

Reversing DNA repair gene hypermethylation in breast cancer: The role of phytochemicals (Review)

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Received July 31, 2025; Accepted January 15, 2026

DOI: 10.3892/wasj.2026.432

Abstract. Breast cancer (BC) is one of the most prevalent and lethal malignancies affecting women globally, and its progression is influenced by both genetic and epigenetic factors. Among the epigenetic modifications, the DNA hypermethylation of DNA repair genes has been linked to the progression of breast cancers. Notably, these epigenetic modifications can be reversed through natural dietary interventions. The present review discusses the role of natural phytochemicals, plant-based compounds capable of reversing epigenetic modifications, which provide a promising alternative to conventional cancer therapies. Compounds such as genistein, curcumin, epigallocatechin gallate, sulforaphane, quercetin and apigenin have demonstrated the ability to reverse hypermethylated DNA repair genes, thereby restoring normal repair processes and improving cellular sensitivity to therapeutic agents. The present review emphasizes the importance of phytochemicals in causing epigenetic modifications and their potential as safer, more focused, affordable and low-toxicity treatment options that could transform breast cancer management.

Contents

1. Introduction
2. Epigenetic modifications in breast cancer
3. Hypermethylated DNA repair genes in breast cancer
4. Phytochemicals causing the reversal of hypermethylation in DNA repair genes
5. Critical analysis, limitations and future directions
6. Conclusion

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Key words: breast cancer, phytochemicals, epigenetic modifications, DNA repair genes, tumor suppressor gene

1. Introduction

Cancer is a medical condition in which somatic cells undergo genetic or epigenetic changes, causing aberrant cell proliferation that can spread to other parts of the body (1). Breast cancer (BC) is one of the most detrimental and heterogeneous diseases in modern times, affecting a large number of individuals globally. It is the second most common type of cancer among females worldwide, accounting for 685,000-related deaths (16% of the total female cancer-related deaths) (2,3). In India, BC has become the most frequent type of cancer among women, particularly in younger age groups (4). BC is a heterogeneous disease with various clinical, molecular and biological features; some tumors exhibit a high estrogen receptor expression, which influences the methods of treatment, as well as the prognosis of patients (5). Numerous factors influence the development of breast tumors, as illustrated in Fig. 1.

The processes of epigenetic modification [such as DNA methylation, the post-transcriptional modification of histone proteins and regulation through non-coding RNAs (ncRNAs)] are critical in controlling the normal functions of a cell throughout the developmental and differentiation states (6). These processes also help cells adapt to environmental changes, including dietary changes or exposures to chemicals or radiation. It is known that the action of cigarette smoke and hormones is responsible for inducing epigenetic changes. However, aberrant epigenetic changes lead to the development of cancer (7). A key mechanism of gene inactivation in breast cancer is promoter CpG island hypermethylation, which targets CG-rich regions associated with promoters of protein-coding genes (8). This epigenetic damage inactivates several cellular processes, such as DNA repair, leading to mutator pathways. Notably, patients with breast cancer frequently exhibit hypermethylation of DNA repair genes, including breast cancer gene 1 (*BRCA1*), breast cancer gene 2 (*BRCA2*), Abraxas1/*BRCA1* A complex subunit (*ABRA1*), *MRE11*, *BRCA1*-associated RING domain 1 (*BARD1*), mediator of DNA damage checkpoint 1 (*MDC1*), ring finger protein (*RNF168*), *UBC13*, partner and localizer of *BRCA2* (*PALB2*), *RAD50*, *RAD51*, *RAD51C*, *RNF8*, *NBS1*, *CtIP* and *ATM*. The ability of cells to respond to DNA damage is disrupted by epigenetic alterations, resulting in increased tumor growth. Given that epigenetic alterations are potentially reversible, they are an attractive target for the

development of treatments (9). Surgical intervention, chemotherapy and radiation therapy continue to form the backbone of treatment options for breast cancer; however, there are limitations to their effectiveness, including dose-dependent toxicity, limited selectivity, the potential for treatment resistance and significant side-effects leading to the damage of non-cancerous cells. Metastatic disease remains one of the key challenges of treatment and is the principal cause of mortality in women with breast cancer (10). Dietary phytochemicals (natural compounds derived from plants) are being recognized as potentially effective chemopreventive and therapeutic agents for the treatment of breast cancer due to their low toxicity levels, minimal side effects, affordability, and ease of access in comparison to synthetic pharmaceuticals (11). Natural plant extracts, such as *Piper longum*, *Curcuma longa*, *Withania somnifera*, *Nigella sativa*, *Amora rohituka* and *Dimocarpus longan* contain anticancer compounds with demonstrated anti-BC characteristics (12). This approach is particularly promising as epigenetic changes, unlike genetic mutations, are reversible and influence early cancer progression. Although this exhibits immense potential, a knowledge gap currently exists in the research of phytochemicals and their role in epigenetics in BC. The present review thus aimed to fill this gap in the current literature. The present review discusses the findings from the most contemporary literature available with regard to the reversals of hypermethylation in DNA repair genes by phytochemicals and their mechanisms of action in BC.

2. Epigenetic modifications in breast cancer

The term 'epigenetics', originally used by Waddington in 1942, describes genetic, reversible modifications in gene expression without changing the DNA sequence (13). Breast cancer often involves epigenetic reprogramming despite its genetic origin (14). These epigenetic alterations include DNA methylation, histone modifications and ncRNA expression (15), as illustrated in Fig. 2.

DNA methylation. DNA methylation is an epigenetic process linked to cell development and various critical activities. Aberrant methylation patterns have been observed in cancer cell genomes (16). It is a reversible process in which methyl groups are introduced to the fifth carbon position of the cytosine from S-adenosyl methionine. Of note, two types of methylation exist: Maintenance methylation (when CpG dinucleotides on a single strand of DNA are methylated) and *de novo* methylation (when CpG dinucleotides on both of the strands are unmethylated) (17). DNA methylation is a reversible process facilitated by DNA methyltransferases (DNMTs). *DNMT1*, *DNMT2*, *DNMT3A* and *DNMT3B* encode proteins with different functional specificities. As previously demonstrated, two patterns of aberrant methylation have been identified: Global hypomethylation throughout the genome and hypermethylation at CpG islands within promoter regions (18,19).

DNA hypomethylation. Global DNA hypomethylation, a cancer hallmark coexisting with focal CpG island hypermethylation, involves genome-wide loss of cytosine methylation (20).

Mechanistically driven by an impaired *DNMT1* maintenance, deregulated *DNMT3A/3B* activity and aberrant TET-mediated demethylation, and reduced 5-methylcytosine levels are associated with tumor progression and a poor survival (21). Functionally, hypomethylation destabilizes heterochromatin, causing chromosomal instability. It reactivates transposable elements, inducing mutagenesis, and aberrantly activates oncogenes and metastasis-promoting genes (22).

DNA hypermethylation. The aberrant addition of methyl groups to cytosines in CpG dinucleotides, particularly within promoter-associated CpG islands, is a hallmark epigenetic alteration in cancer, causing stable gene silencing without altering the DNA sequence. In cancer, ~5-10% of promoter CpG islands become hypermethylated, repressing tumor suppressor genes involved in cell cycle control, DNA repair and apoptosis (e.g., *CDKN2A*, *MLH1* and *BRCA1*), contributing to oncogenesis (23,24). These reversible changes provide targets for epigenetic therapy, as well as biomarkers for cancer diagnosis, prognosis and therapeutic stratification (25). Both modifications have commonly been documented in BC and are greatly affected by environmental factors such as aging, stress, alcohol consumption and air pollution (26).

Histone modifications. DNA wraps around a histone octamer in the nucleus. The histone tails are sensitive to several covalent posttranslational modifications (PTMs) that regulate chromatin state. Changes in histone PTM patterns have been widely associated with cancer (27). Key modifications include the following:

Histone phosphorylation. The addition of phosphate groups promoting chromatin relaxation, critical for DNA damage responses (notably γ -H2AX at Ser139), transcriptional regulation and mitotic chromosome condensation (28).

Histone acetylation. Acetylation by histone acetyltransferases leads to decreased histone-DNA interaction, creating euchromatin. This is strongly associated with gene transcription activation. Histone deacetylases remove acetyl groups, compacting chromatin and inhibiting transcription (29).

Histone ubiquitylation. H2A ubiquitination (Lys119) usually causes gene repression, while H2B ubiquitination (Lys120) aids transcription and is required prior to methylation (30).

Histone sumoylation. SUMO conjugation drives transcriptional repression and chromatin compaction, often antagonizing acetylation and ubiquitination (31).

Histone methylation. This occurs on lysine and arginine residues with variable outcomes. Activating markers include H3K4me3; repressive markers include H3K9me3 and H3K27me3. Histone methyltransferases and demethylases control methylation dynamics (32).

ncRNA expression. Non-coding RNAs lack protein-coding ability, and ~52% of the human genome has been encoded, although only 1.2% codify proteins. ncRNAs are categorized into 'housekeeping ncRNAs' (tRNAs, rRNAs, snRNAs and snoRNAs) and 'regulatory ncRNAs' (lncRNAs, >200 nucleotides; and short ncRNAs, <200 nucleotides) (33,34). They play a critical role in controlling signaling pathways linked to tumor development, spread and therapeutic resistance (35).

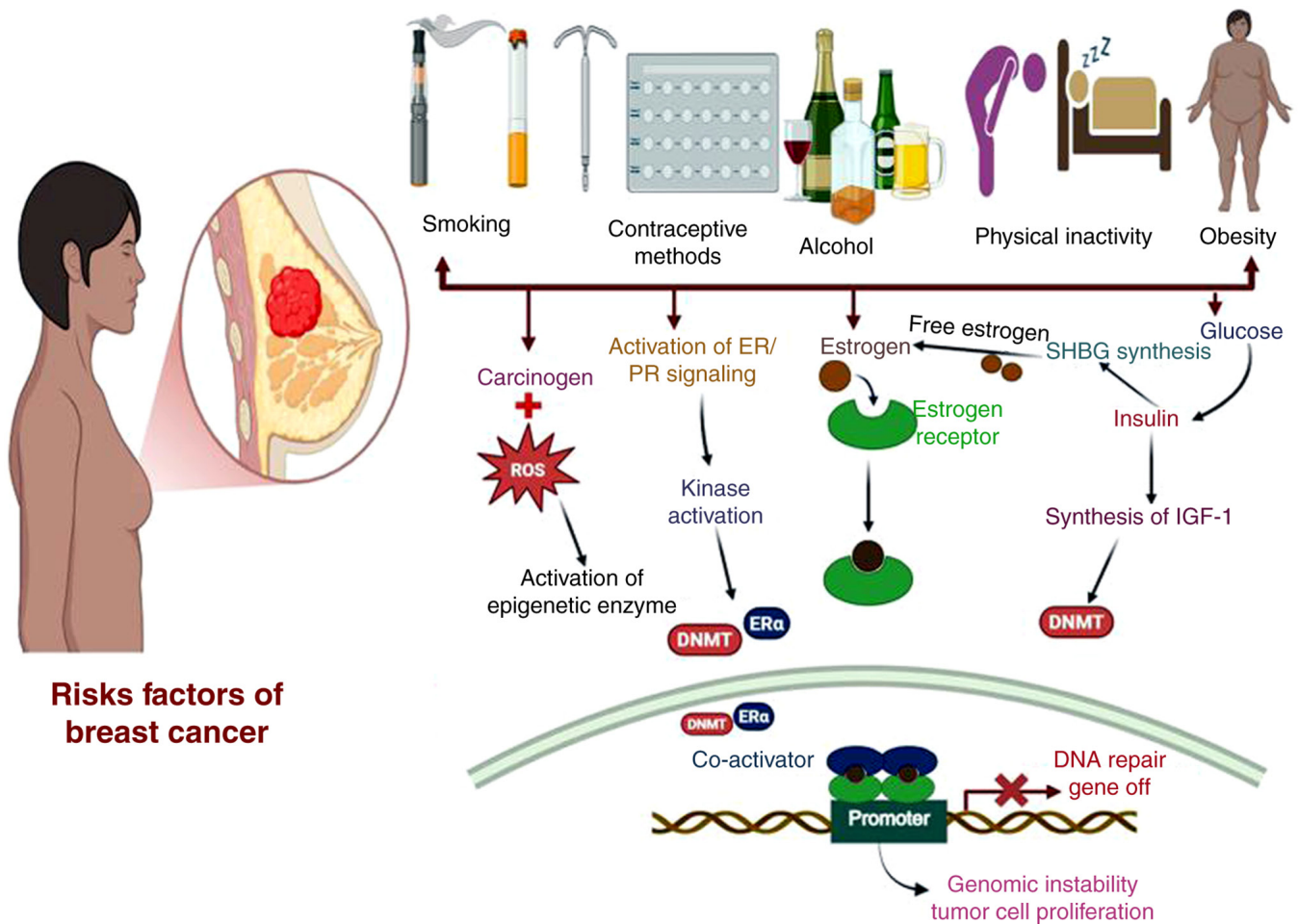


Figure 1. Major risk factors involved in the development of breast cancer.

Short non-coding RNAs (snRNAs). snRNAs are a diverse group under ~200 nucleotides, including microRNAs (miRNAs), small interfering RNAs (siRNAs) and PIWI-interacting RNAs (piRNAs), that regulate gene expression primarily at the post-transcriptional level. These molecules contribute to chromatin modulation, cell differentiation, stress responses and disease processes (36,37).

Long non-coding RNAs (lncRNAs). These RNA species are longer than 200 nt without protein-coding potential (33). The human transcriptome has ~10,000 lncRNAs. They function as oncogenes or tumor suppressors, affecting cancer cell growth, apoptosis, metabolic processes, epithelial-mesenchymal transition (EMT), metastasis and treatment resistance. lncRNAs are usually exclusive to a particular tumor subtype, and BC exhibits abnormal expression levels of several lncRNAs (34,38).

3. Hypermethylated DNA repair genes in breast cancer

DNA repair processes play a crucial role in preserving genomic stability and limiting the growth of mutations that may lead to cancer (39). In BC, these mechanisms are frequently affected not only by genetic mutations, but also by epigenetic alterations, particularly promoter hypermethylation, that can silence essential DNA repair genes without affecting their DNA sequence (40). In BC, promoter hypermethylation is known to

silence certain key DNA repair genes, as discussed below and presented in Table I (41-67).

MutS homolog 6 (MSH6). MSH6 partners with MSH2 to form the MutSα complex, which recognizes and repairs base-base mismatches during DNA replication. In BC, promoter hypermethylation silences MSH6 expression in both ductal carcinoma *in situ* (DCIS) and invasive carcinomas, compromising mismatch repair (MMR) fidelity and elevating mutation rates (41,42). TCGA bioinformatic analyses have demonstrated inverse correlations between promoter methylation and gene expression, establishing MSH6 loss as an early driver of genomic instability in breast tumorigenesis (42,68).

MDC1. MDC1 functions as a molecular scaffold at DNA double-strand breaks (DSBs), binding phosphorylated histone H2AX (γH2AX) and orchestrating the recruitment of the MRN complex, ATM kinase, RNF8, BRCA1 and 53BP1. Promoter-associated transcriptional downregulation in BC is associated with genomic instability, radioresistance, nodal metastasis and adverse clinical outcomes. *In silico* network analyses position MDC1 as a central signaling hub within the ATM-BRCA1-RNF8 axis, where its functional loss accelerates DNA damage accumulation and impairs checkpoint responses (43,44).

Epigenetic modifications in breast cancer

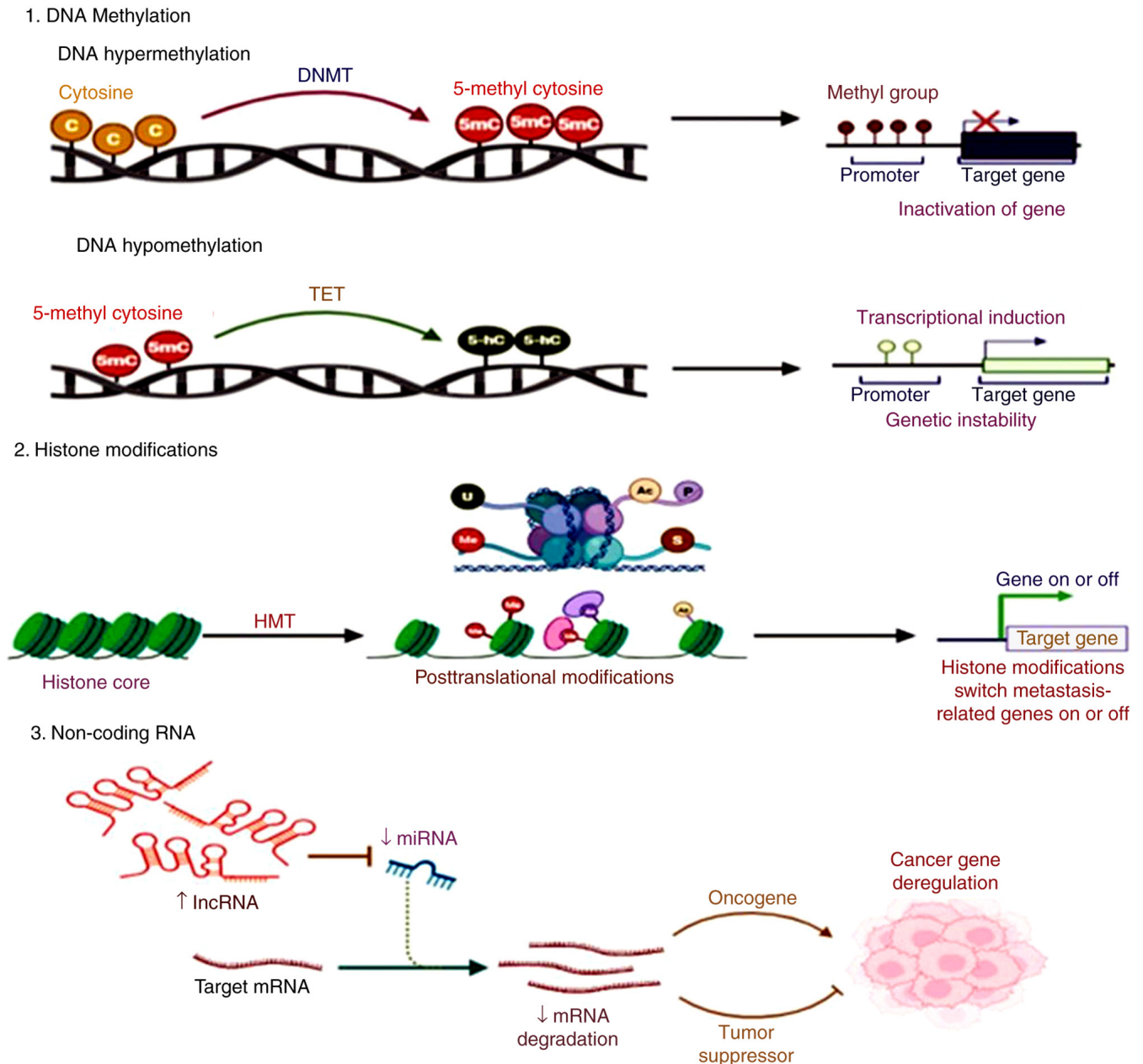


Figure 2. Epigenetic regulatory mechanisms in breast cancer: DNA methylation, histone modifications and non-coding RNAs. DNMT, DNA methyltransferase.

RNF168. *RNF168* (3q29), an E3 ubiquitin ligase, catalyzes histone H2A ubiquitination at lysines 13 and 15, facilitating the recruitment of 53BP1, *BRCA1* and *PALB2* to DSB sites for homologous recombination (HR). TCGA-BRCA and METABRIC dataset analyses reveal that promoter hypermethylation suppresses *RNF168* expression, resulting in HR deficiency, heightened sensitivity to DNA-damaging agents and potential endocrine therapeutic resistance (45,46). TCGA data indicate *RNF168* overexpression in *BRCA1*-mutant BCs and in BCs with HR deficiency (HRD), driven mainly by copy-number amplification and enriched in basal-like tumors. A high expression of *RNF168* is associated with HRD mutational signature 3 and a worse survival, while lower *RNF168* levels are associated with improved outcomes and a reduced risk of developing BC in *BRCA1* mutation carriers (69).

RAD51. *RAD51* (17q23) is the central recombinase in homologous recombination repair, mediating strand invasion and the resolution of HR intermediates. Integrative analyses of TCGA and DNA methylation arrays identify promoter hypermethylation-mediated *RAD51* silencing predominantly in triple-negative breast cancer (TNBC), where it is associated with HR-deficiency molecular signatures and reduced transcript abundance (47,48). TCGA and drug-response datasets demonstrate that a low expression of *RAD51* is associated with a poor overall survival, but increased sensitivity to DNA-damaging chemotherapy, particularly in BC, reflecting homologous recombination deficiency that can be therapeutically exploited (70).

MLH1. *MLH1* heterodimerizes with *PMS2* to execute mismatch repair, correcting replication errors including

Table I. Role of hypermethylated DNA repair genes in breast cancer.

Gene	Function in DNA repair	Impact of hypermethylation in breast cancer	Locus	(Refs.)
<i>MSH6</i>	Forms MutS α complex with <i>MSH2</i> to repair base mismatches and small insertion/deletion loops, preserving genomic stability.	Promoter hypermethylation in both DCIS and IDC leads to early gene silencing, impairing mismatch repair and promoting genomic instability.	2p16	(41,42)
<i>MDC1</i>	Scaffold protein in DNA damage response, binds γ H2AX at DSBs, recruits MRN complex, ATM, RNF8, BRCA1, 53BP1, amplifies ATM signaling	Hypermethylation/downregulation linked to radioresistance, nodal failure, poor prognosis, and genomic instability	6p21.3	(43,44)
<i>RNF168</i>	E3 ubiquitin ligase; ubiquitinates H2A at K13/K15, recruits 53BP1, BRCA1, PALB2, promotes homologous recombination (HR)	Hypermethylation may reduce expression, impair DNA repair, increase sensitivity to DNA damage, or drive endocrine resistance	3q29	(45,46)
<i>RAD51</i>	Key protein in homologous recombination repair (HRR), mediates HR intermediate formation and resolution	Promoter hypermethylation causes gene silencing, seen in TNBC, linked to HR deficiency, and poor prognosis	17q23	(47,48)
<i>MLH1</i>	Key component of the mismatch repair (MMR) system, forms a heterodimer with <i>PMS2</i> to correct DNA replication errors	Promoter hypermethylation silences the gene, seen in ~43.5% of breast cancers; linked to advanced stages, genomic instability, and disease progression	3p22.2	(49,50)
<i>RAD50</i>	key element of the MRN complex that enables checkpoint activation, telomere maintenance, and DSB repair through HR and Non-Homologous End Joining (NHEJ)	Promoter hypermethylation reduces expression, linked to impaired DNA repair and increased breast malignancy risk	5q31.1	(51,52)
<i>MRE11</i>	MRN complex member; detects DSBs, initiates end resection, activates ATM, supports HR/NHEJ	Reduced expression (~31%) impairs repair; linked to BRCA1/ATM deregulation and increased risk	11q21	(53,54)
<i>BRCC36</i>	BRCA1-A complex DUB; removes K63-linked ubiquitin, essential for BRCA1 activation and 53BP1 recruitment	Overexpressed in breast tumors; may disrupt BRCA1 function; silencing increases radiosensitivity	Xq28	(55,56)
<i>BRCA1</i>	HR repair; RAD51 recruitment	Well-established promoter hypermethylation in sporadic breast cancer \rightarrow BRCA1 silencing & HRD	17q12-21	(57-59)
<i>BRCA2</i>	HR mediator; loads RAD51	Promoter hypermethylation in subsets, including DCIS \rightarrow reduced HR	13q12	(41,59, 60)
<i>PALB2</i>	Bridges <i>BRCA1</i> and <i>BRCA2</i> ; facilitates RAD51 loading, thereby enabling HR repair of DSBs.	Rare but reported promoter methylation \rightarrow reduced HR competence in subsets	16p12.2	(61,62)
<i>ATM</i>	Serine/threonine kinase that senses DSBs and activates DDR: phosphorylates key effectors(e.g., p53, BRCA1, CHK2), triggering cell-cycle checkpoints, DNA repair, or apoptosis.	Hypermethylation \rightarrow downregulation, larger tumors and an advanced stage	11q22.3	(63-65)
<i>RNF8</i>	E3 ligase promotes K63-Ub chains to recruit repair proteins	Direct methylation is rare; aberrant expression, mostly upregulation, contributes to EMT and chemoresistance	6p21.3	(66,67)

MSH6, MutS homolog 6; *MDC1*, mediator of DNA damage checkpoint 1; *RNF*, ring finger protein; DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma.

base mismatches and insertion-deletion loops. Promoter hypermethylation silences *MLH1* in ~43.5% of BCs, as demonstrated by multi-platform *in silico* analyses

demonstrating strong inverse methylation-expression correlations (49,50). The loss of *MLH1* precipitates MMR deficiency, microsatellite instability, elevated tumor

mutational burden, and the progression toward advanced, genomically unstable disease states (71).

RAD50. *RAD50* is a core part of the ATPase-containing MRN complex, which is critical for the recognition of DSBs, the activation of ATM, telomere maintenance, and selection of DSB repair pathways between HR and non-homologous end joining (NHEJ) repair (51,52). Multi-omics analysis has demonstrated that the hypermethylation of promoters suppresses *RAD50* transcription and disrupts the stability of the MRN complex, resulting in improper DSB signaling, genomic instability and an increased risk of developing BC. *RAD50* suppression is particularly implicated in TNBC carcinogenesis and chemotherapeutic resistance (72).

MRE11. MRE11 provides the nuclease activity within the MRN complex, initiating DNA end resection, activating ATM-dependent checkpoints, and supporting both HR and NHEJ pathways (53,54). Previously, TCGA-BRCA analyses demonstrated a reduced MRE11 expression in a subset of breast cancers, while copy-number alterations affecting MRE11 were observed at a lower frequency. A low expression of *MRE11* was shown to be associated with differential gene expression and pathway enrichment indicating impaired ATM signaling and homologous recombination, consistent with genomic instability and aggressive tumor phenotypes (73).

BRCC36 (BRCC3). *BRCC36* (Xq28) is a K63-specific deubiquitinase within the BRCA1-A complex that removes ubiquitin chains to fine-tune BRCA1 activation and regulate 53BP1 recruitment during DSB repair pathway selection (55,56). TCGA-BRCA transcriptomic data have revealed the dysregulation/overexpression of *BRCC36* in BC (74). Network and pathway analyses have linked altered *BRCC36* levels to a perturbed BRCA1-A complex function and ubiquitin-dependent DSB repair, with computational models suggesting the modulation of DSB pathway choice and potential radiosensitization upon *BRCC36* inhibition (74).

BRCA1. *BRCA1* is a tumor suppressor orchestrating homologous recombination, cell cycle checkpoints, and transcriptional regulation. In sporadic BC, promoter hypermethylation constitutes a major mechanism of *BRCA1* silencing, producing HR deficiency, triple-negative phenotype enrichment, and synthetic lethality with PARP inhibitors (57-59). Integrated bioinformatics analyses of BC cohorts have demonstrated that *BRCA1* promoter hypermethylation is tightly linked to reduced *BRCA1* expression and homologous-recombination-deficient genomic and transcriptomic signatures, closely mirroring *BRCA1*-mutated tumors and supporting epigenetic *BRCA1* silencing as a functional driver of HR deficiency (75).

BRCA2. *BRCA2* functions as a tumor suppressor that regulates *RAD51* nucleoprotein filament assembly during HR-mediated DSB repair. Promoter hypermethylation represents an early and frequent event in breast carcinogenesis, detected even in DCIS, where it induces gene silencing, genomic instability and repair incompetence (41,60). TCGA-based methylation and integrative bioinformatic analyses link *BRCA2* promoter

hypermethylation in pre-invasive breast lesions to homologous recombination deficiency signatures and increased genomic instability (76).

PALB2. *PALB2* serves as a molecular bridge connecting *BRCA1* and *BRCA2*, facilitating *RAD51* loading and enabling efficient HR. While germline *PALB2* mutations confer hereditary breast cancer susceptibility, somatic promoter hypermethylation also suppresses expression in a subset of sporadic cases, resulting in HR deficiency and disease progression (61,62). Bioinformatics methylome profiling in early-onset BC samples has revealed increased methylation at *PALB2* promoter-associated CpG probes in tumor DNA compared with matched blood DNA, consistent with potential epigenetic modulation of *PALB2* expression in a subset of cases (77).

ATM. *ATM* encodes a master checkpoint kinase that phosphorylates numerous substrates, including *p53*, *BRCA1* and *CHK2* in response to DSBs, orchestrating cell cycle arrest and repair pathway activation. Promoter hypermethylation reduces *ATM* expression in BC, and is associated with a larger tumor size, advanced stage and an older patient age (63-65). TCGA-based repair signature analyses have associated *ATM* silencing with checkpoint deficiency and impaired DSB repair capacity, supporting its utility as a prognostic and predictive biomarker in sporadic disease (78).

RNF8. *RNF8* (6p21.3) is an E3 ubiquitin ligase initiating the ubiquitin cascade required for *BRCA1* and 53BP1 recruitment to DSBs, promoting high-fidelity HR, while suppressing mutagenic NHEJ. Paradoxically, *RNF8* is frequently overexpressed in BC, where it drives EMT, metastasis and chemoresistance through the activation of the Twist and β -catenin signaling pathways (66,67). Bioinformatics analyses of BC datasets has demonstrated that *RNF8* promoter methylation is rare; however, *RNF8* is transcriptionally dysregulated and embedded in DDR networks linked to *BRCA1-RAD51-ATM* signaling, indicating an altered homologous recombination and DDR pathway balance (79).

4. Phytochemicals causing the reversal of hypermethylation in DNA repair genes

The hypermethylation of functionally significant genes has been observed in breast carcinoma; silencing of these genes is crucial for carcinogenesis and tumor development (40). Treatment options for BC include surgery, chemoradiotherapy, hormone treatments, monoclonal antibodies, immunotherapy, nanomedicines and small molecule inhibitors. Conventional medicines have limitations, including resistance, a low efficacy and adverse effects, which limit their clinical uses. Anticancer medications derived from plants that have limited or no adverse effects may be a beneficial alternative to chemotherapy (12). The 'phyto' in the word phytochemicals is derived from the Greek word, meaning 'plant'. Therefore, phytochemicals are plant compounds (80). Phytochemicals are plant-based bioactive molecules that plants manufacture to protect themselves. Over a thousand phytochemicals have been identified to date and can be obtained from various foods, including whole grains, fruits, vegetables, nuts, and herbs (81).

Table II. Phytochemicals targeting DNA repair genes through epigenetic modulation in breast cancer.

Phytochemical	Source (plant part)	Target gene	Mechanism	(Refs.)
Curcumin	Turmeric (rhizome)	<i>BRCA2</i> ↓, <i>RAD51</i> ↓, <i>PARP1</i> modulation	<i>In vitro</i> studies report reduced <i>BRCA2</i> and <i>RAD51</i> stability, suggesting homologous recombination deficiency and increased PARP-inhibitor sensitivity	(85-87)
Genistein	Soybeans (seeds)	<i>BRCA1</i> ↑, <i>BRCA2</i> ↑, <i>ATM</i> ↑ (transcriptional); <i>MLH1</i> demethylation	<i>In vitro</i> and limited <i>in vivo</i> data suggest DNMT inhibition and partial promoter demethylation, leading to reactivation of <i>BRCA1</i> and <i>MLH1</i>	(88, 89)
Resveratrol	Grapes, berries, red wine (skin, seeds)	<i>RAD51</i>	<i>In vitro</i> evidence indicates <i>RAD51</i> downregulation, suggesting impaired homologous recombination and increased DNA-damage sensitivity	(90)
Quercetin	Apples, onions, grapes (fruits, peels)	<i>RAD51</i> , <i>Ku70</i> , <i>XRCC1</i> (DNA repair mediators)	<i>In vitro</i> studies report reduced expression of multiple DNA repair genes, suggesting global suppression of repair capacity	(91)
Thymoquinone	Black cumin (seeds)	<i>RAD51</i> , <i>Ku70</i> , <i>XRCC1</i> (DNA repair)	<i>In vitro</i> findings suggest decreased repair gene expression and increased DNA damage markers, indicating impaired DNA repair	(91)
Berberine	Barberry (roots/bark)	<i>XRCC1</i> -mediated BER; <i>BRCA1</i> axis (sensitization)	Preclinical studies report inhibition of <i>XRCC1</i> -mediated BER, sensitizing cells to DNA-damaging agents; <i>BRCA1</i> effects are indirect.	(92)
Epigallocatechin gallate	Green tea (leaves)	<i>DNMT1</i> ↓ → <i>MLH1</i> re-expression, <i>BRCA1</i> promoter demethylation reported	<i>In vitro</i> studies demonstrate <i>DNMT1</i> inhibition and re-expression of <i>MLH1</i> ; <i>BRCA1</i> demethylation has been reported in select models	(93,94)
Withaferin-A	Ashwagandha (leaves, roots)	<i>BRCA1</i> ↓, <i>ATR/ATM</i> -DDR modulation	Preclinical evidence suggests <i>BRCA1</i> degradation and <i>ATR/ATM</i> -DDR modulation, resulting in reduced homologous recombination	(95-97)

DNMT, DNA methyltransferase.

Phytochemicals primarily inhibit BC by reducing the proliferation of cells, inducing apoptosis, limiting cancer cell dissemination, inhibiting angiogenesis and impairing cancerous cell migration. These chemicals have also been shown to improve the curative effectiveness of other anticancer medications, sensitize cells to radiation, and prevent resistance to therapy in malignant tissue (82). Epigenetic alterations are modulated by phytochemicals as inhibiting DNMTs (83), modulating histone acetylation and methylation, and affecting ncRNAs (84). Some of the phytochemicals with targeted genes and their mechanisms are presented in Table II (85-97).

5. Critical analysis, limitations and future directions

Although DNA repair gene hypermethylation is widely reported in BC, much of the evidence remains correlative as it

relies heavily on *in vitro* studies and bulk bioinformatic datasets that fail to reflect the true biological complexity of tumors. Large-scale methylation analyses demonstrate extensive inter- and intra-tumoral epigenetic heterogeneity, indicating that simplified models cannot fully capture patient-specific variation (98). Moreover, the BC microenvironment, including stromal and immune components, strongly influences epigenetic states, yet this context is largely absent from current experimental systems (99). Methodological variability across methylation assays, histone modification profiling, and ncRNA detection platforms further contributes to inconsistent and difficult-to-compare findings in the epigenetics literature (100). Notably, hypermethylation in several DNA repair genes, including *BRCA1*, *BRCA2*, *RAD51*, *MLH1*, *MSH6*, *ATM*, and components of the MRN complex (*MRE11-RAD50-NBS1*), is frequently reported in BC; yet, direct evidence demonstrating

that these epigenetic alterations consistently translate into functional protein loss or impaired DNA repair activity remains limited (101). A number of published studies rely on simplified experimental systems, including *in vitro* cell line models, simplified animal models and bulk bioinformatic analyses, which do not adequately capture the cellular heterogeneity, tumor microenvironment and overall biological complexity of primary breast tumors (14,26,78). For this reason, determining the functional impact of hypermethylation may be challenging as it remains unclear how this process will affect cellular behavior. *In vitro* examples have demonstrated that promoter hypermethylation can be reversed, for example, with genes such as *BRCA1*, *XRCC1*, *ATM* and *RAD51*; however, the majority of these studies are not supported by comprehensive functional assays, either in terms of confirming successful restoration of DNA repair function or establishing the stability, reproducibility and long-term biological impact of such reversions. Furthermore, in the majority of cases, reversal of hypermethylation, in addition to being unstable, may not have any biological significance in the long term.

Such uncertainties in scientific research are inclusive of the challenges related to the developing a medicinal approach targeting hypermethylation reversal, particularly those which are phytochemical-based. Variability in phytochemical composition with respect to species, environmental factors, storage and processing is very high, thus rendering standardization difficult (102). Moreover, study designs for establishing direct causality between phytochemical consumption and subsequent cancer repression are not very feasible due to confounding variables, such as dietary habits (103). The limited understanding of phytochemical pharmacokinetics/pharmacodynamics, in addition, adds complexity to predictive models of safety, efficacy and interaction with conventional therapies (92). Bioavailability is an issue with a number of phytochemicals, in which a large absorption, low solubility, rapid metabolism and poor tissue biodistribution frequently require supraphysiological concentrations *in vitro*, which are not attainable *in vivo* (104). The precise biochemical mechanisms for their actions on epigenetic targets have not yet been fully understood, and numerous compounds have pleiotropic or context-dependent effects that limit their reliability as targeted epigenetic modulators (82).

Collectively, these limitations suggest more integrated and rigorous research is required. Future studies should, whenever possible, evaluate not only methylation and gene expression, but also quantify endogenous protein levels, protein abundance and functional DNA repair restoration in clinically relevant models. In addition, enhancing the phytochemical pharmacokinetics and developing standardized extraction protocols, the use of combinatorial therapeutic approaches might help in overcoming current barriers (105). Ultimately, well-designed clinical trials with clearly defined molecular clinical endpoints become the key to unlocking the true therapeutic potential of DNA repair gene reversal and hypermethylation in breast cancer.

6. Conclusion

BC is a major concern that arises due to both hereditary and epigenetic modifications, with hypermethylation of DNA repair genes playing a critical role in carcinogenesis in BC.

Such epigenetic modifications lead to the inactivation of tumor suppressor genes, resulting in DNA repair systems and promoting genomic instability. Patients with cancer usually undergo unconventional treatment methods, which have weaknesses, including toxicity, resistance and negative side-effects. However, the use of phytochemicals appears to be a promising strategy to reverse such aberrant epigenetic modifications in BC, having multiple advantages, including low toxicity, cost-effectiveness and potential synergy with standard treatments. Phytochemicals are natural molecules found in fruits, vegetables and medicinal plants that are essential components of the human diet and have a large impact in the direction of therapy of cancer. The present review discussed some phytochemicals, such as curcumin, that have shown a committing effect in targeting BC hypermethylated DNA repair genes.

Despite their potential however, several restrictions and challenges related to variability in the compound composition of phytochemicals, low bioavailability, difficult standardization and reproducibility, and a lack of clinical validation prevent them from being widely used. Future studies are thus required to elucidate the epigenetic effects of BC in order to overcome these obstacles. This will aid in the development of more individualized targets for phytochemical-based therapies, which also provide a low-toxicity method of reactivating genes involved in DNA repair and improving patient outcomes.

Acknowledgements

The authors acknowledge the support provided by the School of Biosciences and Technology, Galgotias University, Greater Noida, India, in terms of access to library resources, online databases, and research facilities for the preparation of this review.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

TG wrote the main manuscript, and AKJ provided conceptual guidance. Both authors reviewed, and have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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