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MECHANISTIC INSIGHTS INTO BREAST CANCER DRUG RESISTANCE

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ABSTRACT

Breast cancer remains one of the most prevalent and life-threatening malignancies worldwide, characterized by remarkable molecular heterogeneity and complex therapeutic challenges. Despite substantial progress in surgery, chemotherapy, radiotherapy, endocrine therapy, and targeted treatments, the emergence of drug resistance continues to limit therapeutic success and contributes significantly to cancer-associated mortality, recurrence, and metastasis. Drug resistance in breast cancer occurs in two major forms: intrinsic resistance, which exists prior to treatment due to pre-existing genetic and epigenetic alterations, and acquired resistance, which develops progressively after an initial response to therapy. Multiple molecular and cellular mechanisms contribute to resistance, including overexpression of drug efflux transporters, enhanced DNA repair, dysregulation of apoptotic pathways, activation of compensatory signaling cascades such as PI3K/AKT/mTOR, epithelial–mesenchymal transition, cancer stem cell enrichment, and alterations in the tumor microenvironment. Resistance mechanisms vary among hormone receptor-positive, HER2-positive, and triple-negative breast cancer subtypes, further complicating treatment strategies. Additionally, growing evidence suggests that phytochemicals and novel targeted approaches may help overcome therapeutic resistance and improve treatment outcomes. This review comprehensively discusses the major mechanisms underlying breast cancer drug resistance and highlights emerging therapeutic strategies aimed at enhancing clinical efficacy and patient survival.

Keywords: Breast cancer; Drug resistance; Molecular mechanisms; Targeted therapy; Phytochemicals.

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INTRODUCTION

Breast cancer is a complex and heterogeneous malignancy that predominantly affects women and remains one of the leading causes of cancer-associated mortality worldwide. It contributes to nearly 12 % of global cancer deaths and accounts for approximately 25 % of all diagnosed cancers, making it one of the most common malignancies among women [1]. More than 10 % of newly diagnosed cancer cases each year are attributed to breast cancer. According to the National Breast Cancer Coalition, one woman dies from breast cancer every 13 minutes globally. In 2020, the disease was responsible for approximately 685,000 deaths among women worldwide.

In the United States, breast cancer is the most frequently diagnosed cancer in women. Data from 2024 reported nearly 310,720 new cases of invasive breast cancer in women, around 56,500 cases of ductal carcinoma in situ, and approximately 2,790 newly diagnosed cases in men. Breast cancer-related mortality during the same period was estimated to be about 42,250 in women and 530 in men [2].

Breast cancer also represents a major healthcare burden in India, where it accounts for nearly 28.2 % of all cancer cases. In 2022, an estimated 98,337 Indian women lost their lives due to the disease. Epidemiological data indicate that one woman in India is diagnosed with breast cancer every four minutes, while one death occurs every eight minutes. Alarmingly, for every two women diagnosed, one eventually succumbs to the disease. Reports from 2024 further revealed that invasive breast cancer affected approximately 310,720 individuals in India, with nearly 16 % of the cases occurring in women younger than 50 years of age [3].

Although substantial progress has been achieved in breast cancer management through surgery, chemotherapy, radiotherapy, hormone therapy, and targeted therapies, treatment outcomes are often hindered by tumor heterogeneity and complex molecular mechanisms. These limitations highlight the urgent need for the development of more effective and innovative therapeutic approaches. In this regard, phytochemicals derived from natural sources have gained significant attention due to their diverse biological activities and promising anticancer potential, making them attractive candidates for future breast cancer therapy [4].

Breast cancer is recognized as a highly heterogeneous malignancy and is broadly categorized into three major subtypes: human epidermal growth factor receptor 2 (HER2)-positive breast cancer, hormone receptor (HR)-positive breast cancer, and triple-negative breast cancer (TNBC) [5]. These subtypes differ in their molecular characteristics, clinical behavior, prognosis, and response to therapy.

Resistance to anticancer therapy remains a major challenge in breast cancer management and generally occurs in two forms. The first type, known as intrinsic or inherent resistance, refers to the pre-existing insensitivity of cancer cells to therapeutic agents before treatment initiation. In contrast, acquired resistance develops gradually after an initial favorable response to therapy, where cancer cells adapt over time and become less responsive or completely resistant to treatment, thereby

reducing therapeutic efficacy [6].

Drug resistance is considered one of the principal causes of treatment failure, tumor recurrence, metastasis, and mortality in breast cancer patients. It is estimated to contribute to more than 90 % of cancer-related deaths worldwide [7]. Multiple molecular and cellular mechanisms are involved in the development of resistance, including alterations in drug targets, activation of survival signaling pathways, enhanced drug efflux, defects in apoptosis, tumor microenvironment modulation, and cancer stem cell activity. In this review, the major mechanisms associated with breast cancer drug resistance and their therapeutic implications are comprehensively discussed.

Type of resistance

Intrinsic resistance

Intrinsic resistance in cancer chemotherapy describes the natural capability of tumor cells to withstand the cytotoxic effects of anticancer drugs even before treatment begins. This form of resistance primarily results from pre-existing genetic and epigenetic alterations that render cancer cells less responsive or completely unresponsive to conventional chemotherapeutic agents [8].

One of the well-established mechanisms underlying intrinsic resistance is the overexpression of drug efflux transporters, particularly P-glycoprotein (P-gp), encoded by the multidrug resistance 1 (MDR1) gene. These transporters belong to the ATP-binding cassette (ABC) family and actively expel anticancer drugs from the intracellular environment, thereby lowering intracellular drug accumulation and reducing therapeutic efficacy.

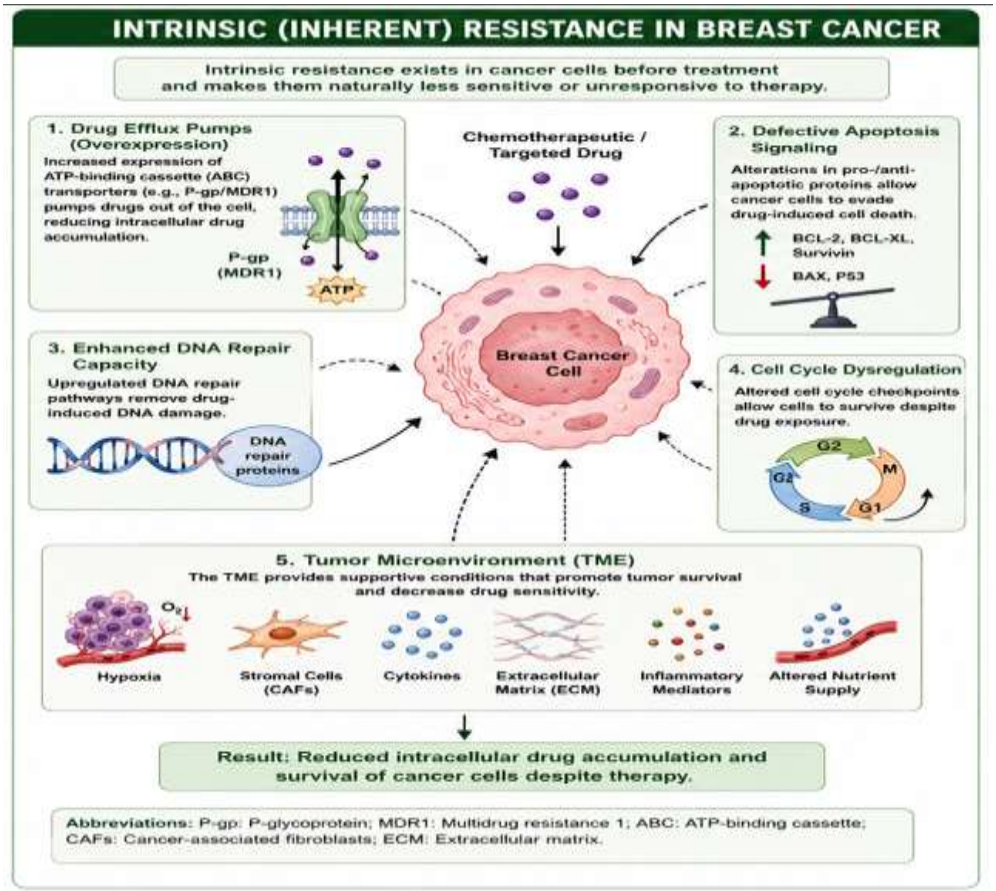

Figure 1. Intrinsic resistance in Breast Cancer

Additional mechanisms contributing to intrinsic resistance include defects in apoptotic signaling pathways, enhanced DNA repair capacity, and dysregulation of the cell cycle. Alterations in these cellular processes enable cancer cells to survive despite exposure to chemotherapeutic agents. Furthermore, the tumor microenvironment (TME) plays a crucial role in mediating intrinsic drug resistance by providing supportive conditions such as hypoxia, inflammatory mediators, stromal interactions, and altered nutrient supply, all of which promote tumor survival and decrease drug sensitivity.

Acquired Resistance

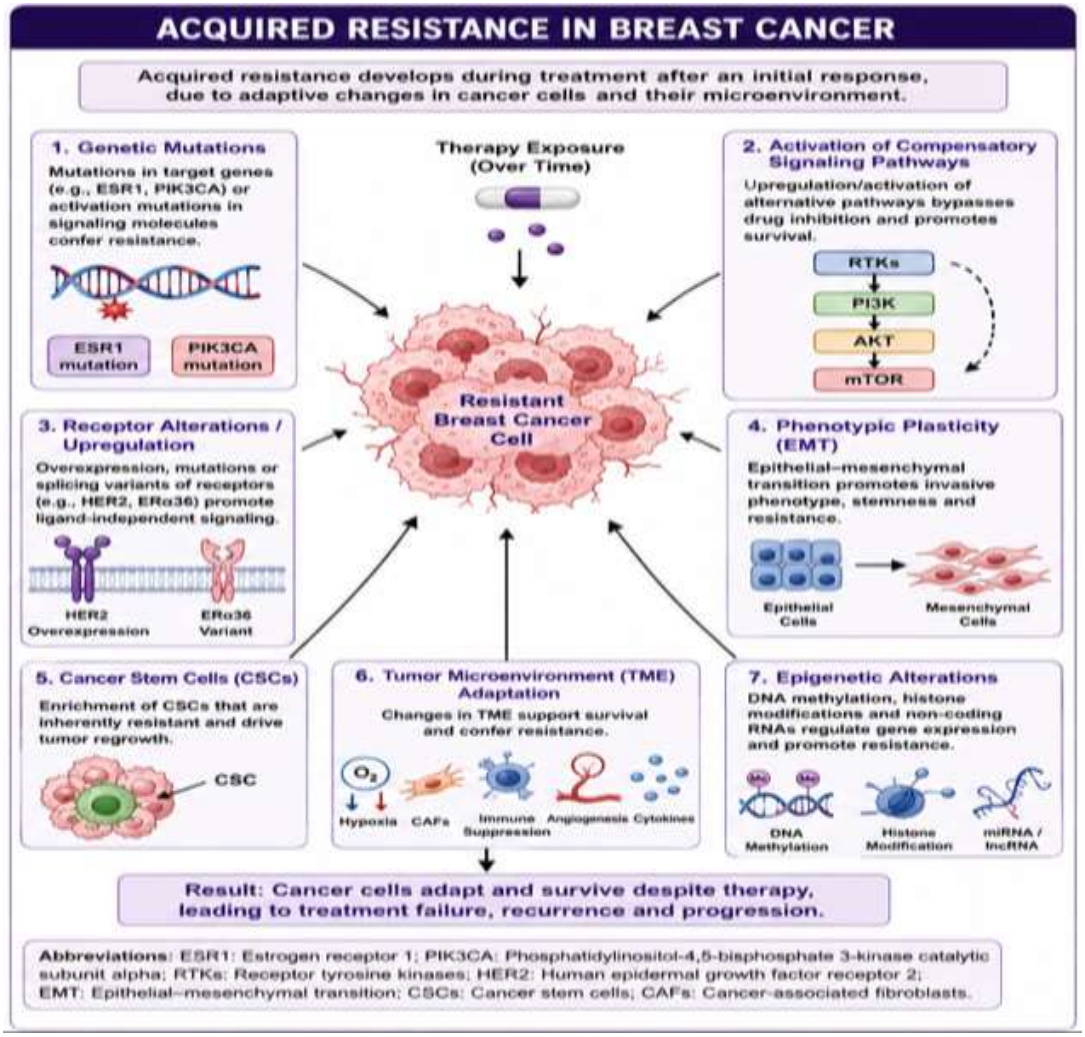

Figure 2. Acquired Resistance in Breast Cancer

Acquired resistance is a multifactorial and dynamic process that develops when cancer cells gradually lose their sensitivity to therapeutic agents after an initial favorable response to treatment. This phenomenon is driven by several factors, including genetic mutations, alterations in the tumor microenvironment (TME), and activation of diverse molecular signaling pathways that allow cancer cells to survive and proliferate despite chemotherapy exposure [9].

The emergence of acquired resistance poses a major obstacle in successful cancer management, often leading to treatment failure, tumor recurrence, and disease progression. To counteract this challenge, therapeutic strategies frequently require modification through the use of alternative drugs, targeted

therapies, or combination treatment approaches aimed at overcoming resistance mechanisms [10].

In breast cancer, resistance to endocrine therapy represents a significant clinical concern, particularly resistance to tamoxifen, which greatly reduces the long-term efficacy of treatment in hormone receptor-positive breast cancer patients. Studies have demonstrated that hexokinase 2 (HK2), a key glycolytic enzyme involved in cellular energy metabolism, is markedly upregulated in tamoxifen-resistant MCF-7 breast cancer cells. Evidence from both cell-based experimental studies and bioinformatics analyses suggests that increased HK2 expression contributes to metabolic reprogramming and enhanced survival of resistant cancer cells, thereby promoting tamoxifen resistance.

Resistance in hormone receptor-positive breast cancer

The estrogen receptor (ER) signaling pathway plays a fundamental role in the initiation, progression, and survival of hormone receptor-positive breast cancer. Endocrine therapies such as selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), and selective estrogen receptor degraders (SERDs) have substantially improved patient survival and disease management. Despite these therapeutic advancements, the clinical effectiveness of endocrine therapy is frequently compromised by the development of intrinsic and acquired resistance, particularly in advanced and metastatic breast cancer [11,12].

Several molecular mechanisms are responsible for endocrine resistance. One of the most common mechanisms involves the loss, downregulation, or mutation of estrogen receptor alpha (ERα), which reduces the sensitivity of tumor cells to hormonal agents such as tamoxifen. In addition, truncated receptor variants, including ERα36, can promote resistance by activating downstream signaling pathways independently of ligand binding. Alterations in ER co-regulatory proteins also contribute significantly to therapy failure. For example, overexpression of co-activators such as steroid receptor coactivator-3 (SRC-3) enhances abnormal ER signaling and promotes tumor cell survival. Furthermore, post-translational modifications of ER, including phosphorylation and methylation, may alter receptor activity and contribute to resistance development [13-15].

Another important mechanism underlying endocrine resistance is the interaction between ER signaling and growth factor receptor pathways, particularly the HER2 and PI3K/AKT/mTOR signaling cascades. Activation of these pathways can bypass ER-dependent signaling, enabling cancer cells to proliferate and survive even in the presence of endocrine therapy. This molecular crosstalk not only decreases therapeutic responsiveness but also promotes disease progression and aggressive tumor behavior.

Resistance in HER2-Positive Breast Cancer

HER2-positive breast cancer is defined by the overexpression or amplification of the human epidermal growth factor receptor 2 (HER2), a condition associated with aggressive tumor growth, increased metastatic potential, and poor clinical prognosis [54]. Targeted therapies against HER2 have significantly improved treatment outcomes, with trastuzumab being the first humanized

monoclonal antibody developed specifically for HER2-positive breast cancer. Trastuzumab exerts its therapeutic effect by binding to the extracellular domain of the HER2 receptor, thereby inhibiting HER2-mediated signaling pathways, although its complete mechanism of action has not been fully elucidated [16,17].

Studies have suggested that trastuzumab more effectively suppresses HER2 homodimer signaling compared to HER2 interactions with HER1 (epidermal growth factor receptor; EGFR) or HER3 heterodimers [18]. In addition to blocking receptor signaling, trastuzumab also promotes antibody-dependent cellular cytotoxicity (ADCC), which enhances immune-mediated destruction of tumor cells. The combination of trastuzumab with conventional chemotherapy has substantially reduced recurrence rates and improved survival among patients with HER2-positive breast cancer.

Despite these clinical benefits, resistance to trastuzumab remains a major therapeutic challenge. Both acquired resistance, which develops after an initial response, and de novo resistance, where tumors fail to respond from the beginning of treatment, are frequently observed in HER2-positive breast cancer patients [19,20]. Multiple mechanisms contribute to resistance, including HER2 receptor alterations, activation of compensatory signaling pathways such as PI3K/AKT/mTOR, increased signaling through HER family heterodimers, loss of PTEN function, and modifications within the tumor microenvironment. These resistance mechanisms limit the long-term effectiveness of HER2-targeted therapies and highlight the need for novel therapeutic strategies to improve patient outcomes.

CONCLUSION

Breast cancer drug resistance remains a major barrier to successful therapy and is responsible for poor clinical outcomes, disease recurrence, metastasis, and increased mortality worldwide. Both intrinsic and acquired resistance mechanisms involve complex interactions among genetic mutations, epigenetic alterations, dysregulated signaling pathways, tumor microenvironment adaptations, and cancer stem cell survival. Resistance to endocrine therapy, HER2-targeted therapy, and chemotherapy significantly limits the long-term effectiveness of current treatment strategies in different breast cancer subtypes. Understanding these molecular mechanisms is essential for the development of more precise and personalized therapeutic interventions. Recent advances in targeted therapies, combination treatment approaches, immunotherapy, nanotechnology-based drug delivery systems, and phytochemical-based therapeutics have shown promising potential in overcoming resistance and improving therapeutic efficacy. Furthermore, continuous exploration of biomarkers and molecular targets may facilitate early detection of resistance and guide individualized treatment planning. Future research should focus on integrating innovative therapeutic strategies with molecular profiling to enhance treatment response, minimize resistance development, and ultimately improve survival and quality of life among breast cancer patients.

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