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REVIEW

# Molecular Insights into Phytochemicals Mediated Epigenetic Regulation in Preclinical Models of Breast Cancer

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**Abstract:** One of the most common malignant tumors in women worldwide is breast cancer, which affects even more than one-third of all female tumor patients. Patient outcomes and effective therapeutic strategies are frequently determined by molecular subtypes in breast cancer. However, the underlying epigenetic characteristics that could further divide breast cancer patients into groups and affect their outcomes could be the reason for the differences in therapeutic response. It is true that there have been recent findings about the role of epigenetic abnormalities in cancer, and that therapeutics targeting particular epigenetic pathways have been developed. Phytochemicals function as gene regulators in a variety of cancers and are crucial to the pathophysiology of many human cancers, including breast cancer. Preclinical studies have revealed that phytochemicals exhibit promising therapeutic efficacy against breast carcinoma by modulating several epigenetic alterations including DNA methylation, histone modifications, non-coding RNA and estrogen associated epigenetic changes. Nevertheless, despite promising in vitro and in vivo results, the clinical application of phytochemicals targeting epigenetic markers in breast cancer is limited. Further research is required to confirm their effectiveness and safety in clinical settings. Thus, this study provides a thorough summary of how epigenetic changes contribute to the development of breast cancer. This article also explores the potential benefits of phytochemicals, such as flavonoids, terpenoids, alkaloids, isothiocyanates, and quinones, in modulating these epigenetic markers in preclinical models of breast cancer.

**Keywords:** breast cancer, phytochemicals, epigenetic regulation, cancer therapy

## Introduction

Breast cancer continues to be a tough foe of global health challenges. Complex pathophysiology and extensive range of clinical manifestations of breast cancer present significant hurdles for the development of promising treatment and prevention strategies.[1,2] Breast cancer can be categorized into three principal subtypes with respect to receptor expression status including luminal A, luminal B, HER2-enriched, and triple-negative variants.[3] Various breast cancer subtypes display unique biological characteristics, resulting in differences in prognosis and therapeutic efficacy.[4,5]

When classifying breast tumors into various molecular subgroups, the expression levels of HER2, progesterone, and estrogen play crucial roles. However, it is essential to realize that genetic variants play a substantial role in the progression of the disease, as well as the therapeutic response.[6,7] Numerous studies have shown that epigenetics, apart from genomic aberrations, is a significant factor in breast cancer development. These studies focused on the initiation of molecular pathways in carcinogenesis, prediction of biomarkers for breast cancer aggressiveness and remarkable possibilities of epigenetics therapy.[8,9] Recently, it has

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become widely recognized that abnormal gene expression, breast cancer tumorigenesis, and metastasis are linked to epigenetic dysregulation, including deregulated histone modification and DNA methylation.[10,11]

Phytochemicals are considered as a promising therapeutic approach that can be used to decrease side-effects related to conventional methods and increase the therapeutic efficacy for breast cancer by inhibiting disease progression. These phytochemicals have been used for decades to cure a wide range of disorders, including cancer, by modulating several cellular and molecular targets.[12] In fact, a number of compounds that influence epigenetic pathways have been marketed as anticancer medications under the name "epidrugs".[13] One of the main sources of epidrugs is nature, which has a limitless supply of bioactive natural compounds that precisely target epigenetic pathways and have exceptional anticancer properties. In fact, natural compounds found in medicinal plants have demonstrated epidrug activity.[14–16] Phytochemicals have been identified in a number of studies as possible regulators that can restore abnormal epigenetic changes that cause tumor growth and ultimately cancer.[17,18] In this regard, many secondary metabolites that have been isolated from plants, such as alkaloids, quinones, terpenoids, and flavonoids, have demonstrated chemopreventive benefits by reversing epigenetic changes and modifying the molecular pathways linked to carcinogenesis.[19–21] Phytocompounds have multiple uses and may hold great promise as a treatment for breast cancer due to their ability to target different cellular pathways that are involved in the disease's epigenetics.[22–24] Several promising phytochemicals suffer from low bioavailability and limited absorption rates. Additionally, there is a lack of reliable clinical studies validating the effects of phytochemicals on epigenetic markers in breast cancer patients. Precise mechanistic studies and comprehensive reviews of the epigenetic modulation of breast cancer by phytochemicals are limited.[25] Thus, this study focused on the possible applications of specific phytochemicals in anticancer therapies, as well as their ability to combat epigenetic aberrations that support the initiation and progression of breast carcinoma in humans. As a result, a detailed description of the most studied phytochemicals that have been shown to significant modulate the epigenetic landscape in breast cancer, along with their limitations, is provided in detail.

## Breast Cancer and Epigenetic Regulation

The development and advancement of cancers are significantly influenced by epigenetic changes including dysregulation of the ncRNAs, histone modifications, localized hypermethylation of CpG promoters of tumor suppressor genes, and loss of DNA methylation throughout the genome. Numerous forms of cancer, including glioblastoma, leukemia, liver, lung, prostate, breast, and gastric cancers, have been linked to abnormal DNA methylation patterns.[26–32] In addition to genetic abnormalities, various epigenetic changes play a role in the development and progression of breast carcinoma. The main epigenetic alterations directly associated with breast cancer are DNA methylation, histone modifications, nucleosome rearrangement and non-coding RNAs regulation. These alterations may serve as markers for prognosis, early identification and therapy effectiveness in breast carcinoma.[33–35] Additionally, a thorough understanding of underlying epigenetic regulatory markers of breast carcinoma could open up new avenues for drug development. Altogether, epigenetic abnormalities linked to the onset and spread of breast cancer significantly affect the genes that govern cell proliferation, invasion, motility, and apoptosis (Figure 1).[36,37]

### DNA Methylation

DNA methylation, a prominent epigenetic process, involves the covalent linkage of a methyl group ($CH_3$) to the 5′-site of cytosine preceding guanine in the DNA structure. Methylation inside CpG dinucleotides, which are densely clustered in regions known as CpG islands, affects gene expression and, consequently, influences the primary biological processes associated with cancer.[38,39] Methylation results in the formation of a 5-methylcytosine (5mC) structure, which can obstruct transcription factors from retrieving DNA-binding locations or engage methyl-binding domain proteins (MBDs) alongside histone protein modifications, thereby inhibiting the expression of methylated genes. In this situation, extensive methylation of promoters of crucial tumor suppressor genes results in their suppression, whereas reduced methylation of oncogenes leads to their abnormal activation.[40,41]

DNA methylation is a reversible mechanism regulated by a specific class of enzymes, known as DNA methyltransferases (DNMTs). Three DNA methyltransferases are actively involved in this process: DNMT1, DNMT3a, and DNMT3b. DNA demethylation is facilitated by a family of enzymes known as ten-eleven translocation methylcytosine dioxygenases (TETs), which convert 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5-hmC) via hydroxymethylation. Three such enzymes,

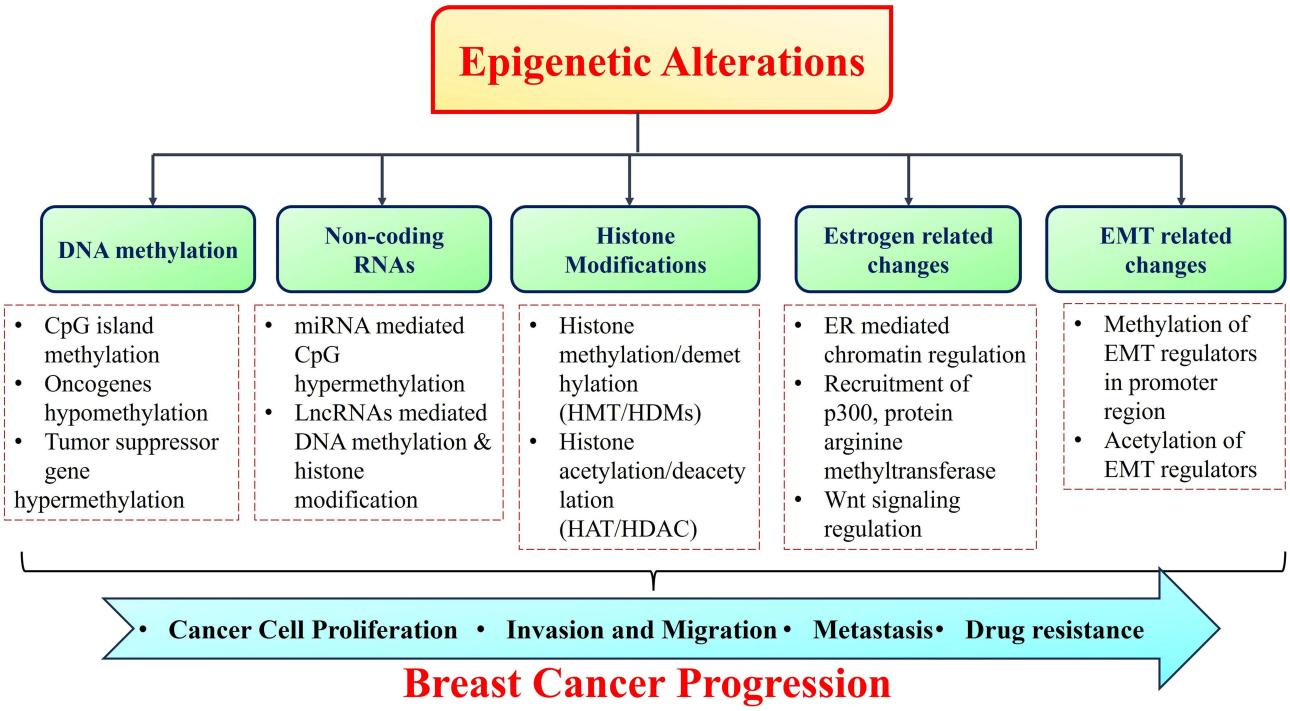



**Figure 1** Illustration of epigenetic alterations associated with breast cancer progression, metastasis and drug resistance.

TET1, TET2, and TET3, are engaged in DNA demethylation, which restores genes that have been silenced as a result of DNMTs. This process collectively affects the transcriptional activation of critical genes associated with tumorigenesis and genomic stability.[42–44] Numerous additional proteins exhibiting DNA demethylase activities associated with breast carcinoma such as growth arrest and DNA-damage-inducible protein (GADD45) and the cytidine deaminase family, specifically activation-induced cytidine deaminase (AID) and Apolipoprotein B mRNA editing catalytic polypeptide-like family (APOBEC). GADD45A is significantly correlated with DNA repair and epigenetic control genes.[45] The relationship between GADD45 and the BRCA1 gene in breast cancer is proposed to affect the etiology of the disease, likely by activating nucleotide excision repair pathways. GADD45A exhibits aberrant methylation in breast cancer.[46] AID proteins play crucial roles in active DNA demethylation, specifically the deamination of 5-mC to thymine. AID is known for its role in promoting DNA demethylation and is crucial for epithelial-mesenchymal transition (EMT) in mammary epithelial cells (non-transformed).[47] Moreover, although APOBEC1 exhibits DNA demethylase activity,[48–50] it has been shown that APOBEC mutagenesis affect tumor progression in ER+/HER2-positive breast carcinoma.[51] Recent findings have indicated that APOBEC mutagenesis inhibits breast cancer growth by triggering immunogenic responses.[52]

Numerous genes associated with breast cancer demonstrate CpG island hypermethylation, and in several cases, aberrant activity of DNA methyltransferases results in the hypermethylation and silencing of tumor suppressor genes like HOXA5, RASSF1A, TMS1, p16, and BRCA1.[53,54] Moreover, genes repressed by promoter hypermethylation include E-cadherin, GSTP1, TMS1, and p16.[55–57] Some of the important biological functions of these genes include estrogen signaling, pro-apoptosis (HOXA5 and TMS1), cell cycle progression (RASSF1A and p16), and DNA repair pathways (BRCA1). BRCA1, a prominent breast cancer susceptibility gene often suppressed in sporadic breast cancers, has been related to CpG hypermethylation linked to DNMT3b upregulation.[58] The initial phases of sporadic breast cancer demonstrate the loss of the cell cycle checkpoint gene p16INK4a due to abnormal promoter methylation of CpG, and approximately 80% of breast tumors show downregulation of the CDK inhibitor p21, due to its hypermethylation.[59,60]

## Non-Coding RNAs

Several epigenetic alterations are associated with breast cancer. Non-coding RNAs, especially microRNAs (miRNAs), play a role in the post-transcriptional control of breast cancer development, progression, and metastasis.[61] miRNAs, non-

coding RNA of 17–25 nucleotides, can modulate gene expression in both healthy and cancerous cells. Polymerase II facilitates transcription of primary miRNAs. Primary miRNAs are converted into pre-miRNAs by the Drosha–Dicer complex, which enables mature versions of miRNAs to control post-transcriptional levels of gene expression. In cancer, miRNAs improperly control genes due to CpG hypermethylation in miRNA genes or deregulation of miRNA manufacturing mechanisms.[62] Aberrant miRNA mechanisms have been implicated in all phases of cancer, from carcinogenesis to metastasis in breast carcinoma. For instance, miRNA profiling has revealed that tumor suppressor miRNAs, such as miR-4458 linked to SOC1 signaling, are downregulated, while the oncogenic miRNA miR-214, involved in PI3K/Akt/mTOR signaling, is elevated in breast tumors.[63] Dysregulated expression of these miRNAs is responsible for the emergence of cancer characteristics such as cell proliferation, hypoxia, metastasis, apoptosis, and angiogenesis.[64] Breast tumor is represented by the presence of both miRNAs and long noncoding RNAs. LncRNAs, which are noncoding RNAs measuring between 200 nucleotides and 100 kilobases, can inhibit target genes by facilitating DNA methylation or histone modification. The development of tumors can result from dysregulation of these mechanisms.[65,66] The lncRNA GAS5 functions as a tumor suppressor by modulating several tumor suppressor proteins, including PTEN, PDCD4, FOXO1, OKK2, and SUFU, and is significantly decreased in breast cancer. Moreover, GAS5 expression is inhibited by promoter methylation in triple-negative breast cancer, indicating that lncRNAs are pivotal in the pathogenesis of breast cancer.[67]

## Histone Modifications

Histones function as crucial proteins for DNA packaging, thus preserving the chromatin architecture. Histone proteins (H2A, H2B, H3, and H4) facilitate the formation of nucleosomes by encasing octamers of approximately 147 bp of DNA. Post-translational modifications of histones induce alterations in the chromatin structure, thereby influencing gene expression regulation.[68] Multiple modifications were carried out on particular residues located at the amino and carboxy ends of the histone tails. These modifications include methylation, acetylation, ubiquitination, phosphorylation, SUMOylation, and glycosylation. These changes are facilitated by various enzymes, including histone acetyltransferases (HATs), histone methyltransferases (HMTs), histone deacetylases (HDACs), and histone demethylases (HDMs). The development and progression of cancer are also linked to changes in the expression of these enzymes. Multiple changes have been observed in breast carcinomas, including overexpression of HDAC1, HDAC2, HDAC3, and HDAC6.[69]

Breast cancer cell proliferation and metastasis have been associated with histone methyltransferases, such as lysine methyl transferase 2 (KMT2). KMT2 promotes the expression of oncogenes and metastatic genes through the methylation of H3K4 at enhancer and promoter sites.[70] Abnormal expression of the essential histone methyltransferase enhancer of zeste homolog 2 (EZH2) is prevalent in breast tumors. EZH2 promotes transcriptional silencing of various genes by inducing H3K27 methylation, thereby altering the EMT and metastasis in breast carcinoma.[71,72] In addition, another important HMT known as Disruptor silencing 1 like (DOT1L), is also recognized to be able to enhance metastatic in breast cancer cells.[73] The development of breast cancer is also linked to a number of histone demethylases, such as lysine-specific demethylase 4A (KDM4A), Lysine Specific Demethylase 4B (KDM4B), and lysine-specific demethylase 4C (KDM4C). Cells of the ERα-positive subtype demonstrate overexpression of KDM4A and KDM4B, whereas triple-negative breast cancer is characterized by elevated levels of KDM4C.[74] KDM4A activates a Notch1-dependent signaling cascade that facilitates breast cancer proliferation and metastasis.[75] KDM4B modulates estrogen signaling and its downregulation restricts breast cancer proliferation.[76] KDM4C functions as a coactivator of the HIF-1α/VEGF pathway, thereby facilitating breast cancer tumorigenesis.[77]

## Estrogen Associated Epigenetic Alterations

Breast cancer subtypes can be distinguished based on their epigenetic processes. ER-linked epigenetic modifications in breast tumors are governed by transcription factors and co-regulators. Estrogen governs mitotic and epigenetic processes involved in mammary gland development. Estrogen is categorized into five distinct forms: estrogen, estrone, 17-estradiol, estriol, and estrone sulfate.[78] Estradiol (E2) serves as a catalyst for breast cancer development. E2 treatment promotes breast cancer carcinogenesis in vitro through anchorage-independent growth, loss of ductulogenesis in collagen, and increased invasiveness.[79] E2 activation is facilitated by the ER and involves the recruitment of numerous co-regulators to chromatin, including the p160 family, p300, protein arginine methyltransferases, and certain mediator complexes.[80,81] Polycomb proteins

serve as a connection between the ER and Wnt signaling networks. One significant component that can directly interact with ER and beta-catenin is the polycomb group protein enhancer of zeste homolog 2 (EZH2), which connects the estrogen and Wnt pathways, indicating a strong correlation between Wnt signaling and carcinogenesis as well as metastasis in ER-positive breast carcinoma.[82] In breast cancer, DNA methylation-mediated epigenetic silencing controls Wnt antagonist genes including SERP and DKK. Methylation of Wnt antagonistic genes constantly stimulates β-catenin, which in turn triggers Wnt-associated genes. This increases the rate of stem cell growth and regeneration, leading to poor prognosis and cancer recurrence.[83] For instance, DKK3 promoter methylation was observed in 78% of individuals with primary breast cancer, and these individuals had a worse prognosis and elevated metastatic rates than those without DKK3 methylation.[84] Furthermore, epigenetic silencing of DKK3 led to lymph node metastases and positive ERα status.[85] Targeting these epigenetic mechanisms typically regulates oncogenic signals such as Wnt signaling.

### Epigenetic Alterations and EMT

The EMT plays a pivotal role in cancer metastasis. In various malignancies, including breast cancer, the interplay between EMT transcription factors and epigenetic regulators is significant, resulting in EMT through the modulation of genes associated with this process.[86,87] In breast cancer, DOT1L interacts with c-Myc and p300 to facilitate the methylation and acetylation of H3K79 in the promoter regions of EMT transcription regulators, resulting in enhanced levels of associated genes. Thus, this mechanism enhances the hallmarks of cancer stemness related to epithelial-mesenchymal transition (EMT). Moreover, invasive breast cancer cells exhibit abnormally elevated CDH1 methylation, which is associated with downregulated E-cadherin production.[88] E-cadherin is a tumor suppressor that promotes cell-to-cell contact between adjacent cells.[89] The interaction between G9a and Snail in breast cancer inhibits transcription at E-cadherin promoter sites. By reducing Slug expression, the histone deacetylase inhibitor Trichostatin A (TSA) can reverse epithelial-mesenchymal transition (EMT) in breast carcinoma.[90,91] Furthermore, blocking bromodomain protein 4 (BRD4) inhibits Gli1, which is essential for transcriptional promotion of Snail proteins. This indicates that BRD4 modulates the tumorigenicity of breast cancer cells via regulation of Snail expression and post-translational processes.[92] Consequently, recognizing the interaction between EMT and epigenetics presents novel opportunities for cancer therapy. As a result, epigenetic pathways present numerous avenues for breast cancer treatment. Given that epigenetic modifications caused by DNMTs and HDACs are temporary and reversible, numerous investigations are presently underway to determine the optimal dosage and treatment regimens for various epigenetic agents associated with breast cancer.

## Phytochemicals as Epigenetic Modulators in Breast Cancer

Numerous studies have elucidated the potential of phytochemicals in cancer therapy. These plant-derived therapeutic substances are mainly extracted from fruits, vegetables, cereals, spices, and medicinal herbs.[93] There has been data from preclinical, clinical, and epidemiological studies that a high intake of plant-based diets high in phytochemicals is associated with a lower incidence of certain types of cancer.[94] The mechanisms that collectively strengthen the chemopreventive and therapeutic effects of these phytochemicals include antioxidant, antiproliferative, apoptosis-inducing, anti-inflammatory properties, alteration of oncogenic signaling, anti-angiogenesis, modulation of the tumor microenvironment, and immune checkpoints.[95] Additionally, several phytochemicals demonstrate significant potential as epigenetic regulators in cancer therapy.[96] For example, a phytochemical sulforaphane exposure resulted in DNMT downregulation and promoter demethylation in prostate and colon cancer cells.[97,98] In a similar manner, various other phytochemicals including quercetin, rosmarinic acid, ursolic acid, and resveratrol also modulated the crucial targets linked to epigenetic dysregulation in cancer.[99–102] Numerous preclinical studies have shown that phytochemicals can regulate epigenetic alterations for chemotherapy, but clinical trials are limited. A phase II clinical investigation on the effect of sulforaphane in males with recurrent cancer revealed an enhancement in histone acetylation subsequent to sulforaphane administration[103]. A phase I clinical trial examined the influence of quercetin on EGCG absorption in prostate cancer, while simultaneously evaluating the inhibitory efficacy of quercetin on enzymatic activity and expression of catechol-O-methyltransferase (COMT) and DNMT1 (NCT01912820).

Recent studies have indicated that phytochemicals may demonstrate health-promoting benefits through epigenetic pathways. These phytochemicals contribute to the regulation of gene expression related to cancer and age-associated

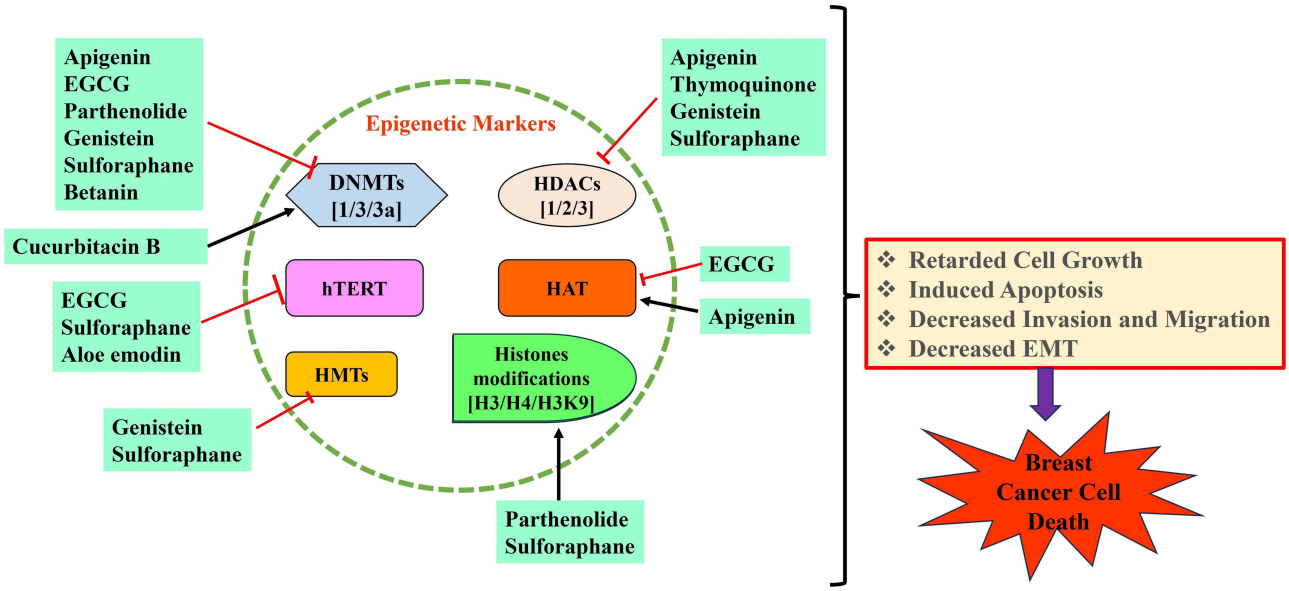
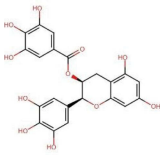
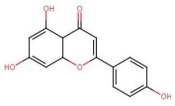
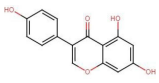



**Figure 2** An overview of mechanistic effects of natural phytochemicals in modulation of epigenetic pathways in breast cancer cells.

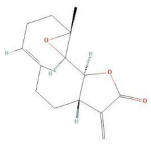
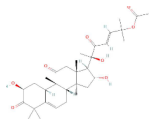
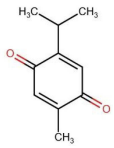
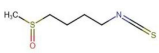
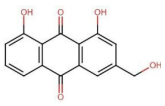
illnesses linked to oxidative stress and inflammation.[104] Various plant-derived phytochemicals, including flavonoids, isothiocyanates, quinones, and alkaloids, have been investigated as effective agents for modulating epigenetic pathways. In this regard, phytochemicals could offer an alternative therapeutic approach for the management of cancers, including breast cancer, by targeting epigenetic pathways (Figure 2).[105] Phytochemicals that target epigenetic regulatory mechanisms in breast cancer are listed in Table 1.

**Table 1** List of Phytochemicals Implicated in Epigenetic Alterations in Breast Cancer

| Class | Phytochemical | BC Model | Dose | Mechanism | References |
|---|---|---|---|---|---|
| Flavonoid | Epigallocatechin-3 gallate  | MCF-7 and MDA-MB-231 cells | 20, 40 μmol/L | Decreased expression of hTERT, DNMT, HAT, acetyl-H3, acetyl-H3K9, and acetyl-H4 | [106] |
| | | MCF-7 and MDA-MB-231 cells | 5-50 μM | Decreased protein expression of DNMT1, HDAC1,and MeCP2 | [107] |
| | | MCF-7 and MDA-MB-231 cells | 10, 20 μmol/L | Decreased expression of enhancer of zeste homolog 2 (EZH2) and class I HDAC proteins | [108] |
| | | MCF-7, MDA-MB -231 and HCC1806 cells | 5 μM | Alteration in histone modifications, decreased HDAC activity | [109] |
| | Apigenin  | MDA-MB-231 cells | 50-100 μM | Repressed HDAC activity, stimulated histone H3 acetylation | [110] |
| | | MDA-MB-231 cells | 10-60 μM | Repressed HDAC and DNMT activity, upregulated HAT activity | [111] |
| | Genistein  | MCF-7 and MDA-MB-231 cells | 5-50 μM | Decreased protein expression of DNMT1, HDAC1,and MeCP2 | [107] |
| | | MCF-7 and MDA-MB-231 cells | 5-25 μM | Downregulated HDAC2 and HDAC3 level, suppressed HMT activity | [112] |

(*Continued*)

**Table 1** (Continued).

| Class | Phytochemical | BC Model | Dose | Mechanism | References |
|---|---|---|---|---|---|
| Terpenoids | Parthenolide  | MDA-MB-231 cells | 10 μM | Downregulated DNMT1 expression, stimulated hyperacetylation of histones H3 and H4 | [113] |
| | Cucurbitacin B  | MCF-7 and MDA-MB-231 cells | 5, 10 μM | Up-regulated the DNMT1 and induced hypermethylation | [114] |
| | Thymoquinone  | MCF-7 cells | 34 μM | Suppressed HDAC activity | [115] |
| Isothiocyanates | Sulforaphane  | MCF-7 and MDA-MB-231 cells | 2.5, 5, 10 μM | Downregulated *hTERT*, DNMT1, DNMT3a, trimethyl-H3K9 and trimethyl-H3K27, Upregulated the acetyl-H3, acetyl-H3K9 and acetyl-H4 | [116] |
| | | MCF-7 and MDA-MB-231 cells | 5μM | Downregulated DNMT1, DNMT3a, DNMT3b | [117] |
| | | MCF-7 and MDA-MB-231 cells | 5μM | Decreased HDAC and HMT activity, downregulated *HDAC2* and *HDAC3, hTERT* expression | [112] |
| | | MCF-7 and MDA-MB-231 cells | 22 and 46 μM | Induced the hypomethylation of PTEN and RARbeta2 promoters with concomitant gene up-regulation | [118] |
| | | MCF-7 cells | 10 μM | Influenced the expression of COMT through methylation mechanisms | [119] |
| Anthraquinone | Aloe emodin  | MDA-MB-453, MDAMB-231 and MCF-7 cells | 10, 30 and 50 μM | Downregulated hTERT and c-myc expressions | [120] |

(*Continued*)


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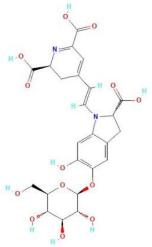
**Table 1** (Continued).

| Class | Phytochemical | BC Model | Dose | Mechanism | References |
|---|---|---|---|---|---|
| Alkaloid | Betanin  | MCF-7 cells | 20 μM and 40 μM | Repressed DNMT activity | [121] |

## Flavonoids

Among the several possibilities for the treatment of breast cancer, flavonoids, which belong to the polyphenol subgroup, show great therapeutic potential. Recent data indicate that beyond their antioxidant capabilities, flavonoids can directly engage with proteins, rendering them suitable small molecules for the control of enzymes, transcription elements, and cell surface receptors.[122] A number of flavonoids, including apigenin, genkwanin, silymarin, kaempferol, icariin, silibinin, and luteolin, have been found to repress cell proliferation and trigger apoptosis, cell cycle arrest and autophagy related cell death in breast cancer cells.[123–127] The potential of flavonoids to alter the epigenetic regulatory mechanisms in breast cancer is particularly intriguing. Nonetheless, the clinical use of flavonoids in cancer trials has been limited.[128] Phytochemicals, a family of pleiotropic compounds, have shown considerable promise in modifying several cancer processes through epigenetic mechanisms. The green tea polyphenol, epigallocatechin-3-gallate (EGCG), is one of the most widely studied flavonoids. The majority of studies indicate that the inhibitory mechanisms of EGCG include alterations in cell cycle progression, proliferation, and apoptotic cell death through the modulation of various signaling pathways. Besides these, another mechanism elucidating the diverse effects of EGCG in tumors is the epigenetic alteration through multiple processes.[129]

Meeran et al[106] found that EGCG and pro-EGCG blocked the transcription of hTERT (human telomerase reverse transcriptase) via epigenetic pathways in MCF-7 and MDA-MB-231 cells. At least largely due to DNA methyltransferase and histone acetyltransferase suppression, hTERT promoter hypomethylation and histone deacetylation downregulate hTERT expression. Furthermore, EGCG and pEGCG can alter the chromatin architecture of the hTERT promoter by reducing the levels of acetyl-H3, acetyl-H3K9, and acetyl-H4. EGCG and pEGCG prompted chromatin modifications that enhanced the association of numerous hTERT repressors such as E2F-1 and MAD1.[106]

Mirza et al[107] elucidated the efficacy of many phytochemicals, including EGCG, in reversing epigenetic alterations in breast cancer. This study demonstrated that EGCG administration significantly reduced the transcript levels of all the examined DNMTs. The levels of HDAC1, DNMT1, and MeCP2 proteins were significantly reduced as a result of these phytochemicals.[107]

A separate study demonstrated the capacity of EGCG to epigenetically induce the expression of tissue inhibitor of matrix metalloproteinase-3 (TIMP-3) in breast cancer cells. The molecular mechanism demonstrated that TIMP-3 suppression in breast cancer cells is facilitated by epigenetic regulatory mechanisms involving the enhanced activity of EZH2 and class I HDACs, irrespective of promoter DNA hypermethylation. Administration of GTP and EGCG to these cancer cells markedly decreased expression of EZH2 and class I HDAC proteins. Moreover, the transcriptional activation of TIMP-3 was correlated with reduced EZH2 localization and a higher level of H3K27 trimethylation at the TIMP-3 promoter, alongside a rise in histone H3K9/18 acetylation.[108] Steed et al[109] further revealed that EGCG reduced the levels of cIAP2, while augmenting the level of the pro-apoptotic marker caspase-7. Histone modifications also exhibited alterations, indicating the involvement of epigenetic factors in the variations in cIAP2 expression. A substantial reduction in AcH3 enrichment within the selected promoter region was observed in the two breast cancer cell lines after

the combinatorial administration of SAHA and EGCG. A notable reduction in HDAC activity was observed in all three breast cancer cell types, as well as in the MCF-7 cell line, when treated with SAHA and EGCG in combination. Notably, the combinatorial action of SAHA and EGCG enhanced the transcription of HMTs in MCF-7 cells.[109]

An example of a plant flavone is apigenin, which can be isolated from a variety of fruits and vegetables, such as parsley and celery. Apigenin is recognized as a powerful anticancer compound that interacts with oncogenes and obstructs DNA replication, induces apoptosis via caspase activation and ROS generation in diverse cancer types including colon, breast, skin, leukemia, prostate, and thyroid, thus inhibiting cancer progression.[130] In this context, preclinical findings have revealed that apigenin significantly influences cancer management by altering epigenetic processes and tumorigenesis. Apigenin treatment reduced cell growth and cell cycle arrest (G2/M) in MDA-MB-231 breast cancer cells. Immunoblot analysis revealed that apigenin modulated the expression of cell cycle markers, including cyclin A, cyclin B, CDK1, and p21WAF1/CIP1, and augmented its association with proliferating cell nuclear antigen (PCNA), thereby inhibiting cell cycle progression. Moreover, apigenin markedly suppresses HDAC activity and promotes histone H3 acetylation. Apigenin enhanced the acetylation of histone H3 in the p21WAF1/CIP1 promoter, leading to increased p21WAF1/CIP1 expression. In a tumor xenograft model, apigenin significantly inhibited tumor proliferation. As a result of apigenin treatment, cyclin A and cyclin B levels decreased in these xenograft model, but p21WAF1/CIP1 and acetylated histone H3 levels increased.[110] A separate study examined the anti-breast cancer efficacy of apigenin and its combination with Vorinostat against MDA-MB-231 cells. The findings indicated that apigenin decreased the expression of class I HDACs at both transcriptional and proteomic levels. Apigenin suppresses the enzymatic function of HDAC/DNMT and enhances HAT activity. Apigenin has been shown to affect miRNA expression by stimulating the tumor suppressor miR-200b and downregulating oncomiR-21. The combinatorial treatment repressed the growth of breast carcinoma cells by regulating the levels of epigenetic and apoptotic markers. The in vitro investigations were supported by in-silico findings, which investigated the mechanism of catalytic suppression by HDAC1 and HDAC3.[111]

Genistein is a bioactive isoflavone present in soybeans and in several soy-derived products. They are referred to as phytoestrogens or estrogenic substances with anti-cancer effects. Genistein exhibits dose-dependent epigenetic effects on DNMT suppression, gene transcription, and histone acetylation.[131] Mirza et al[107] also reported the ability of genistein to reverse epigenetic alterations in breast cancer. This study demonstrated that genistein therapy significantly reduced the expression levels of all the examined DNMTs. Significantly, these natural substances reduced the expression of HDAC1, DNMT1, and MeCP2 in breast cancer.[107]

Paul et al[112] revealed the synergistic benefits of genistein and sulforaphane in inhibiting breast tumors through epigenetic regulation. These findings demonstrated that the synergistic effect of genistein and sulforaphane significantly surpassed their individual dosages in enhancing apoptotic rates and reducing the colony-forming capacity of breast cancer cells. These phytochemicals augmented cell cycle arrest at G2-phase in MDA-MB-231 cells and at G1-phase in MCF-7 breast cancer cells. Moreover, the results indicated that the combination functioned effectively as an HDAC and HMT repressor. This combination also reduced the expression of HDAC2 and HDAC3 at both the gene and protein level. Likewise, the combination of genistein and sulforaphane is efficacious in diminishing hTERT levels, which are known to be activated upon KLF4 binding to its promoter region.[112]

## Terpenoids

Terpenoids, the predominant class of chemicals synthesized by plants, are formed from mevalonic acid and are distinguished by a molecular structure composed of isoprene units.[132] Terpenoids have considerable significance in biology, chemistry, and pharmacology. In addition to many other biological features, its anticancer effects are particularly remarkable. These effects include anti-proliferative, apoptosis-inducing, anti-migratory, and anti-metastatic properties.[133] Terpenoids are extensively found in nature and have also shown anti-breast cancer effects through the targeting of epigenetic markers. Parthenolide is a sesquiterpene lactone extracted from the medicinal plant, Tanacetum parthenium. Because of its multi-targeted modes of action, parthenolide has emerged as a potentially useful therapeutic compound. These mechanisms of action interfere with important signaling pathways that are associated with the proliferation and survival of cancer cells.[134] In recent years, the emergence of epigenetic therapy has unveiled a growing number of

parthenolide's epigenetic modifications in breast carcinoma. Carlisi et al[113] demonstrated that treatment with parthenolide alone activated the Akt/mTOR survival pathway and subsequently facilitated the nuclear transport of Nrf2, whereas administration with SAHA alone prompted autophagic effect. Nevertheless, when cancer cells were exposed to SAHA and parthenolide in combination, the impact of parthenolide on Akt/mTOR/Nrf2 signaling was mitigated by SAHA, and the autophagic action of SAHA was diminished by parthenolide. The combinatorial treatment with these two compounds resulted in GSH depletion, a decrease in MMP, cytochrome c release, and caspase-mediated apoptosis. Ultimately, they exhibited that the combination treatment preserved both the hyperacetylation of histones H3 and H4 caused by SAHA and the decreased expression of DNMT1 caused by parthenolide.[113]

Cucurbitacin B, another terpenoid, has similarly demonstrated an antiproliferative action against a variety of human breast cancer cells. Dittharot et al[114] investigated the effect of cucurbitacin B derived from *Trichosanthes cucumerina* on the promoter methylation levels of cyclin D1, c-Myc, and survivin in breast cancer. These findings demonstrate that cucurbitacin B can impede cellular proliferation in breast carcinoma cells. Oncogene promoters are typically hypomethylated in neoplastic cells. Following treatment with cucurbitacin B, there was an overexpression of DNMT1 and significant methylation in the promoters of target genes, resulting in the downregulation of these oncogenes.[114]

Thymoquinone is the active compound in black cumin seeds and has been utilized in various conventional healthcare systems for thousands of years. Thymoquinone is a natural phytochemical predominantly extracted from *Nigella sativa* (black cumin or black seed), utilized in various ancient traditional medicines, particularly within Ayurvedic and Unani practices across Arabian, South Asian, Mediterranean, and African countries. Numerous studies have demonstrated that thymoquinone has significant effects on the management of multiple illnesses, including cancers, by regulating diverse biochemical, molecular, and physiological processes.[135] Thymoquinone has been shown to suppress DNA replication and survival in cancerous cells by disrupting the DNA structure. Thymoquinone is a prospective anticancer agent as it can target several cell signaling pathways implicated in carcinogenesis, including the modification of epigenetic characteristics of cancer cells, including DNA methylation or demethylation and histone acetylation or deacetylation.[136] Parbin et al used an in vitro cell culture investigation to examine the effects of these interactions in addition to an in-silico technique to shed light on the basic interactions of thymoquinone with HDAC. Combined analysis of docking and molecular dynamics modeling revealed the fundamental engagement and stability of thymoquinone with HDACs. Thymoquinone demonstrated HDAC repression at an $IC_{50}$ of 34 mM in a time-dependent manner. MCF-7 cells subjected to thymoquinone treatment for 24 h demonstrated a substantial reduction in HDAC activity compared with the control. A significant alteration in HDAC activity was noted following thymoquinone exposure for 48 and 72 h.[115]

## Isothiocyanates

Cruciferous vegetables contain abundant bioactive compounds, particularly isothiocyanates, which offer various health benefits. Isothiocyanates are the hydrolytic intermediates of glucosinolates. Some examples of isothiocyanates include sulforaphane, allyl isothiocyanate, benzyl isothiocyanate, and phenethyl isothiocyanate.[137] Despite exhibiting numerous features, the most significant attribute of sulforaphane is its anticancer potential. Sulforaphane prevents tumor progression by suppressing the growth of cancer cells, halting the cell cycle, and promoting apoptosis.[138–140] Sulforaphane also offers cancer prevention through the modification of many epigenetic and non-epigenetic processes, as evidenced in multiple cancer types. Sulforaphane inhibits HDAC function in malignant cells. Suppression of histone deacetylase is crucial for cancer prevention because it amplifies various mechanisms, including apoptosis and cell cycle arrest.[141–143] Moreover, sulforaphane inhibits histone phosphorylation by augmenting the activity of phosphatases, particularly PP1β and PP2α.[144] The epigenetic regulation of sulforaphane in breast cancer was evaluated in multiple research.[145]

In MCF-7 and MDA-MB-231 cells, sulforaphane exposure suppressed hTERT activity in a dose- and time-responsive manner. DNMTs, particularly DNMT1 and DNMT3a, were reduced in sulforaphane-treated cells, indicating that sulforaphane may suppress hTERT expression by influencing epigenetic mechanisms. Decreased DNMTs expression in response to sulforaphane induces site-dependent CpG demethylation, predominantly inside the first exon of the hTERT gene, thereby enhancing CTCF binding linked to hTERT repression. Immunoprecipitation study of the hTERT promoter shown that sulforaphane elevated the levels of acetyl-H3, acetyl-H3K9, and acetyl-H4, while concurrently reducing the

inactive chromatin markers trimethyl-H3K9 and trimethyl-H3K27. Sulforaphane-mediated hyperacetylation enhances the association of numerous hTERT repressor proteins, including MAD1 and CTCF, with the hTERT regulatory area. CTCF depletion with siRNA diminished the SFN-mediated reduction in hTERT transcription in these breast carcinoma cells. Moreover, decreased hTERT expression promotes the apoptotic stimulation in breast carcinoma cells.[116]

A separate study conducted by Royston et al examined the combinatorial effect of withaferin and sulforaphane on breast cancer cell growth and HDAC1 and DNMTs activity. This combination reduced the enzymatic function of DNMTs in both the breast cancer cell lines. The combination therapy of withaferin and sulforaphane in MCF-7 cells demonstrated superior efficacy in inhibiting DNMT activity compared to sulforaphane alone; however, withaferin alone did not exhibit similar effectiveness. In MDA-MB-231 cell line, the combinatorial treatment effect was markedly significant, surpassing that of withaferin alone. Sulforaphane, in conjunction with withaferin, downregulated the expression levels of DNMT1, DNMT3A, and DNMT3B in both the cancer cells. Furthermore, combination therapy markedly reduced HDAC1 levels in MCF-7 and MDA-MB-231 breast cancer cell lines.[117]

A different combination of genistein and sulforaphane demonstrated breast tumor suppression through an epigenetic regulatory mechanism. This combination reduced the mRNA and protein levels of HDAC2 and HDAC3. The conjunction of genistein and sulforaphane effectively downregulates hTERT levels, which are activated by KLF4 binding to its promoter region.[112]

Lubecka-Pietruszewska et al[118] demonstrated that sulforaphane induces hypomethylation of PTEN and RARbeta2 promoters, resulting in enhanced gene regulation in breast cancer MCF-7 and MDA-MB-231 cells. The amalgamation of sulforaphane and ClF amplifies these effects, leading to augmentation of cell growth inhibition and apoptotic effects in breast cancer cells.[118] Cao et al[119] examined the metabolic alterations in ER-positive breast cancer MCF-7 cells exposed to estradiol (E2) and sulforaphane to determine critical metabolite profiles that could elucidate the mechanisms behind the anticancer effects of sulforaphane. These findings indicate that the capacity of sulforaphane to epigenetically regulate COMT expression subsequently affects E2 metabolism.[119]

## Alkaloids and Quinones

Quinones are chemical compounds that are distinguished by their cyclic diketone structure. Anthraquinones originating from the rigid, planar tricyclic aromatic structure of anthracene (3), possess two carbonyl groups located at the 9-, 10-positions and the 1-, 4-positions, respectively.[146]

Anthraquinones are a class of natural substances that are distinguished by their extensive structural diversity, significant biological activity, and minimal toxicity. Aloe emodin (anthraquinone derivative) is a phytocompound present in the roots and rhizomes of several plants. This phytochemical has demonstrated growth-inhibitory, antiangiogenic, and antiproliferative properties, along with its capacity to reverse multidrug resistance in cancerous cells. Aloe emodin is a broad-spectrum suppressive agent of cancer cells that has been shown to have anticancer properties in a variety of biological pathways, particularly epigenetic control.[147,148] A study by Wang et al[120] shown that 48 hours of aloe emodin administration leads to telomere shortening and telomerase suppression in breast cancer cells. The expression of hTERT was inhibited by the induction of E2F1 and deactivation of c-Myc proteins. Marked demethylation of CpG islands in the hTERT promoter was found in both breast cancer cells. Aloe emodin contended with dNTP for binding to the enzyme's active site. Aloe emodin functioned as a stabilizer of telomeric G-quadruplex structures, as demonstrated by titration assays and FRET investigations.[120]

Alkaloids are a category of natural chemicals that have garnered significant interest owing to their possible therapeutic applications. Alkaloids frequently influence various critical cellular systems associated with cancer growth including epigenetic regulation. Multitargeting capabilities can provide substantial advantages to alkaloids in surmounting resistance mechanisms. Alkaloids have consistently affected cancer pharmacotherapy and scientific research. Several alkaloids are currently used as chemotherapeutic drugs for cancer treatment.[149,150] A phase 2 study revealed that the combined administration of vinflunine and trastuzumab showed significant efficacy in treating EGFR-2 positive metastatic breast cancer. Furthermore, vinflunine demonstrated efficacy in a phase 3 trial, although its anticancer effectiveness was not superior to that of other alkylating agents.[151] Berberine is notably efficacious against colorectal adenomas and acts as a chemopreventive agent, reducing the recurrence of colorectal adenomas and polypoid lesions when ingested in dietary form (0.3 g twice daily).[152,153]

Betanin, a water-soluble nitrogenous substance derived from beetroot, possesses several advantageous biological properties, including antioxidant, anti-inflammatory, and anti-tumor effects, attributed to its aromatic amino molecular constituents. Furthermore, it affects the mechanisms of altered cells by slowing their development, promoting apoptosis through the upregulation of specific apoptotic proteins, and inducing alterations in membrane integrity, including apoptotic pathways.[154,155] Paluszczak et al[121] assessed the impact of various dietary phytochemicals, including betanin, on the expression of DNMTs in human breast cancer MCF7 cells as well as their influence on DNA and histone H3 methylation. The results indicated that betanin reduced DNA methyltransferase activity in breast cancer MCF-7 cells at concentrations of 20 μM and 40 μM.[122]

## Limitations and Challenges

This review focused on the anti-breast cancer potential of phytochemicals by targeting on epigenetic regulatory markers; nevertheless, it is important to note that there are several limitations. The low solubility, high metabolism, and rapid elimination rate of many phytochemicals result in poor bioavailability.[156] In order to improve solubility and stability, liposomal and nanoformulations based delivery methods have been employed. These drug delivery methods enhance pharmacokinetics, improved absorption and prevent drug degradation.[157] To confirm the effectiveness of phytochemicals in breast cancer treatment, more extensive and rigorous clinical trials are needed. Limited sample size and inadequate standardization are common problems in contemporary research. To address these problems, greater industry-researcher cooperation should be encouraged, and phytochemicals should be incorporated into traditional treatments to enable more thorough studies and improved clinical trials.[158] Dose optimization is crucial for phytochemicals because, despite their natural origin, they can have adverse effects if used in high dose range. Determining the ideal dosage that optimizes effectiveness while limiting toxicity is crucial for safe and long-term use.[159] The quick metabolism and excretion of phytochemicals from the body limit their potential as medicinal drug or formulation. Many of these phytochemicals including polyphenols, flavonoids, terpenoids and alkaloids, undergo substantial metabolism by cytochrome P450 and phase II conjugation enzymes in the liver and gastrointestinal tract. Drug delivery methods have been revolutionized by nanotechnology, significantly improving the stability, solubility, and bioavailability of phytochemicals employed in breast cancer treatment.[160] Targeting overexpressed proteins and enhancing therapeutic results in breast cancer can be accomplished in various ways via combination therapy, which combines phytochemicals with traditional cancer treatments. Altogether, to advance the use of phytochemicals as viable drug candidate options for breast cancer therapy, it is imperative to address these limitations through rigorous clinical studies, enhanced drug delivery systems, and standardized extraction techniques.[161]

## Conclusion and Future Directions

This study emphasizes the potential of phytochemicals including flavonoids, terpenoids, isothiocyanates, quinones, and alkaloids in mitigating the epigenetic instabilities associated with breast cancer, along with the prospective therapeutic advantages that may arise from further exploration in this domain. Various studies have underscored the potential of phytochemicals to inhibit breast cancer carcinogenesis by regulating epigenetic modifications through the targeting of DNMTs, HDACs, HMTs, and other indicators. The investigated phytochemicals appeared to regulate epigenetic alterations in vitro and in certain in vivo cancer models, thereby limiting or reducing cancer cell survival, metastasis, and angiogenesis.

Nonetheless, limitations persist in utilizing these phytochemicals as chemopreventive agents, especially concerning the effective concentration range of individual natural product compounds in preliminary in vitro models, which complicates the identification of optimal and biocompatible concentrations in in vivo models. Moreover, in many instances, the in vivo outcomes are not as favorable or encouraging as those observed in in vitro investigations; hence, they are not suitable for clinical trials. Furthermore, a detailed examination of the proper validation and administration routes for natural products is necessary because of their reactivity and ambiguous characteristics. Future research should concentrate on clinical studies, the optimization of drug delivery technologies, including nanoparticles, micelles, and liposomes, and synergistic effects of phytochemicals in conjunction with conventional therapies to enhance efficacy. Phytochemical therapy combined with genetic profiling and biomarker identification may allow for therapy customization, optimize outcomes, reduce toxicity and provide

a cost-effective approach for low-income populations. To enhance breast cancer management, research into phytochemical mode of action, dosage strategies, and dietary inclusion is prioritized.

## Data Availability Statement

Not applicable as this is a review article.

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## Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest.

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