent on the immunological synapse [73]. Carrying lower clonal heterogeneity and fewer neoantigens, triple-negative breast cancer (TNBC) cells achieve immune escape via the Lgals2-CSF1-CSF1R axis, which represents a unique mechanism in breast cancer immune evasion. The interaction between breast cancer cells and host antitumor immunity determines coexisting immune escape mechanisms within the same patient, emphasizing the need for combination immunotherapies and biomarker development [74].

Oxidative Stress

During cellular metabolism, various reactive oxygen species (ROS) are produced, including short-lived and long-lived forms such as superoxide ($O^2 \cdot -$), hydroxyl radical ($OH \cdot$), and hydrogen peroxide (H_2O_2). Depending on their concentration, location, and the cellular environment, ROS can either induce toxicity or serve as signaling molecules [75]. Emerging evidence supports this dual role, showing that ROS function inside cells as second messengers in intracellular signaling pathways or contribute to the maintenance of the oncogenic phenotype in cancer cells. Conversely, ROS can also promote cellular senescence and apoptosis, thereby acting as antitumor

agents [76,77]. In cancer cells, ROS levels are elevated due to increased metabolic activity and relative hypoxia, which leads to genetic mutations, alterations in transcriptional regulation, and ultimately cancer progression [78]. Moreover, cancer cells adapt to high ROS levels by upregulating antioxidant defense mechanisms, resulting in enhanced ROS scavenging [79].

Antioxidant Systems

Cellular reactive oxygen species (ROS) levels are regulated through two primary mechanisms. The first involves nonenzymatic antioxidant systems, including glutathione, thioredoxin, and vitamins such as C and E. The second consists of enzymatic antioxidant systems (illustrated in **Figure 3**). This set of enzymes, which plays a key role in managing ROS, includes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), thioredoxin reductase (TrxR), and peroxiredoxin (Prx) [80].

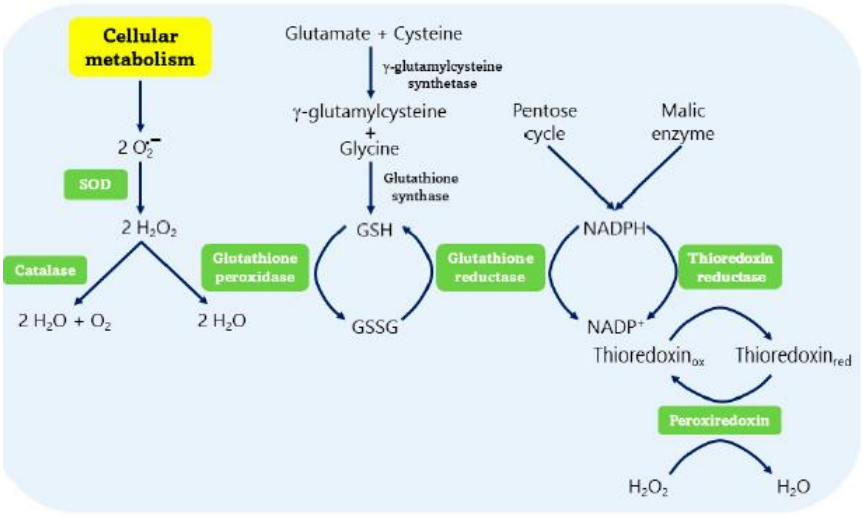

Figure 3: The antioxidant enzymatic system is made up of six enzymes: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), thioredoxin reductase (TrxR), and peroxiredoxin (Prx). SOD eliminates the 2 O_2 ・ −, generating two H_2O_2 molecules and CAT destroys them, producing H_2O and O_2. GPx, GR, TrxR, and Prx remove H_2O_2 by regulating the redox conditions of glutathione, thioredoxin, and NADPH.

Antioxidants

The antioxidant system is essential for defending cells against oxidative stress and maintaining redox balance. It neutralizes the damaging effects of reactive oxygen species (ROS), which are generated either through normal metabolic activities or in response to environmental stressors. This system includes both enzymatic and non-enzymatic antioxidants that collaborate to protect cellular macromolecules from widespread oxidative harm. To preserve cellular homeostasis, the antioxidant system relies on a combination of externally derived (exogenous) and internally produced (endogenous) antioxidants [81].

A- Enzymatic Antioxidants

Antioxidants help defend the body against oxidative stress by removing reactive species and preserving redox balance. Among the enzyme-based antioxidants, catalase, glutathione peroxidase (GPX), and superoxide dismutase (SOD) are especially important [84].

Superoxide dismutases (SODs): SOD protects DNA, cell membrane components, and

proteins from oxidative harm. It exists in three forms, each with distinct cofactors: Cu/Zn SOD1, Mn SOD_2, and extracellular Cu/Zn SOD_3, found across many species [82]. In breast cancer (BC), SOD plays a dual role. Research shows that SOD levels rise as the disease advances, yet its ability to lower oxidative stress may inhibit tumor growth. The generation of O_2 and H_2O_2 stimulates SOD and catalase (CAT) activity. Higher SOD activity in inflammatory cells leads to increased hydrogen peroxide production [83]. The SOD family is physiologically crucial for counteracting reactive oxygen species (ROS) [84]. Overexpression of SOD reduces the growth, clonogenic survival, and invasion of triple-negative breast cancer (TNBC) cells in vitro, partly by blocking heparanase-mediated breakdown of cell surface proteoglycans and lowering VEGF availability. Moreover, SOD overexpression significantly curbs tumor spread in experimental lung and spontaneous metastasis mouse models, further highlighting how these extracellular enzymes suppress tumor progression [85].

Glutathione peroxidase (GPX): GPX is a key enzymatic antioxidant that protects cells by catalyzing the reduction of hydrogen peroxide and organic peroxides byproducts of cellular metabolism that can cause oxidative stress [86]. GPX uses glutathione (GSH) as a co-substrate, oxidizing GSH to glutathione disulfide (GSSG). Glutathione reductase, with NADPH as a reducing agent, then regenerates GSH from GSSG, allowing GPX to function continuously as an effective antioxidant. To maintain normal ROS levels, cells employ a systematic detoxification process. For instance, in preadipocytes, N-acetylcysteine (NAC) lowers ROS levels and reduces adipogenesis. Chemotherapy drugs may decrease levels of reduced glutathione and antioxidant enzymes such as glutathione S-transferase (GST) and GPX, likely due to increased oxidative stress induced by treatment [87,88].

The primary defenses against damage from H_2O_2 and lipid hydroperoxides include glutathione, thioredoxin, and CAT. GPXs are enzymes that use glutathione as a donor of reducing equivalents [89,90]. They convert H_2O_2 to H_2O by oxidizing glutathione (to GSSG), which is then recycled to its reduced form (GSH) by the NADPH-dependent enzyme glutathione reductase. Most GPXs contain selenocysteine in their active site and can reduce both organic and inorganic hydroperoxides [91].

Catalases: Catalase reduces oxidative stress by breaking down cellular hydrogen peroxide into water and oxygen, playing a vital role in cellular defense [92]. Impaired catalase function is linked to several diseases, including diabetes, vitiligo, cardiovascular disease, Wilson's disease, hypertension, anemia, skin disorders, Alzheimer's disease, bipolar disorder, and schizophrenia [93]. Genetic changes in the *CTTI* gene can affect cellular oxidative status and contribute to diseases such as cancer [94]. In certain breast cancer cells, catalase expression and activity are elevated, which may help cancer cells survive and proliferate. However, catalase can also have tumor-suppressive effects in breast cancer by protecting cells from oxidative injury, preventing DNA damage, and reducing mutations that could drive cancer development. Chemotherapy can lower catalase and SOD levels in breast cancer patients, leading to oxidative stress and reduced antioxidant capacity. Strengthening the body's antioxidant system through supplements or dietary antioxidants is important [90]. Curcumin, for example, shows antiproliferative effects in breast cancer, possibly related to its influence on catalase activity and protection against oxidative stress [89]. Modifying catalase or using nanozymes with catalase-like activity offers promising therapeutic approaches to increase CD4+ and CD8+ effector T cells while reducing immunosuppressive cell infiltration in the tumor microenvironment (TME) [95].

Glutathione Reductase (GR): GR maintains adequate glutathione levels by converting GSSG back to GSH, making it critical for cellular redox status [96]. GR activity and expression are elevated in many cancers, including breast, lung, colorectal,

and prostate cancers, affecting GSSG levels and treatment responses [97]. In cell lines such as A-431, MCF-7, NCI-H226, and OVCAR-3, increased GR activity is associated with resistance to radiation therapy [98,99]. Conversely, inhibiting GR leads to GSSG accumulation, making cells more vulnerable to ROS-induced damage [100].

Thioredoxin Reductase (TrxR): TrxR catalyzes the NADPH-dependent reduction of thioredoxin (Trx) [101]. By keeping protein thiols reduced, Trx and TrxR help maintain a reducing cellular environment and sustain transcription factor activity [102]. These enzymes are selenium-containing pyridine nucleotide-disulfide oxidoreductases [103]. Three TrxR isoforms exist: TrxR1 in the cytosol, TrxR2 in mitochondria, and TrxR3 (thioredoxin glutathione reductase), mainly found in the testes where it aids sperm maturation [104].

TrxR1 is an oxidoreductase with an active-site dithiol disulfide that reduces oxidized cysteine residues in cellular proteins. This cytosolic enzyme is overexpressed in many human cancers, including breast cancer, making it a useful biomarker [105]. TrxR2 appears to protect cells during external insults such as radiation and certain anticancer drugs. Along with peroxiredoxin (Prx), TrxR2 is thought to regulate cytochrome c release, thereby shielding cells from apoptotic processes associated with cancer [106].

Peroxiredoxin (Prx): Prxs form a family of peroxidases divided into six groups (Prx I–VI), all capable of reducing H_2O_2 using Trx or other oxidative substrates [107]. They act as H_2O_2 sensors in cell signaling, differentiation, apoptosis, and redox homeostasis [108]. Human Prxs are found in various subcellular compartments, and each isoform's specific function depends on its oligomeric and redox states [109]. Oligomerization can be influenced by ionic strength, pH, or protein concentration [110]. Prxs can also be inhibited by tyrosine or threonine phosphorylation and by hyperoxidation. These enzymes act as redox relays, transferring disulfide groups between proteins for redox signaling [111]. Prxs are overexpressed in many cancer tissues, suggesting their proliferative role may relate to disease development or progression [108]. High Prx expression in mammalian tumors indicates that antioxidant defenses offer a survival advantage for tumor growth. Therefore, Prx inhibitors are being explored as therapeutic agents in various cancer models, and Prx is proposed as a potential cancer biomarker due to its overexpression in malignant cells relative to survival [106].

B-Non-Enzymatic Antioxidants

The use of antioxidant supplements as health enhancers and their potential anticancer effects have been topics of ongoing discussion. This debate extends not only to individuals in good health but also to patients diagnosed with cancer [112]. Natural antioxidants, such as vitamins A, C, E, and various plant-based compounds, possess the ability to counteract excessive free radicals in cancer cells by acting as hydrogen donors, quenching singlet oxygen, and delaying oxidative reactions [113]. Antioxidants derived from dietary sources, particularly from plants, including carotenoids, flavonoids, phenols, and vitamins, have shown distinct effects in inhibiting different stages of cancer development. They can induce cell cycle arrest and promote cancer cell death.

Vitamin A and Carotenes: Vitamin A, or retinol, is present in animal products such as liver and eggs [114]. Carotenes, the precursors of vitamin A, are often found in plant-based foods. For example, lycopene is a type of carotene that provides red color in tomatoes, and it is particularly important in the prevention of prostate cancer. Vitamin A is effective at reducing the risk of gliomas, lung cancer, colorectal cancer, and breast cancer. As an antioxidant, vitamin A prevents DNA damage due to reactive oxygen species (ROS), which contributes to carcinogenesis [115,116].

Vitamin C: Vitamin C, also known as ascorbic acid, has cancer-preventing properties depending on the dose provided [117]. It can be found in many fruits and vegetables, such as citrus fruits, peppers, and broccoli. For many decades, the role of ascorbate as an anticancer agent has been debated. Moreover, the unregulated use of vitamin C as a dietary supplement or pharmacologically applied intravenous infusion by cancer patients, with numerous reports of clinical benefits, has made it difficult to postulate authenticity. However, the lack of understanding of the mechanism of action has hindered the design of appropriate clinical trials. Vitamin C promotes apoptosis of pre-carcinogenic and carcinogenic cells at high doses but promotes cell differentiation of pre-carcinogenic and carcinogenic cells at low doses [118].

Vitamin D: Vitamin D can be obtained from fish, dairy, eggs, and mushrooms, or synthesized in the skin from cholesterol in the presence of sunlight. It is important for maintaining the metabolism of minerals, primarily calcium and phosphorus, in the intestine, kidneys, and bones. This lipid-soluble vitamin participates in all proliferation, apoptosis, differentiation, metastasis, and angiogenesis. Liu and colleagues showed the relationship between vitamin D and lowering the risk of lung cancer as well as breast cancer and its better prognosis [119]. A variety of food, such as meat, seafood, grains, fruits, and vegetables, is required to obtain all the necessary micronutrients in the diet (**Table 1**).

Table: Micronutrients as breast cancer prevention.

Micronutrient	Food Sources	Genes Affected	Beneficial Effects	Preventable Cancers	References
Vitamin A	Liver, fish oils, eggs, milk,leafy green vegetables	JAK-STAT 1, RARs 2,RXRs 3, JNK 4, Pakt/pERK/ Pegfr-genes pathway, COX2 pathway, 5-lipoxygenase catalyzed Eicosanoids pathways	Antioxidant, apoptosis, immune response	Breast cancer	[120,121]
Vitamin E	Peanuts, almonds, sunflower seeds		Apoptosis, anti-inflammatory	All cancer types	[122]
Vitamin K	green leafy vegetables	CYP1 1A1-driven non-canonical metabolite pathway	Apoptosis, Anti inflammatory, cell–cell adherence	All carcinomas	[123]
Zinc	Red meat, poultry, milk	Component of many transc	Antioxidant, p53 4,	All cancer types	[124]

		ription factors and enzymes	immune function		
Magnesium	Legume dark green leafy vegetables	Component of many transcription factors and enzymes	apoptosis, immune response, anti-inflammatory	All cancer types	[125]
Selenium	Organ meats, seafood, Brazil nuts	Methyltransferase pathway, histone deacetylase pathway	Antioxidant, apoptosis, immune response, anti-inflammatory	Leukemia, prostate, lung, colorectal	[126]

Nanotechnology for Delivering Antioxidants

Nanotechnology-based drug delivery systems hold promise for cancer prevention, diagnosis, and treatment. These systems encapsulate or conjugate drugs with varying solubility profiles using biocompatible and biodegradable nanocarriers. A major challenge in cancer therapy is overcoming biological barriers and achieving targeted drug delivery. Nanocarriers can target tumors through passive mechanisms, leveraging the enhanced permeability and retention (EPR) effect, or through active targeting using site-specific ligands [127].

Lipid-based nanocarriers are widely employed to enhance the bioavailability, targeting accuracy, and delivery of therapeutic agents. Their advantages include low toxicity, scalability, excellent biocompatibility, and high drug-loading capacity [128]. Owing to a favorable surface-to-mass ratio, these nanocarriers show improved uptake in the testes via mechanisms such as solubilization in the intestinal environment, intestinal lymphatic transport, and enterocyte-mediated transport [129]. Common lipid-based nanostructures for drug delivery include emulsions, liposomes, niosomes, solid-lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) (**Figure 4**). Liposomes and niosomes are vesicular structures with aqueous cores, whereas emulsions consist of lipid droplets stabilized by surfactants. SLNs feature dense lipid cores, while NLCs contain liquid lipid droplets within tightly packed cores. Liposomes are particularly versatile, encapsulating hydrophilic drugs in their inner cavity and hydrophobic drugs within the lipid bilayer [130].

Polymer-based nanostructures are often used to modulate biodistribution and enhance the intrinsic antioxidant properties of nanocarriers. The biodistribution of nano-encapsulated bioactive compounds is largely governed by the size, shape, chemical composition, and surface characteristics of the nanoparticles, making it less dependent on the physicochemical properties of the encapsulated active pharmaceutical ingredients. Other nanoparticle types, such as dendrimers and mesoporous silica nanoparticles, have also demonstrated potential for controlled antioxidant delivery. For successful translation into clinical antioxidant therapy, regulatory considerations and manufacturing processes must be addressed [130].

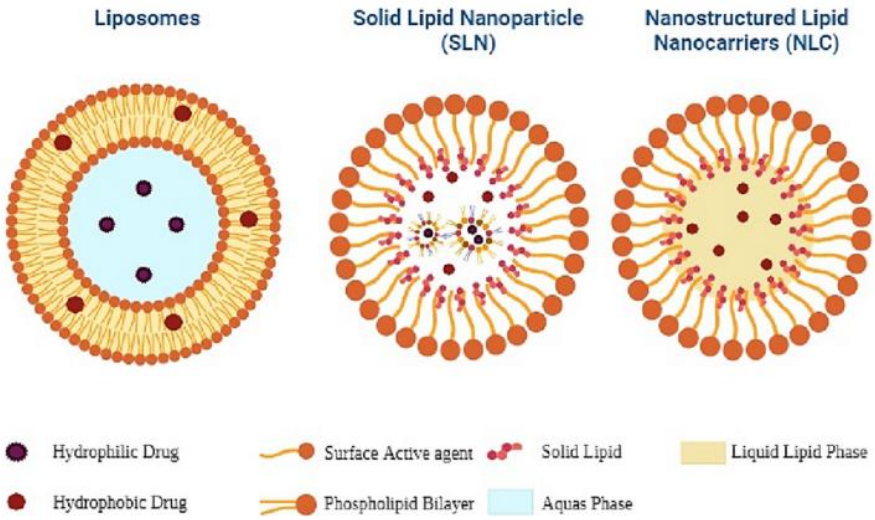

Figure 4: Nano-particles used in breast cancer.

Biological Types of Breast Cancer

Routinely assessed pathological features are often inadequate for predicting the clinical course of breast cancer, which complicates optimal treatment decisions. The varying outcomes of tumors with similar morphological appearances can be attributed to differences in their genetic profiles. Gene expression studies have led to the identification of five intrinsic molecular subtypes of breast cancer: luminal A, luminal B, HER2-positive non-luminal, basal-like, and special histological types. These subtypes correspond to immunophenotypes determined by pathological criteria.

Luminal A tumors show high expression of estrogen receptor (ER)-related genes and low expression of proliferation-related genes as well as HER2-associated genes. Luminal B tumors are also ER-positive but exhibit lower expression of ER-related genes and higher expression of proliferation-related genes, including Ki-67, compared to luminal A. According to the St. Gallen panel, Ki-67 expression levels help distinguish luminal A from **luminal B**, which is clinically important because luminal A carries a better prognosis.

Basal-like breast carcinoma, often referred to as triple-negative breast cancer due to the absence of ER, progesterone receptor (PR), and HER2, lacks expression of genes linked to these receptors. Patients with this subtype who develop cerebellar metastases represent a particularly interesting group. In such cases, biomarkers like CK5/6, HER1, and c-KIT may help differentiate basal-like from non-basal-like tumors, although their clinical utility remains uncertain.

The **HER2-positive** molecular subtype is defined by HER2 overexpression along with the absence of ER and PR. Breast cancer remains the most common malignancy among women. Each year, numerous clinical trials are published, but only a few lead to changes in clinical practice. Treatment guidelines for early-stage breast cancer are updated biennially as part of the St. Gallen International Breast Cancer Conference consensus. Similarly, the European Society for Medical Oncology (ESMO) issues its own recommendations for early-stage disease. The 2019 St. Gallen guidelines emphasize recent progress, particularly in managing HER2-positive and triple-negative breast cancers that show residual disease after neoadjuvant therapy [132].

CONCLUSION

Breast cancer remains a predominant global health challenge, with rising incidence and disproportionately high mortality in low- and middle-income countries, including Pakistan, due to delayed diagnosis and limited healthcare access. The pathogenesis

involves complex genetic alterations (e.g., BRCA1/2, *PIK3CA*, *TP53*), hormonal imbalances, and immune evasion within the tumor microenvironment. Oxidative stress plays a dual role in carcinogenesis—promoting tumor development when antioxidant defenses are insufficient, yet offering therapeutic potential when controlled. Both enzymatic (SOD, catalase, GPx, GR, TrxR, Prx) and non-enzymatic (glutathione, thioredoxin, vitamins A, C, D, E, and micronutrients like zinc, magnesium, selenium) antioxidants demonstrate anticancer properties through various molecular mechanisms. Emerging nanotechnology-based delivery systems, particularly lipid-based and polymeric nanocarriers, offer promising strategies for targeted antioxidant delivery, enhancing bioavailability and therapeutic efficacy. This review underscores the urgent need for integrated preventive, protective, and treatment strategies against breast cancer, especially in resource-limited settings, while highlighting the potential of antioxidant-based approaches as adjunctive therapies in breast cancer management.

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