Polyphenol-based interventions in breast cancer: Signaling pathways, molecular mechanisms and translational therapeutic strategies (Review)

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Abstract. Breast cancer (BC) comprises multiple molecular subtypes with distinct epidemiological, biological and therapeutic features. Although advances in diagnosis and systemic therapy have improved patient outcomes, therapeutic resistance, treatment-related toxicity and disease recurrence remain major clinical challenges. Growing evidence suggests that plant-derived polyphenols may influence BC progression through multiple biological mechanisms. These compounds can inhibit tumor-cell proliferation, migration, angiogenesis, inflammation, epithelial-mesenchymal transition and metastasis, while promoting apoptosis, autophagy, cell-cycle arrest and tumor-suppressive responses. Mechanistically, polyphenols may regulate several interconnected signaling pathways involved in BC development and progression, including PI3K/AKT/mTOR, p53, NF-κB, STAT3, Wnt/β-catenin and MAPK signaling. In addition to their direct effects on tumor cells, polyphenols may interact with the gut microbiome, which in turn influences polyphenol metabolism, estrogen homeostasis, immune regulation, inflammation and bioavailability. Probiotics, prebiotics and microbiota-derived metabolites may further influence this polyphenol-gut microbiome-BC axis. Polyphenols have also been explored as adjuvant or supportive agents in combination with chemotherapy, endocrine therapy and radiotherapy, as well as in novel delivery systems designed to improve their bioavailability and therapeutic efficacy. However, most current evidence remains preclinical. Well-designed clinical trials are therefore needed to define the optimal formulations, doses, safety profiles, pharmacokinetics and therapeutic relevance of polyphenol-based interventions in BC.

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Contents

1. Introduction

Breast cancer (BC) is one of the most common malignancies among women worldwide (1). It remains a leading cause of cancer-related mortality and may occasionally present with nonspecific symptoms, such as breast pain (2). Clinically, BC is commonly classified according to hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status into several major subtypes, including HR-positive/HER2-negative, HER2-positive and triple-negative BC (TNBC) (3). These subtypes differ in epidemiological characteristics, molecular features, therapeutic sensitivity, recurrence patterns and clinical outcomes. Standard treatments for BC include surgery, radiotherapy, chemotherapy, endocrine therapy, targeted therapy, immunotherapy or combinations of these approaches, depending on tumor subtype, disease stage, molecular profile and the patient's overall condition. Although these strategies have substantially improved patient survival, therapeutic resistance, recurrence, metastasis and treatment-related toxicity remain major clinical challenges (4).

In this context, plant-derived bioactive compounds have attracted increasing attention as potential adjuvant or supportive agents in BC management (5). Polyphenols constitute a large family of natural compounds characterized by one or more hydroxylated aromatic rings. They are widely distributed in dietary sources, including fruits, vegetables, tea, coffee, herbs and soy products.

Polyphenols have been investigated for a range of biological activities, including antioxidant, anti-inflammatory, immunomodulatory, metabolic and anticancer effects (6). In BC models, representative polyphenols have been reported to affect tumor-cell proliferation, apoptosis, autophagy, cell-cycle progression, angiogenesis, epithelial-mesenchymal transition (EMT), invasion, metastasis and therapeutic resistance (7). Molecular alterations, including changes in metabolites, proteins and gene expression profiles, contribute to cancer development and provide important bases for clinical detection (8,9). Accordingly, therapeutic strategies capable of modulating cancer-related molecular networks, such as polyphenol-based interventions, have attracted increasing attention in BC research (10). Mechanistically (5,6), the effects of polyphenols are closely related to their regulation of multiple cancer-associated signaling networks. Accumulating evidence suggests that polyphenols may modulate pathways such as PI3K/AKT/mTOR, p53, NF-κB, STAT3, Wnt/β-catenin and mitogen-activated protein kinase (MAPK) signaling. These pathways are involved in cell survival, inflammation, oxidative stress, immune regulation, tumor invasion and drug resistance. However, these signaling cascades do not function independently. Instead, they interact with one another and converge on shared downstream targets that jointly influence BC progression. Therefore, polyphenols should be understood as multi-target modulators rather than single-pathway inhibitors. Beyond direct tumor-cell regulation, the gut microbiome has emerged as an important factor influencing BC progression and therapeutic response. Gut microorganisms can transform dietary polyphenols into smaller and potentially more bioavailable metabolites, while polyphenols can reshape microbial composition and metabolic activity (11). This bidirectional interaction may influence estrogen homeostasis, inflammation, immune regulation and systemic metabolism. Probiotics, prebiotics and microbiota-derived metabolites may further participate in this polyphenol-gut microbiome-BC axis. Nevertheless, the clinical relevance of these interactions remains incompletely defined, and patient-specific factors such as diet, age, menopausal status, antibiotic exposure, tumor subtype and treatment history should be considered.

This review mainly covers research on polyphenol-based interventions in BC over the past 5 years. A particular emphasis is placed on signaling pathways, molecular mechanisms, microbiome-related regulation, combinations with conventional therapies, emerging delivery systems and clinical translation. This review also discusses pathway cross-talk, methodological limitations, preclinical evidence gaps and the current status of human clinical studies. Given that most available evidence is derived from *in vitro* experiments, animal models or mechanistic studies, the interventions of polyphenols in BC should be interpreted cautiously. Polyphenols may have potential as adjuvant or supportive agents. However, their efficacy, safety, optimal formulation, dose-response relationships, pharmacokinetics and clinical applicability require further validation in well-designed clinical studies.

A structured literature search was conducted in PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/), Scopus (https://www.scopus.com/) and Google Scholar (https://scholar.google.com/) to identify studies related to polyphenols and BC. The search primarily focused on studies published from 2020 onward, while earlier landmark studies were included when they provided important mechanistic or clinical background. Search terms included 'breast cancer', 'polyphenols', 'curcumin', 'resveratrol', 'quercetin', 'EGCG', 'genistein', 'gut microbiome', 'PI3K/AKT', 'p53', 'NF-κB', 'STAT3', 'Wnt/β-catenin', 'MAPK', 'chemotherapy', 'radiotherapy', 'drug delivery' and 'clinical trial'. Studies were included if they investigated polyphenols or related plant-derived phenolic compounds in BC and addressed molecular mechanisms, signaling pathways, gut microbiome regulation, therapeutic combinations, delivery systems, clinical outcomes, safety and/or pharmacokinetics. Studies were excluded if they were unrelated to BC, did not involve polyphenols or related compounds, lacked mechanistic or therapeutic relevance, were conference abstracts without sufficient details or were not available in English. Titles and abstracts were screened first, followed by full-text assessment of potentially relevant articles. As this is a narrative review rather than a systematic review or meta-analysis, no formal risk-of-bias assessment or quantitative synthesis was performed.

2. Signaling pathways of polyphenols in breast cancer

Natural compounds, especially polyphenols, exhibit diverse anti-breast cancer effects through multiple biological mechanisms, including inhibition of tumor-cell proliferation, migration, metastasis, angiogenesis, inflammatory signaling and EMT, as well as induction of apoptosis, autophagy, cell-cycle arrest, immunomodulation and tumor-suppressive responses. Fig. 1 summarizes how polyphenols regulate BC progression through two complementary mechanisms. Polyphenols can activate antitumor responses, including apoptosis and cell-cycle arrest, while suppressing tumor-promoting processes represented by tumor growth, angiogenesis, inflammation, EMT and metastasis.

These biological effects are closely associated with the modulation of cancer-related signaling networks. Targeting dysregulated signaling molecules has emerged as an important direction in BC therapy (12,13). As shown in Fig. 2, representative polyphenols may regulate several interconnected pathways involved in BC progression, including PI3K/AKT/mTOR, p53-related signaling, NF-κB, IL-6/JAK/STAT3, Wnt/β-catenin and MAPK signaling. Fig. 2 further illustrates that these pathways converge on shared downstream regulators, thereby affecting proliferation, inflammation, invasion, metastasis and cell-cycle progression (6) (Fig. 2).

To complement these schematics, Table I summarizes representative preclinical studies of polyphenols targeting BC-related signaling pathways. The table compares the polyphenols investigated, their doses or concentrations, experimental models, targeted pathways and quantitative outcomes. For example, quercetin combined with sulforaphane reduced the half-maximal inhibitory concentration to 19.48 μM in MDA-MB-231 cells and increased the expression of apoptosis-related proteins. In another representative study, pterostilbene-isothiocyanate reduced BC cell migration by ~97% and invasion by ~60% (Table I). These quantitative examples distinguish the study-specific evidence presented in

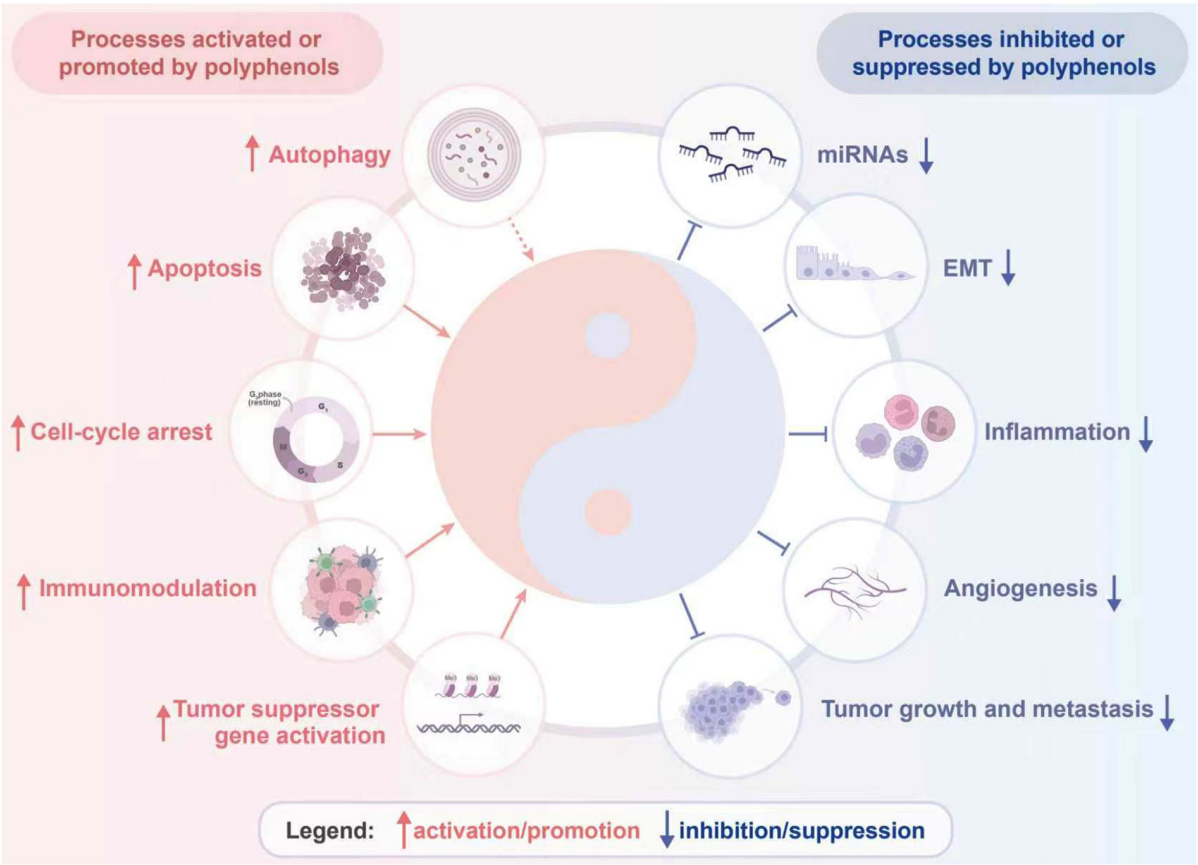

Figure 1. Overview of the major biological effects of polyphenols in BC. This schematic summarizes the major biological processes regulated by polyphenols in BC. Polyphenols may activate or promote antitumor processes, including apoptosis, autophagy, cell-cycle arrest, immunomodulation and tumor suppressor gene activation. They may also inhibit or suppress tumor-promoting processes, including oncogenic miRNAs, EMT, inflammation, angiogenesis, tumor growth and metastasis. Arrows indicate activation or promotion, whereas blunt arrows indicate suppression or inhibition. BC, breast cancer; EMT, epithelial-mesenchymal transition; miRNA, microRNA.

the table from the conceptual pathway information shown in the figures. Because most available pathway-related evidence remains preclinical, these findings should be interpreted as mechanistic or hypothesis-generating evidence.

PI3K/AKT signaling pathway. The PI3K/AKT signaling pathway is the hub of cell survival circuitry, proliferative output and cell-cycle regulation. Repression of this axis is a promising strategy for blunting BC progression. Substantial evidence has demonstrated that the PI3K/AKT signaling pathway plays a crucial role in the progression of BC, contributing to numerous cellular processes, including cell growth, angiogenesis, proliferation and metastasis. Components of this pathway are often dysregulated during the progression of BC. Loss of phosphatase and tensin homolog (PTEN), activating mutations in PIK3CA and alterations in AKT can lead to persistent activation of the PI3K/AKT signaling pathway. These changes appear in many subtypes, including HR-positive/HER2-negative, HER2-positive and triple-negative breast cancer, making PI3K/AKT a promising target for a new therapeutic opportunity. Numerous studies have documented the potency of polyphenols. They act as crucial modulators in the PI3K/AKT axis.

Metformin synergizes with dendrosomal nano-curcumin to inhibit mTOR complex 1 signaling, induce S-phase arrest and activate Bax/Bcl-2-mediated apoptosis in BC cells (14). Polydatin (PD) is the glucoside form of resveratrol. PD is being investigated as a strategy to mitigate the side effects induced by sorafenib and to cope with multidrug resistance in cancer. A study revealed that combining the two agents exerted enhanced anticancer effects in BC cells by repressing the PI3K/AKT/mTOR pathway and reducing therapeutic resistance (15). Further work has shown that biochanin A inhibited BC cell survival and induced apoptosis through the mitochondrial route, while simultaneously attenuating PI3K/AKT signaling and regulating cell cycle markers (16). Li *et al* (17) showed that sinigrin impeded BC cell proliferation by inhibiting PI3K/AKT/mTOR phosphorylation, thus inducing cell cycle arrest. Another study suggested that capsaicin reduced BC cell viability, induced G2/M cell cycle arrest, decreased cyclin-dependent kinase (CDK)8 levels, inhibited PI3K/AKT phosphorylation, and reduced Wnt and β-catenin levels (18).

Taken together, these studies suggest that PI3K/AKT/mTOR inhibition is a recurrent mechanism of several polyphenols in BC models. However, most evidence is based on selected cell lines or xenograft models and the relative contribution of PI3K/AKT suppression to the overall antitumor effect often remains difficult to separate from parallel effects on apoptosis, oxidative stress, cell-cycle arrest and therapeutic resistance pathways.

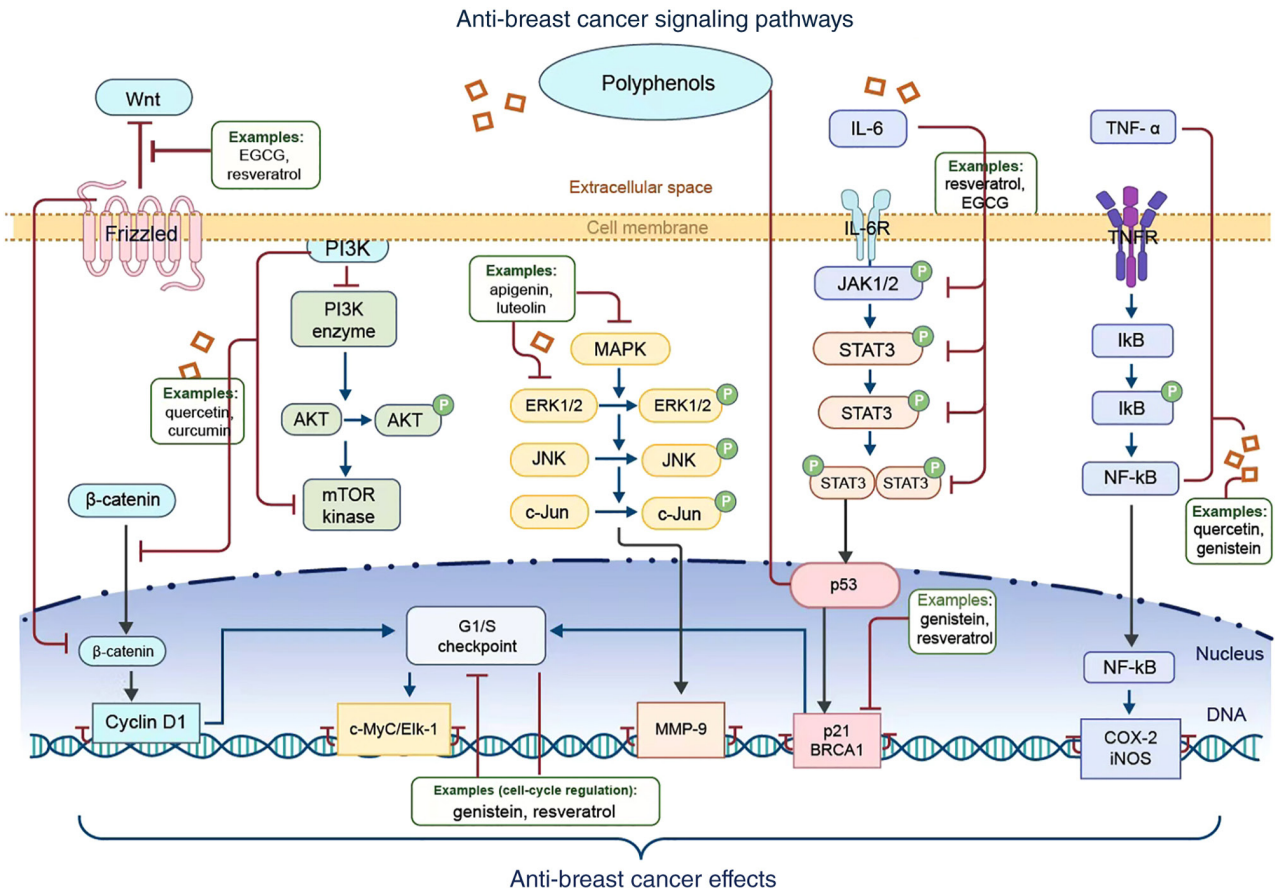

Figure 2. Major signaling pathways regulated by polyphenols in breast cancer. Polyphenols modulate Wnt/β-catenin, PI3K/AKT/mTOR, MAPK/ERK/JNK/c-Jun, IL-6/JAK1/2/STAT3, TNF-α/NF-κB and p53-related signaling pathways. These effects converge on downstream regulators involved in cell-cycle progression, proliferation, inflammation, invasion and metastasis. Representative polyphenols associated with each pathway are indicated in green boxes. Blue arrows indicate pathway activation or signal transduction, red blunt-ended lines indicate inhibition, and P indicates phosphorylation. Akt, protein kinase B; BC, breast cancer; BRCA1, breast cancer susceptibility gene 1; COX-2, cyclooxygenase-2; EGCG, epigallocatechin-3-gallate; ERK1/2, extracellular signal-regulated kinases 1 and 2; IL-6, interleukin-6; IL-6R, interleukin-6 receptor; IκB, inhibitor of nuclear factor κB; iNOS, inducible nitric oxide synthase; JAK1/2, Janus kinases 1 and 2; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MMP-9, matrix metalloproteinase-9; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor κB; PI3K, phosphoinositide 3-kinase; STAT3, signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor-α; TNFR, tumor necrosis factor receptor.

p53. The molecular basis of cancer pathophysiology remains incompletely understood, yet an important focus of oncology research is tumor-suppressor proteins, particularly the p53 family. p53 is involved in a range of antitumor mechanisms, including the induction of cell-cycle arrest, apoptosis and senescence, as well as the suppression of proliferative signaling. Polyphenols, especially the catechins in green tea, have attracted increasing attention for their ability to modulate p53-related signaling.

Santos *et al* (19) reported that green tea extract (GTE) suppressed BC cell growth by inducing p53 signaling and inhibiting BC cell migration. Notably, GTE was effective in reducing MDA-MB-231 and MCF-7 cell migration. GTE was associated with decreased p21 and p53 expression in MDA-MB-231 cells, whereas the opposite pattern was observed in MCF-7 cells, along with an altered subcellular distribution of mutant p53. These findings support the potential anticancer activity of GTE on BC cells. Metastatic BC remains a major cause of cancer-related mortality despite advances in systemic therapy. In BALB/c mice bearing aggressive 4T1 BC tumors, chlorogenic acid (CGA) induced apoptosis through p53-mediated signaling (20). Abdel-Latif *et al* (21) revealed that methoxylated quercetin glycoside (MQG) showed potential anticancer activity, enhancing immune recognition of tumor cells and reducing TNBC-associated markers. MQG-mediated modulation of the p53 pathway altered the oncogenic and immunogenic profiles of BC. However, further clinical studies are needed to fully assess its therapeutic potential. Elsayed *et al* (22) developed a novel encapsulated chitosan-quercetin-functionalized copper oxide nanoparticle and showed its potential in rat models of BC by modulating p53.

Overall, these findings indicate that p53-related regulation may represent an important mechanism by which polyphenols induce apoptosis, senescence, cell-cycle arrest and tumor-suppressive responses in BC. Nevertheless, the effects of polyphenols on p53 signaling may be influenced by the p53 status of the experimental model, as wild-type and mutant p53 can produce different biological outcomes. Therefore, future studies should distinguish whether polyphenols restore wild-type p53 function, modulate mutant p53 behavior or activate p53-independent mechanisms.

NF-κB. BC progression and metastasis are regulated by multiple signaling axes. Of note, the NF-κB signaling

Table I. Polyphenols and signaling pathway.

Polyphenol	Dose	Pathway	Study type/subject	Quantitative outcome
Curcumin	DNC 6.25 μM; IC50-based, 24-48 h	PI3K/AKT/mTOR	IVV/MDA-MB-231 and MCF-7 BC cells	Metformin/DNC showed synergism in MDA-MB-231 and MCF-7 cells, with CI values of 0.45 and 0.60 (14)
Polydatin	Polydatin 31.25-500 μg/ml; sorafenib 3.125-50 μg/ml	PI3K/AKT/mTOR	IVV/MCF-7, HepG2 and HFF1 cell	MCF-7 IC50: PD 453.9 μg/ml, SOF 10.66 μg/ml at 24 h; CI <1; sub-G1 increased to 38.6% (15)
Capsaicin	10-200 μM	CDK8/PI3K/AKT/Wnt/β-caten	IVV/Mda-MB-231 BC cell and McF10a healthy breast cell	G2/M phase increased from 11.46 to 25.63%; ↓ CDK8, p-PI3K, p-Akt, Wnt, β-catenin (18)
Green tea extract	31.2-1250 μg/ml	p53	IVV/human breast epithelial carcinoma cells and MCF-7 cells	IC50: 133 μg/ml in MDA-MB-231 and 324 μg/ml in MCF-7; migration reduced by 50 and 30% (19)
Chlorogenic acid	40 mg/kg, 14 d	p53, Bax, Bcl-2 and caspase-3	IVV&IVT/4T1 BC cells, BALB/c female mice	Tumor volume reduced from 177.19 to 25.92/6.76 mm^3; liver metastatic nodules reduced from 6.75 to 2.5/0.75 (20)
MQG	MQG 1-200 μM; IC50= 12 μM	MALAT-1/p53/miR-155/miR-146a	IVV/different cancer cell line	IC50=12 μM; ↓ MALAT-1, TNF-α, IL-10; ↑ miR-155, miR-146a and NK-activating ligands (21)
Novel quercetin	CuO-ChNPs-Q 4 mg/kg, 16 d; Q 100 mg/kg	p53	IVT/Sprague Dawley rats	MCF-7 IC50: CuO-ChNPs-Q 46.89 vs. Q 118.55 μg/ml; tumor weight reduced vs. DMBA group; ↑ p53, cytochrome c, caspase-3; ↓ PCNA (22)
Curcumin	Curcumin 150 mg/ml, 0.2 ml, gavage, 28 d	NF-κB/ubiquitin-proteasome-system axis	IVT/BALB/c mice	↓ Tumor growth; ↑ grip strength and gastrocnemius weight; ↑ ATP; ↓ IL-6, TNF-α, atrogin-1, MuRF-1, p-NF-κB (25)
Genistein	Genistein diet 400 mg/kg, 105 d	PPAR-γ pathway, NF-κB	IVT/C57BL/6J mice	↓ Obesity-associated tumor growth; ↓ CAAs and M2-like macrophage recruitment; ↑ PPAR-γ; ↓ nuclear NF-κB and inflammatory factors (26)
Pterostilbene-isothiocyanate	PTER-ITC 2.5-80 μM; *in vivo*: 20/100 mg/kg BW, oral, 3x/wk, 1 mo	NF-κB	IVT/BALB/c mice	↓ Migration ~97%, ↓ invasion ~60%; 100 mg/kg reduced tumor weight/volume ~3-4-fold; lung metastatic nodules ↓ ~2.5-fold; Snail1/Twist ↓ 5-/10-fold (28)
Genistein	Genistein diet 250 mg/kg; from PDX tumor size 2 mm	NF-κB/Bcl-xL/TAp63	IVT/TNBC PDX models NSG mice	↓ Tumor volume/weight in TNBC PDX models; RNA-seq: Cd74 log2FC -4.760, Lpl-2.806, Ifi44-2.191, Fzd9-1.186 (27)

Table I. Continued.

Polyphenol	Dose	Pathway	Study type/subject	Quantitative outcome
Chlorogenic acid	CA 1.5625-25 mM; EMT: 2.5 mM; *in vivo*: 10 mg/kg q.d., 3 wk	Wnt/β-catenin	IVV/MCF-7 and MDA-MB-231 cells	CA bound LRP6 with Kd=2.47±0.45 mM; ↓ migration/invasion; ↓ LRP6, p-LRP6, β-catenin, MMP-2/9; ↓ xenograft tumor volume/ weight (36)
Quercetin and sulforaphane	QT + SFN 0-70 μM, 24 h; combination: 10/20/30 μM	ERK/MAPK pathway	IVV/MDA-MB-231 cells, human breast epithelial HBL-100 cells	IC50: QT 28.74 μM, SFN 39.87 μM, QT+SFN 19.48 μM; Bax ↑ ~3-fold, caspase-3 ↑ ~2.8-fold, caspase-9 ↑ ~3.5-fold; Bcl-2 ↓ to ~1/3 (40)
Rutin and quercetin	ZSC extract 10-100 μg/ml, 48 h; migration/ angiogenesis: 40/60 μg/ml	MAPK	IVV/HER2-positive BC cell lines ZR-75-1 and SK-BR-3	IC50: 60±0.3 μg/ml in ZR-75-1 and 40.4±0.38 μg/ml in SK-BR-3; angiogenesis reduced to 51.4±4.4 and 51.2±4.0%; ↓ migration, HER2, p-HER2, p38 MAPK (41)

Akt, protein kinase B; ATP, adenosine triphosphate; Bax, Bcl-2-associated X protein; BC, breast cancer; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; BW, body weight; CAA, cancer-associated adipocyte; CDK8, cyclin-dependent kinase 8; CGA, chlorogenic acid; CI, combination index; CuO-ChNPs-Q, quercetin-encapsulated chitosan-functionalized copper oxide nanoparticles; DMBA, 7,12-dimethylbenz[a] anthracene; DNC, dendrosomal nanocurcumin; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; HER2, human epidermal growth factor receptor 2; IC50, half-maximal inhibitory concentration; IL, interleukin; Kd, dissociation constant; LRP6, low-density lipoprotein receptor-related protein 6; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MAPK, mitogen-activated protein kinase; miR, microRNA; MMP, matrix metalloproteinase; MQG, methoxylated quercetin glycoside; mTOR, mechanistic target of rapamycin; MuRF-1, muscle RING-finger protein 1; NF-κB, nuclear factor κB; NK, natural killer; NSG, NOD-scid gamma; PCNA, proliferating cell nuclear antigen; PDX, patient-derived xenograft; PI3K, phosphoinositide 3-kinase; PPAR-γ, peroxisome proliferator-activated receptor γ; PTER-ITC, pterostilbene-isothiocyanate; RNA-seq, RNA sequencing; TAp63, transactivation domain-containing p63 isoform; TNBC, triple-negative breast cancer; TNF-α, tumor necrosis factor α; ZSC, Ziziphus spina-christi. ↑, increased or upregulated; ↓, decreased or downregulated; p-, phosphorylated.

pathway is important. This pathway comprises a family of sequence-specific DNA-binding factors. It regulates various biological processes, including viral infection, inflammatory diseases and oxidative stress, as well as metabolic disorders and cell proliferation. In BC, dysregulated NF-κB signaling modulates cell proliferation, differentiation, angiogenesis, metastasis and apoptosis. Furthermore, previous research has revealed that pharmacological inhibition of aberrantly activated NF-κB can induce apoptosis and suppress metastasis in BC cells. Thus, developing effective inhibitors of NF-κB offers a potential strategy for BC treatment.

CGA has been reported to inhibit BC growth through suppression of NF-κB signaling. CGA markedly blunted the NF-κB and EMT signaling axis. Its antitumor efficacy was assessed in a subcutaneous mouse tumor model. CGA significantly retarded BC growth and improved survival in tumor-bearing mice (23). CGA enhanced antitumor immunity, exerting its antitumor effects by inhibiting NF-κB/EMT signaling. This research demonstrated that CGA is a promising candidate for BC treatment. Capsaicin is a natural product derived from chili peppers. It has attracted increased interest for its anticancer effects, particularly in BC. The proto-oncogene factor that binds to inducer of short transcripts 1 (FBI-1), also known as zinc finger and BTB domain-containing protein 7A, can repress multiple tumor-suppressor genes and promote BC progression. Capsaicin markedly repressed proliferation and triggered apoptosis in BC, as evidenced by caspase 3 activation, increased Bax protein expression and reduced FBI-1 protein expression. Furthermore, FBI-1 overexpression significantly alleviated the pro-apoptotic effect. In addition, as a target gene of FBI-1, NF-κB signaling was also suppressed, with capsaicin reducing p65 nuclear translocation, which was perceptibly increased with FBI-1 silencing or decreased with FBI-1 overexpression (24). Therefore, targeting the FBI-1/NF-κB axis may contribute to the anticancer activity of capsaicin in BC. Zhang *et al* (25) revealed that curcumin, by acting on the NF-κB/ubiquitin-proteasome system axis, improved muscle atrophy in TNBC cachexia mice. Dietary genistein markedly ameliorated systemic inflammation, obesity and metabolic disorders in ovariectomized mice (26). Of note, it also repressed tumor growth. Within the tumor microenvironment, genistein curbed the recruitment of M2d macrophages and the generation of cancer-associated adipocytes. *In vitro*, genistein blocked the transition of adipocytes

and reduced inflammatory factor production by activating the peroxisome proliferator activated receptor (PPAR)-γ pathway and reducing NF-κB. Furthermore, it impaired the acquisition of invasive properties and EMT in BC cells by interrupting the Wnt3a/β-catenin pathway. Dietary genistein also exerted potent therapeutic activity against TNBC by reshaping epigenetic mechanisms. These findings suggest that this soybean-derived bioactive compound may have potential as a supportive strategy for BC management (27). Notably, the PPAR-γ inhibitor T0070907 reversed the influence of genistein in the coculture system, supporting the involvement of PPAR-γ-dependent mechanisms. This research suggested that genistein could mitigate the side effects of obesity on BC by regulating the microenvironment of the tumor (26). Collectively, these data provided new evidence on how a soy-based diet and genistein intake can reduce BC risk. The inhibitor of NF-κB (IKK) complex is a critical regulator of NF-κB signaling. Pterostilbene-isothiocyanate (PTER-ITC) selectively impaired NF-κB activation in malignant cells (28). It hindered NF-κB/p65 activation and its subsequent nuclear translocation, contributing to the transcriptional repression of NF-κB target genes. PTER-ITC disrupted IKK complex formation and inhibited the interaction between the IKK complex and IKK kinase regulatory subunit gamma, which is central to NF-κB activation.

Overall, these findings support the role of NF-κB as an important inflammatory and survival-related target of polyphenols in BC. Nevertheless, because NF-κB signaling is closely connected with EMT, immune regulation, oxidative stress and the tumor microenvironment, future studies should distinguish direct inhibition of NF-κB signaling from secondary changes caused by broader anti-inflammatory or cytotoxic effects.

STAT3. The STAT family consists of 7 transcription factors, STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6. These proteins are among the key transcriptional regulators involved in BC biology. These proteins share a highly similar architecture and share a conserved domain structure comprising six functional regions. STAT3 is particularly important because it promotes tumor metastasis, multidrug resistance and sustained proliferation (29). A growing body of preclinical data demonstrates that increased expression and persistent activation of STAT3 fuel BC progression, cell proliferation, metastasis and chemoresistance.

Previous research showed that epigallocatechin-3-gallate (EGCG) repressed adipose-derived mesenchymal stem cell differentiation into adipocytes and disrupted paracrine oncogenic regulation of the invasive phenotype of TNBC cells via STAT3 suppression (30). Quercetin suppressed high-glucose-induced BC progression by targeting the IL6/JAK1/STAT3/MMP9 pathway (31). It reduced proliferation, resistance to apoptosis, EMT and metastatic potential *in vitro* and in diabetic tumor models. These findings support quercetin as a potential STAT3-targeting polyphenol for BC associated with diabetic comorbidity. Several epimedium-derived flavonoids, including icariin and icariside I, have been reported to regulate JAK/STAT3-related signaling in BC models. Icariin inhibited TNBC proliferation, invasion and pulmonary metastasis (32). Mechanistically, icariin downregulated spindle apparatus coiled-coil protein 1 and suppressed JAK2/STAT3 phosphorylation. Icariside I inhibited BC cell growth, migration, invasion and lung metastasis (33). It suppressed IL-6/STAT3 activation, reduced Cyclin D1, CDK4, Bcl-2, MMP9 and vimentin, and increased Bax and cleaved caspase-3, supporting its STAT3-targeting anticancer potential in BC. 5-Desmethylsinensetin inhibited BC stem cell proliferation and mammosphere formation (34). It reduced CD44/CD24, aldehyde dehydrogenase 1, Oct4, c-Myc, Nanog homeobox and CD44 by suppressing STAT3/IL-6 and STAT3/Yes-associated protein (YAP)1 signaling.

These studies indicate that STAT3 may represent a central convergence point linking cytokine signaling, tumor-cell survival, invasion, immune regulation and therapeutic resistance in BC. However, compared with PI3K/AKT or NF-κB, the current evidence regarding polyphenol-mediated STAT3 regulation remains relatively limited. Further studies are needed to clarify whether polyphenols directly inhibit STAT3 phosphorylation and dimerization, or indirectly modulate STAT3 activity through upstream regulators.

Wnt/β-catenin. Mammary gland development is normally regulated by several pathways, including Wnt, estrogen, Hedgehog and Notch signaling. However, dysregulation of these signaling pathways can contribute to cancer development, and increased Wnt activity, along with elevated β-catenin abundance, is associated with BC development and progression. In addition, β-catenin-dependent Wnt signaling is frequently activated in TNBC and is associated with poorer overall survival in patients with BC. Numerous studies have focused on the effect of polyphenols to suppress BC development and progression by modulating crucial cell survival pathways (35).

Xue *et al* (36) showed that CGA binds to low density lipoprotein receptor related protein 6 (LRP6), a coreceptor in the Wnt/β-catenin pathway, and decreases total LRP6, phosphorylated LRP6 (p-LRP6) and β-catenin levels in MCF-7 BC cells. One study showed that targeting CD73 with flavonoids could suppress cancer stem cells (CSCs) and boost lymphocyte influx in TNBC mice through Wnt signaling (37). They identified that luteolin and quercetin showed high binding affinity for CD73. The combination of luteolin and quercetin with paclitaxel (PTX) effectively reduced CSC-promoting pathways, including YAP, PTX-increased CD73 expression and Wnt signaling. CD73 is essential for maintaining the CD44high/CD24low CSC population, and co-targeting YAP, CD73 and Wnt signaling effectively suppressed TNBC progression. Furthermore, this combined treatment repressed PTX-enriched CSCs while promoting lymphocyte infiltration in syngeneic TNBC. A stilbenoid-flavanone hybrid with a polyphenol-like structural scaffold inhibited Wnt/β-catenin signaling and induced G2/M cell-cycle arrest and apoptosis (38). Although mechanistic validation was conducted in colon cancer cells, its activity against breast tumor cells suggests potential relevance for BC-related Wnt/β-catenin targeting. Curcumin nano-chitosan reduced microRNA (miR-221), miR-222 and β-catenin expression in MCF-7 and MDA-MB-231 cells. It also increased Wnt inhibitory factor 1 expression (39). These findings suggest that curcumin nanoparticles may inhibit BC progression partly through miRNA-mediated Wnt/β-catenin pathway regulation.

Taken together, the available evidence suggests that Wnt/β-catenin signaling is an important pathway through which polyphenols may suppress BC cell stemness, proliferation, EMT and metastasis. However, Wnt/β-catenin signaling often interacts with other oncogenic pathways, including PI3K/AKT, NF-κB and estrogen-related signaling. Therefore, the antitumor effects observed after polyphenol treatment may reflect broader network regulation rather than isolated Wnt/β-catenin inhibition. Further studies using pathway-specific rescue experiments and genetic validation are needed to confirm the causal role of Wnt/β-catenin modulation.

MAPK. The MAPK signaling pathway serves as a crucial mediator linking extracellular stimuli to intracellular responses, thereby influencing gene expression and epigenetic regulation. MAPKs govern fundamental cellular processes. MAPKs mainly include JNK, ERK1/2 and p38. Additionally, the MAPK signaling pathway plays a critical role in BC chemoresistance. Therefore, targeting the MAPK pathway represents a potential strategy for overcoming drug resistance and enhancing the efficacy of anticancer agents in BC.

Wei *et al* (40) reported that combining quercetin with sulforaphane could inhibit BC cell growth by activating the ERK/MAPK signaling pathway. *Ziziphus spina-christ*i (ZSC) is a kind of medicinal plant rich in polyphenolic bioactive compounds. It contains multiple bioactive constituents and it exerts substantial biological effects, including cytotoxicity. A study reported that ZSC extract repressed cell migration and proliferation in HER2-positive BC through the p38 MAPK signaling axis (41). Inhibition of p38 and JNK was associated with reduced tumor progression and enhanced therapeutic efficacy. Anhydroicaritin showed selective cytotoxicity against ER-positive BC cells (42). It may act through estrogen receptor 1 regulation. It reduced ERα phosphorylation, inhibited MAPK signaling and induced apoptosis. These findings suggest its potential as a subtype-specific lead compound for ER-positive BC. Khongsti *et al* (43) reported that genistein reduced secreted osteopontin expression and suppressed colony formation, migration and invasion in metastatic breast cancer cells, including MDA-MB-231 cells. Mechanistically, MAPK signaling and SIRT1 activation contributed to these effects. Another study demonstrated quercetin exerted its anticancer efficacy by promoting apoptosis and regulating the MAPK/ERK signaling in the MDA-MB-231 BC cell line (44). Polyphenol-rich *Crataegus oxyacantha* berry extract inhibited proliferation in MCF-7 and MDA-MB-231 BC cells. It induced G1/S cell-cycle arrest. It downregulated Wnt pathway agonists and upregulated Wnt antagonists (45). These findings suggest potential anti-BC effects through regulation of the canonical Wnt/β-catenin pathway.

Pathway cross-talk, evidence synthesis and methodological limitations. Although the above pathways are discussed separately for clarity, they should not be interpreted as independent, linear cascades in BC. PI3K/AKT/mTOR, Wnt/β-catenin, MAPK, IL-6/JAK/STAT3, TNF-α/NF-κB and p53-related signaling form an interconnected regulatory network that jointly controls proliferation, apoptosis, inflammation, EMT, invasion, metastasis and therapeutic resistance (46). For example, PI3K/AKT/mTOR and Wnt/β-catenin signaling both converge on proliferative regulators such as Cyclin D1 and c-Myc, whereas STAT3, NF-κB and MAPK signaling jointly contribute to inflammatory signaling, survival, invasion and metastatic progression (29). The p53-related pathway further intersects with these oncogenic cascades by regulating p21-mediated cell-cycle arrest, apoptosis-related molecules and genomic stability. Therefore, the antitumor effects of polyphenols should be understood as network-level regulation rather than modulation of any single isolated pathway.

Across available studies, several polyphenols, including curcumin, resveratrol, EGCG, quercetin, genistein, apigenin and luteolin, appear to regulate multiple pathways simultaneously. This multi-target property may partly explain their broad effects on BC cell proliferation, apoptosis, inflammation, EMT, metastasis and drug resistance. However, this property also complicates mechanistic interpretation. A reduction in cell viability or tumor volume cannot always be attributed to one specific pathway unless supported by pathway-specific inhibition, rescue experiments, genetic validation or pharmacological controls. Therefore, pathway-level conclusions should be interpreted cautiously, particularly when studies rely mainly on changes in protein expression or phosphorylation without functional validation.

Methodological limitations should also be considered when interpreting the current evidence. Most pathway-related findings are derived from *in vitro* BC cell lines or animal models and the results may be influenced by receptor status, p53 status, metastatic potential, drug sensitivity and the genetic background of the model. Commonly used cell lines, such as MCF-7, MDA-MB-231 and 4T1, represent only selected biological contexts and cannot fully capture the heterogeneity of human BC. In addition, several *in vitro* studies evaluated polyphenols at relatively high concentrations, including capsaicin, chlorogenic acid and quercetin combined with sulforaphane (18,36,40). The clinical relevance of these findings may be limited by poor solubility, rapid metabolism, low systemic bioavailability and uncertain tissue distribution (6,7). Animal studies provide important *in vivo* evidence, immune-microenvironment interactions, long-term toxicity or pharmacokinetic behavior.

Overall, the current evidence supports the potential of polyphenols as multi-target modulators of BC-related signaling networks. Nevertheless, most findings remain preclinical and should be interpreted as mechanistic or hypothesis-generating evidence. Future studies should include standardized dosing, pharmacokinetic assessment, subtype-specific models, quantitative pathway validation and clinically relevant endpoints to determine whether the pathway-regulating effects of polyphenols can be translated into meaningful therapeutic benefits for patients with BC.

3. Potential therapeutic strategies of polyphenols in breast cancer

The therapeutic relevance of polyphenols in BC extends beyond their direct modulation of tumor-cell signaling pathways. Although numerous polyphenols have shown antiproliferative, pro-apoptotic, anti-inflammatory, anti-metastatic and chemosensitizing effects in preclinical models, their clinical application is influenced by bioavailability, metabolic

transformation, tumor accumulation, formulation design, safety and interactions with standard anticancer therapies. Therefore, polyphenols should be considered as potential adjuvant or supportive agents whose value depends on biological context, delivery strategy, combination regimens and clinical validation (47,48). This section discusses polyphenol-based therapeutic strategies in BC from four interconnected perspectives. The polyphenol-gut microbiome axis is examined as a mechanism linking dietary polyphenols, microbial metabolism, estrogen homeostasis, inflammation, immune regulation and BC progression. The combination of polyphenols with conventional BC therapies is then reviewed to clarify their potential roles in chemosensitization, endocrine therapy support, radiosensitization and photodynamic therapy enhancement, while also emphasizing that not all combinations are synergistic. Emerging delivery systems are further discussed as a strategy to improve solubility, cellular uptake, tumor targeting, controlled release and the reversal of multidrug resistance. Finally, representative clinical studies are summarized to evaluate the current translational relevance of polyphenols in BC, with attention to efficacy, safety, bioavailability, herb-drug interactions and supportive-care applications.

Polyphenol-gut microbiome interactions. The therapeutic relevance of polyphenols in BC should be understood within a broader biological context. Although numerous polyphenols have been shown to regulate cancer-related signaling pathways, their biological effects *in vivo* depend on absorption, metabolism, tissue distribution and interactions with the host microenvironment. Among these factors, the gut microbiota has attracted increasing attention because it can transform dietary polyphenols into bioactive metabolites while being reshaped by polyphenol intake in turn. This bidirectional relationship provides a mechanistic link among diet, microbial metabolism, estrogen homeostasis, inflammation, immune regulation and BC progression (49).

The interaction between polyphenols and gut microbiota may contribute to the efficacy of combination treatment. In a 4T1 TNBC mouse model, dietary quercetin combined with cyclophosphamide showed potential antitumor effects through complementary microbiome- and immune-mediated mechanisms (50). Mechanistically, quercetin reshaped the fecal microbiome and enriched bacteria such as *Akkermansia muciniphila*, a species previously associated with improved responses to anti-programmed cell death-1 therapy. These findings suggest that quercetin may potentiate chemotherapy partly through microbiome-mediated mechanisms that complement the immunomodulatory effects of cyclophosphamide. Nevertheless, this evidence remains preclinical, and whether such microbiome-centered dietary polyphenol interventions can improve chemotherapy responses in patients with TNBC requires further clinical validation. Natural polyphenols, with their anti-inflammatory and antioxidant properties, may enhance the stability of probiotics in the gut, while probiotics can modulate polyphenol metabolism (51,52). Polyphenols generally exhibit limited absorption in the small intestine, and a substantial proportion reaches the colon, where intestinal microorganisms metabolize them into smaller and often more bioavailable compounds (53). These microbiota-derived metabolites may differ from their parent compounds in membrane permeability, biological stability and ability to regulate cancer-related pathways. For example, ellagic acid can be converted into urolithins, whereas lignans and isoflavones can be transformed into metabolites with estrogen-modulating properties (54). Resveratrol increased the viability of Lactobacilli by 2.1-fold *in vitro*, and *Lactobacillus plantarum* converts resveratrol to the glycosylated metabolite piceid (55). This potential synergy warrants further preclinical and clinical investigation, particularly in HR-positive BC and TNBC. Zhu *et al* (56) demonstrated that quercetin alleviated BC-related depression in a 4T1 tumor-bearing mouse model by reshaping gut microbiota composition, improving abnormal lipid metabolism and targeting the lipid metabolism-related gene prostaglandin-endoperoxide synthase 2. Although this study did not directly evaluate tumor suppression or a combined polyphenol-probiotic intervention, it supports the broader concept that polyphenols can regulate gut microbiota and immune-metabolic pathways in BC-related pathological conditions.

The gut microbiota is also involved in estrogen homeostasis through the estrobolome, a collection of microbial genes capable of metabolizing estrogens (57). Bacterial β-glucuronidase can deconjugate estrogen metabolites, thereby increasing the levels of biologically available estrogens and potentially contributing to estrogen-driven BC progression, especially in postmenopausal women (58). In this context, polyphenols may interact bidirectionally with the gut microbiome. Microbial metabolism can convert dietary polyphenols into bioactive metabolites, such as enterolactone derived from lignans, which may exert estrogen-modulating or anti-estrogenic effects (59). On the other hand, polyphenols may alter the abundance and metabolic activity of bacteria involved in estrogen metabolism, thereby influencing systemic estrogen exposure. This bidirectional interaction may further affect estrogen-driven signaling pathways, including the ERα/PI3K/Akt axis, which plays a crucial role in the progression of HR-positive BC (60).

Polyphenols may also interact with probiotics or microbiota-derived metabolites to enhance anticancer activity. For example, epigallocatechin-3-gallate, a major green tea polyphenol, has been reported to synergize with probiotics partly through inhibition of the EGFR/Src and NF-κB signaling pathways, both of which are closely associated with inflammation and immune dysfunction in BC (50,61). Similarly, microbiota-derived short-chain fatty acids may interact with polyphenols in BC cells. One study showed that quercetin and sodium butyrate each inhibited MCF-7 cell proliferation, while their combination produced a stronger inhibitory effect than either treatment alone (62). These findings suggest that polyphenols and microbiota-derived metabolites may exert antiproliferative effects against hormone-sensitive BC cells. Microbiota-derived metabolites may influence BC progression by regulating oxidative stress, inflammatory signaling, apoptosis, cell-cycle progression and hormone-dependent pathways.

Probiotics and prebiotics may further influence the polyphenol-gut microbiome-BC axis by regulating microbial composition and metabolic activity. Prebiotics are non-digestible substrates that are selectively utilized by host microorganisms and can promote the growth or activity of

beneficial intestinal bacteria (63,64). In this context, prebiotics may indirectly affect BC-related biological processes by shaping microbial metabolism, increasing short-chain fatty acid production and enhancing the biotransformation of polyphenols. Multiple experiments have evaluated the synergistic value of combined prebiotic-polyphenol interventions and outlined preliminary translational pathways (65-67). Notably, prebiotics may cooperate with natural polyphenols by improving their microbial metabolism and bioavailability (68). Polyphenols such as quercetin and epigallocatechin-3-gallate have relatively low absorption rates in the small intestine, and a large proportion can reach the colon, where they are metabolized by gut microbiota into bioactive compounds (53). These microbiota-derived metabolites may have improved membrane permeability and biological activity, enabling them to regulate BC-related signaling cascades. In a clinical pilot study, co-administration of inulin and green tea extract increased plasma levels of epigallocatechin-3-gallate metabolites compared with green tea extract alone, accompanied by a reduction in circulating IL-6 levels (69). Although this finding is not BC-specific, it supports the possibility that prebiotics may enhance polyphenol metabolism and systemic anti-inflammatory effects. Of note, polyphenols themselves have also been discussed as prebiotic-like compounds. Plămadă and Vodnar (68) proposed that polyphenols represent an important group of plant-derived secondary metabolites with potential prebiotic effects. As many polyphenols have low bioavailability, they can reach the colon in relatively unaltered forms and interact bidirectionally with intestinal microorganisms. Through this interaction, polyphenols may promote beneficial bacteria and increase the production of beneficial microbial metabolites. However, most supporting evidence remains preclinical, and further human studies are needed to determine whether these prebiotic-like effects can be translated into clinically meaningful benefits.

Overall, the interaction between polyphenols and the gut microbiome provides a biologically plausible link among diet, microbial metabolism, estrogen homeostasis, inflammation, immune regulation and BC progression. However, current evidence should be interpreted cautiously. Most mechanistic findings are derived from cell culture studies, animal models or indirect observational evidence. The composition of the gut microbiota varies considerably among individuals, and the same polyphenol may produce different metabolites depending on microbial background, diet, age, menopausal status, antibiotic exposure and cancer treatment history. Although the polyphenol-gut microbiome-BC axis represents a promising area of research, its clinical relevance requires further validation.

Polyphenols in combination with conventional therapies. BC remains a major global health challenge despite advances in chemotherapy, endocrine therapy, targeted therapy and radiotherapy. These treatments are frequently constrained by therapeutic resistance, cumulative toxicity and interpatient heterogeneity. In this context, polyphenols have attracted attention as potential adjuvant agents rather than independent substitutes for standard therapies. Among these strategies, the combination of polyphenols with chemotherapy has been most extensively investigated in preclinical BC models. Several polyphenols have been reported to enhance the sensitivity of BC cells to chemotherapeutic agents through regulation of PI3K/AKT, NF-κB, STAT3, MAPK, p53 and apoptosis-related pathways. Radwan *et al* (70) showed that resveratrol sensitized tamoxifen-resistant BC cells to tamoxifen by downregulating ATP binding cassette transporter-related multidrug resistance genes, modulating miRNAs, increasing reactive oxygen species (ROS) generation and promoting apoptosis. Although resveratrol has been widely proposed as a potential chemosensitizer, recent evidence suggests that its interaction with chemotherapeutic agents is not uniformly synergistic. In MCF-7 BC cells, resveratrol differentially modulated the cytotoxic, antiproliferative, apoptotic and cell-cycle effects of doxorubicin, PTX and cisplatin. The strongest cytotoxic response was observed in the resveratrol-doxorubicin group, whereas the combinations with PTX or cisplatin showed comparatively limited effects under certain experimental conditions (71). This indicates that the therapeutic value of resveratrol may depend on the chemotherapeutic backbone, dose, exposure time and cellular context. Therefore, polyphenol-based combination strategies should be evaluated cautiously, particularly considering their limited bioavailability, uncertain pharmacokinetic behavior and the lack of clinical validation in patients with BC. Liu *et al* (72) demonstrated that quercetin pretreatment followed by doxorubicin treatment, delivered through reduction-sensitive hyaluronic acid-based mixed micelles, could overcome multidrug resistance in BC by suppressing P-glycoprotein (P-gp) expression, increasing intracellular doxorubicin accumulation and promoting mitochondria-dependent apoptosis. Another study revealed that quercetin enhanced the chemosensitivity of MCF-7 BC cells to 5-fluorouracil by promoting apoptosis, increasing Bax, p53 and caspase-9 activity, decreasing Bcl-2 expression and suppressing colony formation (73).

Beyond chemotherapy, polyphenol-containing natural combinations have also been investigated as adjuvant strategies for endocrine therapy. A study showed that hesperidin, piperine and bee venom enhanced the antitumor effects of tamoxifen in MCF-7 xenograft-bearing rats by promoting apoptosis, suppressing angiogenesis-related VEGF expression and inducing cell-cycle arrest (74). Polyphenols have also been investigated as radiosensitizers in BC. For example, resveratrol enhanced the response of MCF-7 BC cells to ionizing radiation by reducing antioxidant enzyme activity, promoting ROS accumulation and increasing the expression of apoptosis-related genes such as Bax, p53 and caspase-8 (75). Research using fisetin micelles further supports the potential of polyphenol-based formulations for radiosensitization in BC treatment (76). A recent study showed that resveratrol enhanced the cytotoxic and pro-apoptotic effects of methylene blue-mediated photodynamic therapy in MDA-MB-231 TNBC cells, with stronger effects than either treatment alone (77).

Importantly, not all combinations of chemotherapeutic agents with natural products are synergistic. A previous study showed that dasatinib plus quercetin or piperlongumine failed to prevent chemotherapy-induced trabecular bone loss in mice, suggesting that senolytic strategies may not effectively mitigate this chemotherapy-related adverse effect in BC (78). In a comparative study using MCF-7 and MDA-MB-231 BC cells, doxorubicin-loaded polyquercetin nanoparticles were combined with curcumin, tannic acid or thymoquinone at

different ratios. Despite the promising properties of the nanoparticle platform, including high drug loading and sustained release, most combinations were antagonistic according to combination index analysis. Only a few combinations showed synergy and these effects were restricted to MDA-MB-231 cells (79). This study provides an important cautionary perspective: Polyphenol-chemotherapy combinations may produce beneficial, neutral or unfavorable effects depending on the cellular context, compound pairing, formulation and dose ratio. Therefore, claims of synergy should be supported by quantitative combination-index analysis rather than inferred from reduced cell viability alone.

Polyphenols may have potential value as adjuvant agents for conventional BC therapies, particularly in combination with chemotherapy. These findings should be interpreted cautiously, as most evidence is derived from *in vitro* or animal studies, and clinically relevant issues such as bioavailability, pharmacokinetics, dose optimization, toxicity and potential interactions with anticancer drugs remain insufficiently clarified.

Emerging delivery systems for polyphenol-based interventions. The clinical translation of polyphenols in BC is mainly limited by their intrinsic pharmacological limitations and insufficient clinical evidence. Engineering delivery systems has therefore become an important strategy for improving the therapeutic applicability of polyphenol-based interventions (80). Current delivery platforms are increasingly designed to enhance cellular uptake, improve tissue penetration, enable controlled or stimuli-responsive release, support combination therapy and overcome multidrug resistance (81).

Nanocarrier-based formulations are a major strategy for addressing the poor aqueous solubility and limited cellular uptake of polyphenols. Improving the solubility and intracellular availability of hydrophobic polyphenols represents a fundamental purpose of nanocarrier design. To address the poor aqueous solubility of resveratrol, polymeric micelles based on Pluronic F127 and vitamin E TPGS were developed to enhance its delivery to BC cells. This formulation improved cellular uptake and showed selective cytotoxicity against MCF-7 and MDA-MB-231 cells (82). Natural exosome-like nanovesicles derived from edible tea flowers, which contain abundant polyphenols and flavonoids, have been reported to suppress metastatic BC through ROS-mediated tumor cell damage and gut microbiota modulation (83). These nanovesicles induced intracellular ROS accumulation, mitochondrial dysfunction, cell-cycle arrest and apoptosis, thereby inhibiting BC cell proliferation and lung metastasis while altering the gut microbial profile. This study supports the broader concept that diet-derived polyphenol-containing systems may regulate BC progression through oxidative stress-related and microbiota-associated mechanisms. Targeted nanocarrier systems may enhance the therapeutic relevance of polyphenol-chemotherapy combinations by improving tumor accumulation, controlling the sequence of drug release and reducing drug efflux. Researchers developed hyaluronic acid (HA)-decorated core-shell polydimethylsiloxane (PDMS) nanoparticles for the sequential delivery of doxorubicin and quercetin in BC models. In an MCF-7 xenograft model, the quercetin-doxorubicin-loaded PDMS-HA nanoparticles achieved stronger tumor inhibition than single-drug-loaded nanoparticles or free drug combinations, with ~65% tumor volume reduction and without obvious systemic toxicity (84). This study supports the potential of nanocarrier-mediated polyphenol-chemotherapy co-delivery for improving tumor targeting, overcoming multidrug resistance and reducing chemotherapy-associated toxicity. In a recent BC study, phenylboronic acid-functionalized resveratrol oligomers were used as active nanocarriers to co-deliver doxorubicin and IR780 for synergistic chemo-photothermal therapy (85). Compared with passive nanocarriers, this design is notable because resveratrol itself contributed intrinsic anticancer activity while also serving as a structural component of the delivery system. The nanoparticles achieved tumor targeting through phenylboronic acid-sialic acid recognition, stimulus-responsive drug release, enhanced cellular uptake and improved *in vivo* antitumor efficacy. Another study showed that quercetin-loaded solid lipid nanoparticles potentiated the apoptotic effect of etoposide in MDA-MB-231 BC cells by enhancing Bax/Bcl-2 imbalance, increasing p53 and p21 expression, and activating caspase-3 and caspase-9 (86). A nanocochleate gel co-loaded with curcumin and quercetin improved controlled release, *ex vivo* skin permeation and MCF-7 cell growth inhibition, suggesting a localized delivery strategy for polyphenol-based BC adjuvant therapy (87). Guo *et al* (88) developed HA-modified, pH/glutathione-responsive polymeric nanoparticles co-delivering PTX and quercetin, which enhanced PTX retention, suppressed P-gp-mediated drug resistance and improved chemotherapy efficacy in drug-resistant BC.

Taken together, these studies indicate that delivery-system engineering is an important strategy for improving the translational potential of polyphenol-based interventions in BC. Compared with free polyphenols, nanocarrier-based systems may enhance solubility, tumor accumulation, cellular uptake, controlled release and combination efficacy in chemo- or photothermal therapy. In particular, co-delivery platforms using quercetin, curcumin or resveratrol may contribute to the reversal of drug resistance and improved antitumor activity. Beyond formulations specifically designed for polyphenols, recent advances in organelle-targeted nanomedicine and intracellular protein degradation technologies may also inspire future translational strategies for polyphenol-based BC therapy. Calcipoptosis-inducing nanoagonists and biomolecular condensate-based protein degradation tools may offer useful conceptual insights for the future development of platforms designed to improve intracellular targeting and modulate cancer-related signaling networks (89,90). However, most current evidence remains preclinical and several challenges still need to be addressed, including carrier safety, long-term biodistribution, batch-to-batch reproducibility, dose standardization and clinical scalability. Future studies should further validate these delivery systems in clinically relevant models and carefully evaluate their pharmacokinetics, toxicity and therapeutic advantages before clinical translation.

Clinical evidence and translational relevance of representative polyphenols. Although preclinical studies have extensively demonstrated that polyphenols regulate multiple BC-related signaling pathways, their clinical relevance ultimately depends on evidence from human studies. Therefore, available

human evidence should be interpreted cautiously, especially because pharmacokinetic behavior, systemic bioavailability, dose-response relationships, toxicity profiles and interactions with anticancer drugs remain insufficiently defined.

To provide a clearer overview of the available human evidence, Table II summarizes representative clinical studies of polyphenols in BC-related settings. The table summarizes intervention type, study design, population and duration, dose or formulation and major clinical findings. It highlights that current clinical evidence is heterogeneous, with variable compounds, formulations, doses, treatment durations, patient populations and endpoints. Although some clinical studies suggest potential adjuvant or supportive-care value, the therapeutic efficacy, optimal dose, safety profile, bioavailability and clinical applicability of polyphenols in BC require further validation.

A randomized controlled study evaluated the efficacy and safety of curcumin as an adjuvant to standard chemotherapy in women with locally advanced or metastatic BC. Compared with chemotherapy alone, the curcumin-combination group showed a significantly higher objective response rate, both in the intention-to-treat analysis and among patients who completed treatment (91). However, improvements in progression-free survival (PFS) and time to tumor progression (TTP) were modest and the study was limited by its single-center design, relatively small sample size, heterogeneous chemotherapy regimens and lack of detailed pharmacokinetic evaluation. Therefore, although this study supports the potential role of curcumin as a safe adjuvant to chemotherapy, larger multicenter, double-blind, placebo-controlled trials are still required to confirm its clinical benefit. Similarly, Saghatelyan *et al* (92) evaluated intravenous curcumin combined with paclitaxel in a randomized, double-blind, placebo-controlled clinical trial involving patients with advanced or metastatic BC. The curcumin-paclitaxel group showed a higher objective response rate than the placebo-paclitaxel group. Rajaram *et al* (93) evaluated soy isoflavone supplements and soy-based dietary intake in Malaysian peri- and postmenopausal women. Overall, neither approach significantly changed mammographic density after 1 year. A larger decline was observed among women closer to menopause. In a randomized, double-blind, placebo-controlled trial, researchers evaluated soy isoflavone supplementation among healthy premenopausal women (94). Soy isoflavones reduced MRI-measured fibroglandular breast tissue in a time- and concentration-dependent manner. This trial suggests that soy-derived polyphenols may have a potential role in BC risk reduction, although further studies are needed to confirm their clinical relevance. Ávila-Gálvez *et al* (95) found that diet-derived polyphenol metabolites were detectable in breast tumor tissues, with curcuminoids showing p53/p21-mediated antiproliferative, pro-senescent and pro-apoptotic effects in BC cells. Researchers conducted the DIANA-5 randomized trial in 1,542 high-risk BC survivors to test whether a Mediterranean dietary intervention could reduce recurrence (96). The intervention showed that a greater improvement in the Dietary Index was associated with reduced subsequent BC events, suggesting adherence may be critical for dietary benefit. PFS and TTP improvements were modest and non-significant, while safety was acceptable. Passildas Jahanmohan *et al* (97) conducted a multicenter, randomized, open-label phase II trial in patients with HER2-negative advanced or metastatic BC receiving docetaxel. Oral curcumin at 6 g/day did not improve the objective response rate compared with docetaxel alone, despite good compliance and acceptable safety. Clinical applications of polyphenols require careful evaluation of safety and herb-drug interactions. Braal *et al* (98) investigated green tea polyphenols during tamoxifen therapy and found no significant changes in the area under the plasma concentration-time curve (AUC) of endoxifen, which reflects overall systemic exposure, or in the maximum plasma concentration (Cmax) and trough plasma concentration (Ctrough) of endoxifen. Although polyphenols are often regarded as low-toxicity natural compounds, their clinical use as adjuncts to BC therapy requires caution. Some polyphenols and plant-derived compounds can modulate cytochrome P 450 (CYP) enzymes and drug transporters, thereby altering the pharmacokinetics of anticancer agents. A clinical case report described moderate neutropenia in a patient with BC receiving ribociclib and letrozole after self-administration of a supplement containing diosmin, escin and resveratrol, suggesting a possible CYP3A4-mediated interaction (99). Conversely, CYP3A4 induction by St. John's Wort may reduce exposure to drugs such as PTX and potentially compromise treatment efficacy. Therefore, the use of polyphenol-containing supplements during BC therapy should be evaluated on a case-by-case basis, especially for agents metabolized by CYP3A4 or drugs with narrow therapeutic windows.

Beyond direct antitumor effects, polyphenols have also been explored as supportive interventions for managing treatment-related toxicities in patients with BC. Lustberg *et al* (100) evaluated nanoemulsion curcumin in postmenopausal patients with BC with aromatase inhibitor-induced arthropathy. Although patient-reported outcomes and grip strength did not differ significantly between groups, the intervention showed good feasibility and adherence, and plasma curcumin was detectable only in patients receiving nanoemulsion curcumin. These findings suggest that nanoemulsion curcumin is clinically feasible, although its symptomatic efficacy requires further validation. Erfanian *et al* (101) investigated silymarin, a polyphenolic flavonolignan mixture from milk thistle, in patients receiving chemotherapy. The trial suggested potential hepatoprotective effects, particularly on alkaline phosphatase and bilirubin levels, while renal markers were not significantly improved. Another randomized controlled trial evaluated oral silymarin in patients with non-metastatic BC receiving doxorubicin-containing chemotherapy. Silymarin at 420 mg/day for 63 days helped prevent chemotherapy-related hepatotoxicity, mainly based on liver ultrasonography (102). These findings support the potential role of polyphenols in supportive care for patients with BC, particularly in reducing treatment-related organ toxicity. However, the current clinical evidence remains limited and larger randomized trials are needed to clarify optimal dosing, formulation, safety and clinically meaningful benefits.

Skin toxicity is a common supportive-care concern in patients with BC receiving radiotherapy or chemotherapy, with manifestations such as radiodermatitis, erythema, pain, desquamation and hand-foot syndrome. Therefore, several clinical studies have evaluated polyphenol-based interventions as adjunctive approaches to mitigate treatment-related skin

Table II. Human clinical evidence of polyphenols related to BC.

Intervention	Study design	Population and duration	Dose/formulation	Major findings
Curcumin + standard chemo	Single-center, SB RCT	Locally advanced/metastatic BC; n=120	Curcumin 1 g/d; 95% curcuminoids + piperine	ORR ↑: 38.33% vs. 8.33%; AEs ↓; PFS/TTP modest ↑ (91)
Curcumin + paclitaxel	Phase II DB, placebo-controlled, parallel-group RCT	Advanced/metastatic BC; n=150; 12 wk + 3-mo follow-up	Curcumin IV 300 mg/wk + paclitaxel, 12 wk	ORR ↑: 50.7 vs. 33.3%; PFS/TTP NS (92)
Soy isoflavone intake	Three-arm RCT	Healthy peri/postmenopausal women; n=118, completed n=91; 12 mo	Soy isoflavones 100 mg/d or 50 mg/d diet	MD: NS; dense area ↓: -1.3 vs. -0.5/-0.8 cm^2 (93)
Soy isoflavone supplement	Single-center, DB, placebo-controlled RCT	Healthy premenopausal women; isoflavone n=99, placebo n=98; ≤2 y	Soy isoflavones 136.6 mg/d, 5 d/wk	FGBT and FGBT% ↓ in time-/dose-dependent manner (94)
Polyphenol mix	Dietary intervention study	Preoperative newly diagnosed BC; intervention n=26, control n=13; 5±2 d	Mixed botanical extracts, 3 caps/d	Tumor curcumin: metabolites 2.5±2.4 μM; free curcumin 0.2±0.2 μM (95)
WFPB diet	Post-hoc analysis of 8-wk dietary RCT	Stage IV metastatic BC; WFPB n=21, usual care n=11; 8 wk	WFPB diet, 3 meals/d	Isoflavone intake ↑: 0.8 to 14.5 mg/d; n-6 ↓: 9.3 to 3.7 (96)
Curcumin + docetaxel	Multicenter, OL phase II RCT	HER2- advanced/relapsed/metastatic BC; n=42, evaluable n=37	Docetaxel q3wk x6 + curcumin 6 g/d	ORR NS: 55.6 vs. 73.7%; OS/TTP/CB similar (97)
Green tea + tamoxifen	Single-center, OL PK crossover RCT	BC on stable tamoxifen; n=14; crossover	Green tea 2 g/d; EGCG 300 mg/d; tamoxifen	Endoxifen exposure unchanged (98)
Nano-curcumin for AIA	Multicenter, DB, placebo-controlled pilot RCT	Postmenopausal ER/PR+ BC with AIA; n=42, completed n=34; 3 mo	Nano-curcumin 200 mg/d, 3 mo	Adherence ≥90%; plasma curcumin detected; clinical scores showed no clear benefit (100)
Silymarin for chemo-related protection	Placebo-controlled RCT	BC scheduled for chemotherapy; n=105, completed n=100; 60 d	Silymarin 140 mg bid; placebo	Liver parameters improved, especially ALP and bilirubin (101)
Silymarin for doxorubicin hepatotoxicity	Triple-blind, placebo-controlled trial	Non-metastatic BC on doxorubicin chemotherapy; n=50; 63 d	Silymarin 420 mg/d; placebo	Fatty liver grade ↓; AST/ALP ↓ at selected time-points (102)
Topical curcumin gel for RD	Multicenter, semi-blind, placebo-controlled phase II RCT	BC receiving fractionated RT; n=191	Curcumin gel tid; HPR Plus/placebo	RDS NS: 2.68 vs. 2.64 vs. 2.63 (103)

Table II. Continued.

Intervention	Study design	Population and duration	Dose/formulation	Major findings
Anthocyanins for RT skin toxicity	DB, placebo-controlled RCT	BC undergoing IMRT; anthocyanin n=97, placebo n=96; follow-up ≤12 mo	Purple corn cob extract 375 mg/d	RT skin toxicity NS; safe; possible lipid benefit (104)
Topical curcumin gel for RD prevention	Pilot DB, placebo-controlled RCT	BC undergoing RT; completed n=52	Topical 2% curcumin gel; placebo	RT redness/irritation, skin burden and pain ↓ (105)

AE, adverse event; AIA, aromatase inhibitor-induced arthropathy; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BC, breast cancer; bid, twice daily; CB, clinical benefit; DB, double-blind; EGCG, epigallocatechin-3-gallate; ER, estrogen receptor; FGBT, fibroglandular breast tissue; HER2, human epidermal growth factor receptor 2; IMRT, intensity-modulated radiotherapy; IV, intravenous; MD, mammographic density; NS, not significant; OL, open-label; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; PR, progesterone receptor; q3wk, every 3 weeks; RCT, randomized controlled trial; RD, radiation dermatitis; RDS, radiation dermatitis severity; RT, radiotherapy; SB, single-blind; tid, three times daily; TTP, time to tumor progression; WFPB, whole-food, plant-based.

toxicity, although their efficacy remains inconsistent. Ryan Wolf *et al* (103) evaluated topical curcumin gel for preventing radiation dermatitis and pain in patients with BC undergoing radiotherapy. Overall, curcumin did not significantly reduce dermatitis severity compared with placebo. However, exploratory subgroup analysis suggested potential benefit in patients with greater breast separation, indicating that curcumin-based supportive care may require risk-stratified patient selection. Another clinical trial further tested whether anthocyanins could protect against radiotherapy-induced skin toxicity in patients with BC (104). In this randomized, double-blind trial, oral anthocyanin supplementation did not improve skin elasticity, erythema, melanin changes or clinical toxicity scores compared with placebo. Heydari *et al* (105) evaluated topical curcumin for preventing radiation-induced dermatitis in patients with BC receiving radiotherapy. Compared with placebo, curcumin gel reduced redness and irritation during treatment and improved pain-related outcomes.

Taken together, current clinical evidence suggests that polyphenols may have translational value in BC management, particularly as adjuvant or supportive-care agents rather than as independent anticancer therapies. However, the available findings remain inconsistent and are limited by small sample sizes, heterogeneous formulations and doses, variable bioavailability, diverse treatment regimens and insufficient pharmacokinetic evaluation. Furthermore, potential herb-drug interactions should not be overlooked, especially in patients receiving chemotherapy, endocrine therapy, CDK4/6 inhibitors or other agents metabolized through CYP enzymes and drug transporters. Future well-designed multicenter, randomized, placebo-controlled trials are needed to clarify which polyphenols, formulations, doses and patient populations are most likely to achieve clinically meaningful benefits. Thus, while polyphenols represent a promising area for BC translational research, their clinical application should be approached cautiously, evidence-based and integrated with standard oncological care.

4. Discussion and perspectives

Polyphenols have attracted increasing attention in BC research because of their potential to regulate multiple biological processes involved in tumor progression, including proliferation, apoptosis, inflammation, EMT, angiogenesis, metastasis, immune regulation and therapeutic resistance. As summarized in this review, representative polyphenols may modulate several BC-related signaling pathways, such as PI3K/Akt/mTOR, p53-related signaling, NF-κB, STAT3, Wnt/β-catenin and MAPK. These pathways are interconnected signaling networks that converge on shared downstream regulators, including Cyclin D1, c-Myc, MMP-9, p21, BRCA1, COX-2 and inducible nitric oxide synthase. Therefore, the biological activity of polyphenols should be understood as network-level regulation rather than the inhibition or activation of any single pathway in isolation.

However, current evidence should be interpreted with caution. Most studies investigating polyphenols in BC are based on cell culture models, animal experiments or mechanistic assays. Although these studies provide important insights into possible molecular mechanisms, they

cannot fully reproduce the heterogeneity of human BC, the complexity of the tumor microenvironment or the pharmacokinetic behavior of polyphenols in patients. The effective concentrations observed *in vitro* may not always be clinically achievable because many polyphenols have poor aqueous solubility, rapid metabolism, limited systemic bioavailability and uncertain tumor accumulation. In addition, BC subtypes, receptor status, p53 mutation status, cellular context and treatment regimens may strongly influence the biological effects of polyphenols. Therefore, preclinical findings should be regarded as hypothesis-generating evidence rather than definitive proof of clinical efficacy.

The gut microbiome provides an important interface linking dietary polyphenols, microbial metabolism, estrogen homeostasis, inflammation, immune regulation and BC progression (83). Gut microorganisms can transform dietary polyphenols into smaller and potentially more bioavailable metabolites, whereas polyphenols may reshape microbial composition and metabolic activity. This bidirectional interaction may partly explain the systemic effects of dietary polyphenols. Nevertheless, the clinical significance of the polyphenol-gut microbiome-BC axis remains uncertain because individual microbiota profiles exhibit a marked variation depending on diet, age, menopausal status, antibiotic exposure, treatment history and host metabolism status. Future studies should integrate microbiome profiling, metabolomics and clinical endpoints to determine which patients are most likely to benefit from microbiome-centered polyphenol interventions.

Polyphenols may also have potential as adjuvant or supportive-care agents in combination with conventional BC therapies. Several preclinical studies suggest that specific polyphenols may enhance sensitivity to chemotherapy, endocrine therapy, radiotherapy or photodynamic therapy and modulate drug-resistance pathways (70-77). Clinical studies have also explored their potential to alleviate treatment-related toxicities, although the findings remain inconsistent (100-105). Some combinations may produce neutral or even antagonistic effects depending on the compound pairing, dose ratio, sequence of administration and cellular context. Therefore, claims of synergy should be supported by quantitative combination-index analysis, pharmacokinetic evaluation and safety assessment. Particular attention should also be paid to herb-drug interactions, especially for anticancer agents metabolized by CYP enzymes or substrates of drug efflux transporters.

Emerging delivery systems may help overcome certain limitations of free polyphenols by improving solubility, stability, cellular uptake, tumor targeting, controlled release and compatibility with chemo- or photothermal therapy. Nanocarriers, natural vesicle-like systems and co-delivery platforms may provide strategies for improving the translational potential of polyphenol-based interventions. However, these systems also introduce new challenges, including carrier safety, long-term biodistribution, manufacturing reproducibility, dose standardization and clinical scalability.

Overall, polyphenols represent a promising but still developing area in BC translational research. Current evidence supports their potential as multi-target adjuvant or supportive-care agents. Future research should prioritize well-designed multicenter randomized clinical trials, standardized formulations, pharmacokinetic and dose-response analyses, subtype-specific patient selection, toxicity monitoring and clinically meaningful endpoints (106). Such rigorous evaluations may facilitate the translation of polyphenols into evidence-based strategies for BC prevention, treatment support and survivorship care.

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Availability of data and materials

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Authors' contributions

JZ and JH wrote the original draft and generated the figures. ZM, SZ, XL, LZ and MS organized the tables, reviewed and edited the manuscript and provided supervision. TL revised and checked the article. Data authentication is not applicable. All authors have read, revised and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

References

1. Barzaman K, Karami J, Zarei Z, Hosseinzadeh A, Kazemi MH, Moradi-Kalbolandi S, Safari E and Farahmand L: Breast cancer: Biology, biomarkers, and treatments. Int Immunopharmacol 84: 106535, 2020.
2. Hu Y: Comment on 'Classifying the clinical significance of common breast pain symptoms using a large language model, ChatGPT (GPT-4)'. Clin Imaging 132: 110741, 2026.
3. Giaquinto AN, Sung H, Newman LA, Freedman RA, Smith RA, Star J, Jemal A and Siegel RL: Breast cancer statistics 2024. CA Cancer J Clin 74: 477-495, 2024.
4. Xiong X, Zheng LW, Ding Y, Chen YF, Cai YW, Wang LP, Huang L, Liu CC, Shao ZM and Yu KD: Breast cancer: Pathogenesis and treatments. Signal Transduct Target Ther 10: 49, 2025.
5. Selvakumar P, Badgeley A, Murphy P, Anwar H, Sharma U, Lawrence K and Lakshmikuttyamma A: Flavonoids and other polyphenols act as epigenetic modifiers in breast cancer. Nutrients 12: 761, 2020.

6. Sichetti M, Giuseffi M, Giglio E, Marino G and Mecca M: Effect of natural polyphenols on breast cancer chemoprevention and treatment. Mol Nutr Food Res 69: e70055, 2025.
7. Luca SV, Macovei I, Bujor A, Miron A, Skalicka-Woźniak K, Aprotosoaie AC and Trifan A: Bioactivity of dietary polyphenols: The role of metabolites. Crit Rev Food Sci Nutr 60: 626-659, 2020.
8. Wang Z, Li T, Sun M, Liu N, Zhang H, Feng Z and Lei N: Metabolomics- and proteomics-based disease diagnostic classifier model for the prediction and diagnosis of colorectal carcinoma. J Proteome Res 24: 2096-2111, 2025.
9. Wang Z, Fu Y, Zhang H, Liu N and Lei N: Diagnostic potential of the B9D2 gene in colorectal cancer based on whole blood gene expression data and machine learning. Discov Oncol 16: 1554, 2025.
10. Peng J, Liu T, Guan L, Xu Z, Xiong T, Zhang Y, Song J, Liu X, Yang Y and Hao X: A highly sensitive Lock-Cas12a biosensor for detection and imaging of miRNA-21 in breast cancer cells. Talanta 273: 125938, 2024.
11. Bouyahya A, Omari NE, El Hachlafi N, Jemly ME, Hakkour M, Balahbib A, El Menyiy N, Bakrim S, Naceiri Mrabti H, Khouchlaa A, *et al*: Chemical compounds of berry-derived polyphenols and their effects on gut microbiota, inflammation, and cancer. Molecules 27: 3286, 2022.
12. Zhu P, Yang Y, Qian J, Han J, Kong D, Sun B, Zhan J, Wei J, Guo Q, Nian S, *et al*: Discovery of novel thiophene (2,3-D) pyrimidine-thiazole derivative as promising MNK inhibitor to treat breast cancer. J Mol Struct 1321: 140125, 2025.
13. Li H, Li X and Du W: Interplay between Wnt signaling molecules and exosomal miRNAs in breast cancer (Review). Oncol Rep 52: 107, 2024.
14. Jahani Z, Sadeghizadeh M and Davoodi J: mTORC1 inhibition by metformin synergizes with dendrosomal nano-curcumin to induce apoptosis via modulation of pro- and anti-apoptotic proteins in breast cancer cells. Med Oncol 43: 94, 2025.
15. Donia T, Ali EMM, Kalantan AA, Alzahrani FA, Eid TM and Khamis AA: Synergistic anticancer efficacy of polydatin and sorafenib against the MCF-7 breast cancer cell line via inhibiting of PI3K/AKT/mTOR pathway and reducing resistance to treatment. Biochem Biophys Res Commun 739: 150972, 2024.
16. Wang D, Zheng C, Chen B and Ma S: Biochanin a induces apoptosis in MCF-7 breast cancer cells through mitochondrial pathway and Pi3K/AKT inhibition. Cell Biochem Funct 42: e70014, 2024.
17. Li S, Lin J, Wei J, Zhou L and Wang P: Sinigrin impedes the breast cancer cell growth through the inhibition of PI3K/AKT/mTOR phosphorylation-mediated cell cycle arrest. J Environ Pathol Toxicol Oncol 41: 33-43, 2022.
18. Wu D, Jia H, Zhang Z and Li S: Capsaicin suppresses breast cancer cell viability by regulating the CDK8/PI3K/Akt/Wnt/β-catenin signaling pathway. Mol Med Rep 22: 4868-4876, 2020.
19. Santos RA, Andrade EDS, Monteiro M, Fialho E, Silva JL, Daleprane JB and Ferraz da Costa DC: Green Tea (Camellia sinensis) extract induces p53-Mediated cytotoxicity and inhibits migration of breast cancer cells. Foods 10: 3154, 2021.
20. Changizi Z, Moslehi A, Rohani AH and Eidi A: Chlorogenic acid induces 4T1 breast cancer tumor's apoptosis via p53, Bax, Bcl-2, and caspase-3 signaling pathways in BALB/c mice. J Biochem Mol Toxicol 35: e22642, 2021.
21. Abdel-Latif M, Riad A, Soliman RA, Elkhouly AM, Nafae H, Gad MZ, Motaal AA and Youness RA: MALAT-1/p53/miR-155/miR-146a ceRNA circuit tuned by methoxylated quercitin glycoside alters immunogenic and oncogenic profiles of breast cancer. Mol Cell Biochem 477: 1281-1293, 2022.
22. Elsayed AM, Sherif NM, Hassan NS, Althobaiti F, Hanafy NAN and Sahyon HA: Novel quercetin encapsulated chitosan functionalized copper oxide nanoparticles as anti-breast cancer agent via regulating p53 in rat model. Int J Biol Macromol 185: 134-152, 2021.
23. Zeng A, Liang X, Zhu S, Liu C, Wang S, Zhang Q, Zhao J and Song L: Chlorogenic acid induces apoptosis, inhibits metastasis and improves antitumor immunity in breast cancer via the NF-κB signaling pathway. Oncol Rep 45: 717-727, 2021.
24. Chen M, Xiao C, Jiang W, Yang W, Qin Q, Tan Q, Lian B, Liang Z and Wei C: Capsaicin inhibits proliferation and induces apoptosis in breast cancer by down-regulating FBI-1-Mediated NF-κB pathway. Drug Des Devel Ther 15: 125-140, 2021.
25. Zhang J, Zheng J, Chen H, Li X, Ye C, Zhang F, Zhang Z, Yao Q and Guo Y: Curcumin Targeting NF-κB/Ubiquitin-proteasome-system axis ameliorates muscle atrophy in triple-negative breast cancer cachexia mice. Mediators Inflamm 2022: 2567150, 2022.
26. Jin S, Zheng Y, Li D, Liu X, Zhu T, Wang S, Liu Z and Liu Y: Effect of genistein supplementation on microenvironment regulation of breast tumors in obese mice. Breast Cancer Res 26: 147, 2024.
27. Sharma M, Arora I, Chen M, Wu H, Crowley MR, Tollefsbol TO and Li Y: Therapeutic effects of dietary soybean genistein on triple-negative breast cancer via regulation of epigenetic mechanisms. Nutrients 13: 3944, 2021.
28. Kumar V, Haldar S, Das NS, Ghosh S, Dhankhar P, Sircar D and Roy P: Pterostilbene-isothiocyanate inhibits breast cancer metastasis by selectively blocking IKK-β/NEMO interaction in cancer cells. Biochem Pharmacol 192: 114717, 2021.
29. Varsha NS and Naveen NR: JAK/STAT3 axis in breast cancer: Opportunities for intervention with natural phytochemical-based nanotherapeutics. Med Oncol 43: 186, 2026.
30. Yatoo GN, Bhat BA, Zubaid-Ul-Khazir, Asif M, Bhat SA, Gulzar F, Rashied F, Wani AH, Ahmed I, Zargar SM, *et al*: Network pharmacology and experimental insights into STAT3 inhibition by novel isoxazole derivatives of piperic acid in triple negative breast cancer. Fitoterapia 175: 105927, 2024.
31. Liu S, Feng D, Xu Y, Lin F and He Z: Quercetin targets IL6/JAK1/STAT3/MMP9 signaling to attenuate breast cancer progression in diabetic comorbidity: A multi-omics and experimental study. Phytomedicine 152: 157819, 2026.
32. Xiao Z, Yang Z, Li X, Chen X, Li J, He Y, Li W and Wang J: Mechanism by which Icariin suppresses pulmonary metastasis in triple-negative breast cancer through downregulation of the SPDL1/JAK2/STAT3 signaling pathway. Cancer Cell Int 26: 135, 2026.
33. Hou M, Li H, He T, Hui S, Dai W, Hou X, Zhao J, Zhao J, Wen J, Kan W, *et al*: Icariside I reduces breast cancer proliferation, apoptosis, invasion, and metastasis probably through inhibiting IL-6/STAT3 signaling pathway. J Pharm Pharmacol 76: 499-513, 2024.
34. Liu R, Choi HS, Ko YC, Yun BS and Lee DS: 5-Desmethylsinensetin isolated from Artemisia princeps suppresses the stemness of breast cancer cells via Stat3/IL-6 and Stat3/YAP1 signaling. Life Sci 280: 119729, 2021.
35. Manandhar S, S.P. Kabekkodu SP and Pai KSR: Aberrant canonical Wnt signaling: Phytochemical based modulation. Phytomedicine 76: 153243, 2020.
36. Xue W, Hao J, Zhang Q, Jin R, Luo Z, Yang X, Liu Y, Lu Q, Ouyang Y and Guo H: Chlorogenic acid inhibits epithelial-mesenchymal transition and invasion of breast cancer by down-regulating LRP6. J Pharmacol Exp Ther 384: 254-264, 2023.
37. Mediratta K, El-Sahli S, Marotel M, Awan MZ, Kirkby M, Salkini A, Kurdieh R, Abdisalam S, Shrestha A, Di Censo C, *et al*: Targeting CD73 with flavonoids inhibits cancer stem cells and increases lymphocyte infiltration in a triple-negative breast cancer mouse model. Front Immunol 15: 1366197, 2024.
38. Hassan AHE, Wang CY, Oh T, Ham G, Lee SK and Lee YS: Discovery of a stilbenoid-flavanone hybrid as an antitumor Wnt/β-catenin signaling pathway inhibitor. Bioorg Chem 145: 107178, 2024.
39. Eslaminejad T, Nematollahi-Mahani SN, Sargazi ML, Ansari M and Mirzaie V: Evaluating the effects of curcumin nano-chitosan on miR-221 and miR-222 expression and Wnt/β-catenin pathways in MCF-7, MDA-MB-231 and SKBR3 cell lines. Diagn Pathol 19: 35, 2024.
40. Wei R, Pan X, Cai D and Pan L: Synergistic inhibition of breast carcinoma cell proliferation by quercetin and sulforaphane via activation of the ERK/MAPK Pathway. Cell Biochem Biophys 83: 2533-2546, 2025.
41. Saeed S, Hassan AF, Suliman A, Moustafa AA and Alali F: Methanolic Leaves extract of Ziziphus spina-christi inhibits cell proliferation and migration of HER2-Positive breast cancer via p38 MAPK signaling pathway. Int J Mol Sci 26: 654, 2025.
42. Ying H, Zheng J, Jiang M, Shi W, Xu X and Ni X: Selective cytotoxicity of anhydroicaritin in ER-positive breast cancer via ESR1-mediated MAPK and apoptotic signaling. Chem Biol Interact 423: 111825, 2026.
43. Khongsti K, Das KB and Das B: MAPK pathway and SIRT1 are involved in the down-regulation of secreted osteopontin expression by genistein in metastatic cancer cells. Life Sci 265: 118787, 2021.
44. Safi A, Heidarian E and Ahmadi R: quercetin synergistically enhances the anticancer efficacy of docetaxel through induction of apoptosis and modulation of PI3K/AKT, MAPK/ERK, and JAK/STAT3 signaling pathways in MDA-MB-231 breast cancer cell line. Int J Mol Cell Med 10: 11-22, 2021.

45. Kombiyil S and Sivasithamparam ND: In vitro anti-cancer effect of crataegus oxyacantha berry extract on hormone receptor positive and triple negative breast cancers via regulation of canonical wnt signaling pathway. Appl Biochem Biotechnol 195: 2687-2708, 2023.
46. Jiménez-Flores E, Reytor-González C, Jima Gavilanes D, Carrillo C, Horowitz R, Carrera JCC, Bigoni-Ordóñez GD and Simancas-Racines D: Bioactive natural compounds in triple-negative breast cancer: Molecular targets and therapeutic perspectives. Pharmaceuticals (Basel) 19: 550, 2026.
47. Chlebowski RT, Aragaki AK, Anderson GL, Pan K, Neuhouser ML, Manson JE, Thomson CA, Mossavar-Rahmani Y, Lane DS, Johnson KC, *et al*: Dietary modification and breast cancer mortality: Long-term follow-up of the women's health initiative randomized trial. J Clin Oncol 38: 1419-1428, 2020.
48. Effiong ME, Cynthia IN, Bella-Omunagbe M, Afolabi IS and Chinedu SN: Microbiome dynamics in breast cancer: Mechanisms, therapeutic impacts and research gaps. Crit Rev Oncol Hematol 215: 104879, 2025.
49. Hasanian-Langroudi F, Ghasemi A, Hedayati M, Siadat SD and Tohidi M: Novel insight into the effect of probiotics in the regulation of the most important pathways involved in the pathogenesis of type 2 diabetes mellitus. Probiotics Antimicrob Proteins 16: 829-844, 2024.
50. Li ZD, Liu F, Zeng Y, Liu Y, Luo W, Yuan F, Li S, Li Q, Chen J, Fujita M, *et al*: EGCG suppresses PD-1 expression of T cells via inhibiting NF-κB phosphorylation and nuclear translocation. Int Immunopharmacol 133: 112069, 2024.
51. Chen J, Deng Y, Long SY, Xu HY, Zeng YT, Peng T, Yang CM, Du J and Zhang XY: Metabolic flux and catabolic kinetics of prebiotic-like dietary polyphenol phlorizin in association with gut microbiota in vitro. Food Chem 440: 138240, 2024.
52. Li M, Xu X, Jia Y, Yuan Y, Na G, Zhu L, Xiao X, Zhang Y and Ye H: Transformation of mulberry polyphenols by Lactobacillus plantarum SC-5: Increasing phenolic acids and enhancement of anti-aging effect. Food Res Int 192: 114778, 2024.
53. Zhu X, Ding G, Ren S, Xi J and Liu K: The bioavailability, absorption, metabolism, and regulation of glucolipid metabolism disorders by quercetin and its important glycosides: A review. Food Chem 458: 140262, 2024.
54. Di Lorenzo C, Colombo F, Biella S, Stockley C and Restani P: Polyphenols and human health: The role of bioavailability. Nutrients 13: 273, 2021.
55. Brito Sampaio K, Luiz de Brito Alves J, Mangueira do Nascimento Y, Fechine Tavares J, Sobral da Silva M, Dos Santos Nascimento D, Dos Santos Lima M, Priscila de Araújo Rodrigues N, Fernandes Garcia E and Leite de Souza E: Nutraceutical formulations combining Limosilactobacillus fermentum, quercetin, and or resveratrol with beneficial impacts on the abundance of intestinal bacterial populations, metabolite production, and antioxidant capacity during colonic fermentation. Food Res Int 161: 111800, 2022.
56. Zhu Q, Han Y, He Y, Meng P, Fu Y, Yang H, He G, Long M and Shi Y: Quercetin inhibits neuronal Ferroptosis and promotes immune response by targeting lipid metabolism-related gene PTGS2 to alleviate breast cancer-related depression. Phytomedicine 130: 155560, 2024.
57. Kang L, Chen H, He C and Li J: Effects of gut microbiota in breast cancer. Front Oncol 15: 1617410, 2025.
58. Hu S, Ding Q, Zhang W, Kang M, Ma J and Zhao L: Gut microbial beta-glucuronidase: A vital regulator in female estrogen metabolism. Gut Microbes 15: 2236749, 2023.
59. Simpson JB, Walker ME, Sekela JJ, Ivey SM, Jariwala PB, Storch CM, Kowalewski ME, Graboski AL, Lietzan AD, Walton WG, *et al*: Gut microbial β-glucuronidases influence endobiotic homeostasis and are modulated by diverse therapeutics. Cell Host Microbe 32: 925-944.e10, 2024.
60. Sabit H, Abouelnour S, Hassen BM, Magdy S, Yasser A, Wadan AS, Abdel-Ghany S, Radwan F, Alqosaibi AI, Hafiz H, *et al*: Anticancer potential of prebiotics: Targeting estrogen receptors and PI3K/AKT/mTOR in breast cancer. Biomedicines 13: 990, 2025.
61. Liu H, Li Z, Xu X, Xu B and Li Z: Network pharmacology and in vitro analyses reveal EGCG inhibits breast cancer progression via suppression of the EGFR/Src pathway. Biochem Biophys Res Commun 769: 151942, 2025.
62. Betts Z, Deveci Ozkan A, Yuksel B, Alimudin J, Aydin D, Aksoy O and Yanar S: Investigation of the combined cytotoxicity induced by sodium butyrate and a flavonoid quercetin treatment on MCF-7 breast cancer cells. J Toxicol Environ Health A 86: 833-845, 2023.
63. Barrea L, Verde L, Auriemma RS, Vetrani C, Cataldi M, Frias-Toral E, Pugliese G, Camajani E, Savastano S, Colao A and Muscogiuri G: Probiotics and prebiotics: Any role in menopause-related diseases? Curr Nutr Rep 12: 83-97, 2023.
64. Duysburgh C, Nicolas C, Van den Broeck M, Lloret F, Monginoux P, Rème C and Marzorati M: A specific blend of prebiotics and postbiotics improved the gut microbiome of dogs with soft stools in the in vitro Simulator of the Canine Intestinal Microbial Ecosystem. J Anim Sci 103: skaf056, 2025.
65. Hu Q, Li J, Wang T, Xu X, Duan Y and Jin Y: Polyphenolic nanoparticle-modified probiotics for microenvironment remodeling and targeted therapy of inflammatory bowel disease. ACS Nano 18: 12917-12932, 2024.
66. Tian R, Yu L, Tian F, Zhao J, Chen W and Zhai Q: Effect of inulin, galacto-oligosaccharides, and polyphenols on the gut microbiota, with a focus on Akkermansia muciniphila. Food Funct 15: 4763-4772, 2024.
67. Xu J, Jönsson T, Plaza M, Håkansson Å, Antonsson M, Ahrén IL, Turner C, Spégel P and Granfeldt Y: Probiotic fruit beverages with different polyphenol profiles attenuated early insulin response. Nutr J 17: 34, 2018.
68. Plamada D and Vodnar DC: Polyphenols-gut microbiota interrelationship: A transition to a new generation of prebiotics. Nutrients 14: 137, 2021.
69. Unno T, Araki Y, Inagaki S, Kobayashi M, Ichitani M, Takihara T and Kinugasa H: Fructooligosaccharides increase in plasma concentration of (-)-epigallocatechin-3-gallate in rats. J Agric Food Chem 69: 14849-14855, 2021.
70. Radwan AM, Abosharaf HA, Sharaky M, Abdelmonem R and Effat H: Functional combination of resveratrol and tamoxifen to overcome tamoxifen-resistance in breast cancer cells. Arch Pharm (Weinheim) 357: e2400261, 2024.
71. Biltekin B, Uzun H and Bilir A: Resveratrol as a modulator of adriamycin-, taxol-, and cisplatin-induced cytotoxicity in MCF-7 breast cancer cells. Int J Mol Sci 27: 2979, 2026.
72. Liu S, Li R, Qian J, Sun J, Li G, Shen J and Xie Y: Combination therapy of doxorubicin and quercetin on multidrug-resistant breast cancer and their sequential delivery by reduction-sensitive hyaluronic acid-based conjugate/d-α-Tocopheryl Poly(ethylene glycol) 1000 succinate mixed micelles. Mol Pharm 17: 1415-1427, 2020.
73. Mawalizadeh F, Mohammadzadeh G, Khedri A and Rashidi M: Quercetin potentiates the chemosensitivity of MCF-7 breast cancer cells to 5-fluorouracil. Mol Biol Rep 48: 7733-7742, 2021.
74. Khamis AA, Ali EMM, Salim EI and El-Moneim MAA: Synergistic effects of bee venom, hesperidin, and piperine with tamoxifen on apoptotic and angiogenesis biomarker molecules against xerographic MCF-7 injected rats. Sci Rep 14: 1510, 2024.
75. Komorowska D, Gajewska A, Hikisz P, Bartosz G and Rodacka A: Comparison of the effects of resveratrol and its derivatives on the radiation response of MCF-7 breast cancer cells. Int J Mol Sci 22: 9511, 2021.
76. Zeng Y, Liu F, Wang J, Shao B, He T, Xiang Z, Wang Y, Zhu S, Yang T, Yu S, *et al*: Fisetin micelles precisely exhibit a radiosensitization effect by inhibiting PDGFRβ/STAT1/STAT3/Bcl-2 signaling pathway in tumor. Chin Chem Lett 36: 109734, 2025.
77. Ghazizadeh M, KhorsandiS K and Najafi A: Synergic anti-tumor effects of photodynamic therapy and resveratrol on triple-negative breast cancer cells. Photochem Photobiol Sci 24: 451-465, 2025.
78. Ali MM, Simmons P, Warren A, Gatrell LB, Resende-Coelho A, McElroy T, Allen AR and Almeida M: The adverse effects of chemotherapy on bone mass are not prevented by senolytics. Sci Rep 15: 17279, 2025.
79. Sunoqrot S, Abusulieh S and Abusara OH: Identifying synergistic combinations of Doxorubicin-Loaded polyquercetin nanoparticles and natural Products: Implications for breast cancer therapy. Int J Pharm 645: 123392, 2023.
80. Li Y, Li C, Liu S, Wang Q, Tang Z, Qu J, Ye J, Lu Y, Wang J, Zhang K, *et al*: Nano-photosensitizers with gallic acid-involved Fe-O-Cu 'electronic storage station' bridging ligand-to-metal charge transfer for efficient catalytic theranostics. J Colloid Interface Sci 676: 974-988, 2024.
81. Li Y, Zhang X, Liu S, Chunsheng L, Qiang W, Jin Y, Yong L and Jiating X: Engineered iron-based metal-organic frameworks nanoplatforms for cancer theranostics: A mini review. Chin Chem Lett 36: 110501, 2025.
82. Gregoriou Y, Gregoriou G, Yilmaz V, Kapnisis K, Prokopi M, Anayiotos A, Strati K, Dietis N, Constantinou AI and Andreou C: Resveratrol loaded polymeric micelles for theranostic targeting of breast cancer cells. Nanotheranostics 5: 113-124, 2021.

83. Chen Q, Li Q, Liang Y, Zu M, Chen N, Canup BSB, Luo L, Wang C, Zeng L and Xiao B: Natural exosome-like nanovesicles from edible tea flowers suppress metastatic breast cancer via ROS generation and microbiota modulation. Acta Pharm Sin B 12: 907-923, 2022.
84. Verma M, Yadav K, Parihar R, Dutta D, Chaudhuri S and Sivakumar S: Active tumor targeting by core-shell PDMS-HA nanoparticles with sequential delivery of doxorubicin and quercetin to overcome P-glycoprotein efflux pump. Nanoscale 17: 5033-5055, 2025.
85. Bi Q, Liu D, Tan Y, Hu P, Tong Q, Ma L, Jiang J, Li X and Yi Z: Phenylboronic acid functionalized resveratrol-based nanomedicines with enhanced targeting for synergistic chemo-photothermal breast cancer therapy. J Mater Chem B 14: 3239-3254, 2026.
86. Afarin R, Ahmadpour F, Hatami M, Monjezi S and Igder S: Combination of Etoposide and quercetin-loaded solid lipid nanoparticles Potentiates apoptotic effects on MDA-MB-231 breast cancer cells. Heliyon 10: e31925, 2024.
87. Tilawat M and Bonde S: Curcumin and quercetin loaded nanocochleates gel formulation for localized application in breast cancer therapy. Heliyon 9: e22892, 2023.
88. Guo Y, Liu S, Luo F, Tang D, Yang T, Yang X and Xie Y: A Nanosized codelivery system based on intracellular stimuli-triggered dual-drug release for multilevel chemotherapy amplification in drug-resistant breast cancer. Pharmaceutics 14: 422, 2022.
89. Cheng C, Hou S, An H, Du C, Wang Z, Ran H, Zhou Z, Jiang W and Ren J: Igniting endogenous calcipoptosis via ER-Mitochondrial calcium shuttle hijacking for potent antitumor immunity. Adv Mater 38: e18631, 2026.
90. Li Y, Jin Z, Ahmed SU, Das J, Bleher R, Chang D, Yu X, Flynn CD, Zhou J, Hu X, *et al*: Biomolecular condensates as protein degradation tools for intracellular targets. Nat Commun: May 13, 2026 (Epub ahead of print).
91. Goyal S, Beniwal SK, Agarwal P, Brar RK, Jain P, Kumar HS and Das BC: Efficacy and safety of curcumin as an adjuvant to standard chemotherapy in advanced and metastatic breast cancer patients: A randomized controlled study. Phytother Res 39: 5006-5024, 2025.
92. Saghatelyan T, Tananyan A, Janoyan N, Tadevosyan A, Petrosyan H, Hovhannisyan A, Hayrapetyan L, Arustamyan M, Arnhold J, Rotmann AR, *et al*: Efficacy and safety of curcumin in combination with paclitaxel in patients with advanced, metastatic breast cancer: A comparative, randomized, double-blind, placebo-controlled clinical trial. Phytomedicine 70: 153218, 2020.
93. Rajaram N, Yap B, Eriksson M, Mariapun S, Tan LM, Sa'at H, Ho ELM, Taib NAM, Khor GL, Yip CH, *et al*: A Randomized controlled trial of soy isoflavone intake on mammographic density among malaysian women. Nutrients 15: 299, 2023.
94. Lu LW, Chen NW, Brunder DG, Nayeem F, Nagamani M, Nishino TK, Anderson KE and Khamapirad T: Soy isoflavones decrease fibroglandular breast tissue measured by magnetic resonance imaging in premenopausal women: A 2-year randomized double-blind placebo controlled clinical trial. Clin Nutr ESPEN 52: 158-168, 2022.
95. Ávila-Gálvez M, González-Sarrías A, Martínez-Díaz F, Abellán B, Martínez-Torrano AJ, Fernández-López AJ, Giménez-Bastida JA and Espín JC: Disposition of dietary polyphenols in breast cancer patients' tumors, and their associated anticancer activity: The particular case of curcumin. Mol Nutr Food Res 65: e2100163, 2021.
96. Berrino F, Villarini A, Gargano G, Krogh V, Grioni S, Bellegotti M, Venturelli E, Raimondi M, Traina A, Zarcone M, *et al*: The effect of diet on breast cancer recurrence: The DIANA-5 randomized trial. Clin Cancer Res 30: 965-974, 2024.
97. Judith PJ, Maureen B, Mélanie P, Fabrice K, Isabelle VD, Pascale DL, Catherine A, Jean-Marc N, Hervé C, Valérie D, *et al*: Curcumin's effect in advanced and metastatic breast cancer patients treated with first or second-line docetaxel: A randomized trial. Health Sci Rep 7: e70052, 2024.
98. Braal CL, Hussaarts KGAM, Seuren L, Oomen-de Hoop E, de Bruijn P, Buck SAJ, Bos MEMM, Thijs-Visser MF, Zuetenhorst HJM, Mathijssen-van Stein D, *et al*: Influence of green tea consumption on endoxifen steady-state concentration in breast cancer patients treated with tamoxifen. Breast Cancer Res Treat 184: 107-113, 2020.
99. Orzetti S and Baldo P: Toxicity derived from interaction between natural compounds and cancer therapeutic drugs metabolized by CYP3A4: Lessons learned from two clinical case reports. Int J Mol Sci 24: 15976, 2023.
100. Lustberg M, Fan-Havard P, Wong FL, Hill K, Phelps MA, Herrera KW, Tsai NC, Synold T, Feng Y, Kalu C, *et al*: Randomized placebo-controlled, double-blind clinical trial of nanoemulsion curcumin in women with aromatase inhibitor-induced arthropathy: An Alliance/NCORP pilot trial. Breast Cancer Res Treat 205: 61-73, 2024.
101. Erfanian SS, Ansari H, Javanmard SH, Amini Z and Hajigholami A: The hepatorenal protective effects of silymarin in cancer patients receiving chemotherapy: A randomized, placebo-controlled trial. BMC Complement Med Ther 24: 329, 2024.
102. Fatemi Shandiz A, Karimi G, Dayyani M, Hosseini S and Elyasi S: Evaluation of oral silymarin formulation efficacy in prevention of doxorubicin induced hepatotoxicity in patients with non-metastatic breast cancer. J Oncol Pharm Pract 31: 965-976, 2025.
103. Ryan Wolf J, Gewandter JS, Bautista J, Heckler CE, Strasser J, Dyk P, Anderson T, Gross H, Speer T, Dolohanty L, *et al*: Utility of topical agents for radiation dermatitis and pain: A randomized clinical trial. Support Care Cancer 28: 3303-3311, 2020.
104. Bracone F, De Curtis A, Di Castelnuovo A, Pilu R, Boccardi M, Cilla S, Macchia G, Deodato F, Costanzo S, Iacoviello L, *et al*: Skin toxicity following radiotherapy in patients with breast carcinoma: Is anthocyanin supplementation beneficial? Clin Nutr 40: 2068-2077, 2021.
105. Heydari B, Sheikhalishahi S, Hoseinzade F, Shabani M, Ramezani V and Saghafi F: Topical curcumin for prevention of radiation-induced dermatitis: A pilot double-blind, placebo-controlled trial. Cancer Invest 43: 173-182, 2025.
106. Duda-Chodak A and Tarko T: Possible side effects of polyphenols and their interactions with medicines. Molecules 28: 2536, 2023.