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Molecular and cellular mechanisms of phytotherapeutic compounds in the chemoprevention and treatment of mammary carcinoma: An integrative review of herbal interventions modulating oncogenic signaling pathways and tumor microenvironment in breast cancer cells

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Abstract
Background: Breast cancer remains a leading cause of cancer-related morbidity and mortality worldwide. Conventional therapies, including chemotherapy, radiotherapy, and endocrine therapy, are effective but often limited by toxicity, resistance, and tumor heterogeneity. Phytotherapeutic compounds have emerged as complementary and alternative strategies with promising anticancer potential.
Objective: This review aims to provide an integrative analysis of the molecular and cellular mechanisms by which phytotherapeutic compounds exert chemopreventive and therapeutic effects in breast cancer, with an emphasis on modulation of oncogenic signaling pathways and the tumor microenvironment (TME).
Methods: We performed a comprehensive analysis of preclinical (*in vitro* and *in vivo*) and clinical studies, focusing on polyphenols, terpenoids, alkaloids, flavonoids, isoflavones, sulfur-containing compounds, and other bioactives. Mechanistic insights, synergy with conventional therapies, and translational challenges were synthesized.
Results: Phytochemicals such as curcumin, resveratrol, EGCG, quercetin, genistein, sulforaphane, thymoquinone, berberine, and withaferin A exhibit anti-proliferative, pro-apoptotic, cell cycle-arresting, anti-metastatic, and autophagy-modulating effects. They target key oncogenic pathways, including PI3K/Akt/mTOR, NF-κB, MAPK/ERK, Wnt/β-catenin, and estrogen receptor signaling, while influencing the TME through angiogenesis inhibition, immune modulation, and extracellular matrix remodeling. Preclinical studies demonstrate enhanced efficacy when combined with chemotherapy, radiotherapy, or endocrine therapy. Clinical data, though limited, indicate favorable safety profiles and biomarker modulation.
Conclusion: Phytotherapeutic compounds offer a multifaceted, mechanistically rational approach to breast cancer management, either as monotherapy or in combination with conventional treatments. Challenges such as bioavailability, standardization, and clinical translation remain, highlighting the need for well-designed trials and advanced delivery systems.

Keywords: Breast cancer, phytotherapy, polyphenols, apoptosis, cell cycle, tumor microenvironment, chemoprevention, signaling pathways, integrative oncology

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Introduction

Breast cancer remains the most frequently diagnosed cancer among women worldwide and continues to be the leading cause of cancer-related mortality, accounting for approximately 2.3 million new cases and nearly 685,000 deaths globally in 2020 alone [1]. The incidence is rising steadily, particularly in low- and middle-income countries, due to urbanization, lifestyle changes, and increased life expectancy [2]. Despite remarkable advances in early detection and targeted therapies, breast cancer heterogeneity and tumor microenvironment complexity continue to pose significant challenges to disease management [3].

Conventional treatment modalities such as surgery, chemotherapy, radiotherapy, endocrine therapy, and targeted therapy have significantly improved survival outcomes; however, these approaches are often limited by systemic toxicity, drug resistance, recurrence, and impact on quality of life [4, 5]. For example, long-term use of chemotherapeutic agents is associated with cardiotoxicity, immunosuppression, and multidrug resistance, while endocrine therapy frequently results in adverse effects including thromboembolic events and endometrial carcinoma [6]. Moreover, resistance to targeted therapies such as trastuzumab and CDK4/6 inhibitors has become a major obstacle, underscoring the urgent need for safer, multi-targeted therapeutic alternatives [7].

Phytotherapeutic compounds, derived from medicinal plants, have gained increasing attention as complementary and alternative therapeutic strategies for breast cancer prevention and treatment [8]. Many bioactive phytochemicals including polyphenols, flavonoids, alkaloids, terpenoids, and sulfur-containing compounds demonstrate pleiotropic actions by modulating oncogenic signaling pathways, inducing apoptosis, inhibiting angiogenesis, and regulating the tumor microenvironment [9, 10]. Unlike single-target chemotherapeutics, phytotherapeutics often act on multiple cellular and molecular pathways simultaneously, thereby reducing the likelihood of resistance development and providing synergistic benefits when combined with conventional therapies [11].

Given the growing body of experimental and clinical evidence supporting the anticancer efficacy of phytochemicals, an integrative review focusing on their molecular and cellular mechanisms in breast cancer is warranted. This approach not only highlights their chemopreventive and therapeutic potential but also emphasizes their role in modulating oncogenic signaling and tumor-host interactions, paving the way for future translational applications in integrative oncology [12].

2. Phytotherapeutic Compounds with Anti-Breast Cancer Potential

Breast cancer progression involves complex molecular pathways, including aberrant signaling, apoptosis evasion, angiogenesis, and immune evasion. Phytotherapeutic compounds, derived from medicinal plants, have shown pleiotropic actions in targeting these hallmarks of cancer. The following subsections summarize major classes of bioactive compounds with potential roles in breast cancer chemoprevention and therapy.

2.1 Polyphenols

Polyphenols are widely distributed plant metabolites with strong antioxidant and anti-inflammatory properties. Curcumin, the principal curcuminoid from *Curcuma longa*, has demonstrated inhibition of NF-κB, PI3K/Akt/mTOR, and Wnt/β-catenin pathways, leading to apoptosis induction and suppression of metastasis [13]. Resveratrol, a stilbene present in grapes and berries, modulates estrogen receptor signaling and inhibits angiogenesis through VEGF suppression [14] Epigallocatechin gallate (EGCG), the major catechin in green tea, exerts cytotoxicity on breast cancer cells by modulating MAPK/ERK and Akt signaling while also enhancing sensitivity to chemotherapeutic agents [15]. Quercetin, a flavonol abundant in onions and apples, induces cell cycle arrest at G2/M phase, suppresses epithelial-mesenchymal transition (EMT), and inhibits tumor invasion [16].

2.2 Terpenoids and Alkaloids

Terpenoids and alkaloids have shown promise as multitargeted phytochemicals. Artemisinin, derived from *Artemisia annua*, generates reactive oxygen species selectively in cancer cells and induces apoptosis via mitochondrial pathways [17]. Betulinic acid, a pentacyclic triterpenoid from birch bark, promotes apoptosis by activating caspases and downregulating anti-apoptotic proteins such as Bcl-2 [18]. Berberine, an isoquinoline alkaloid from *Berberis vulgaris*, suppresses breast cancer cell proliferation by inhibiting PI3K/Akt signaling and induces autophagy-mediated cell death [19].

2.3 Flavonoids and Isoflavones

Dietary flavonoids and isoflavones act as modulators of estrogenic and oncogenic signaling. Genistein, a soy isoflavone, exerts anti-proliferative effects through estrogen receptor modulation and inhibition of tyrosine kinase activity [20]. Apigenin, found in parsley and chamomile, inhibits angiogenesis, NF-κB signaling, and induces apoptosis in triple-negative breast cancer models [21]. Kaempferol, abundant in broccoli and tea, reduces breast cancer metastasis by inhibiting MMP activity and suppressing EMT [22].

2.4 Sulfur-containing Compounds

Sulfur-rich phytochemicals exhibit chemopreventive and detoxifying effects. Sulforaphane, an isothiocyanate from cruciferous vegetables, inhibits histone deacetylase (HDAC), restores tumor suppressor gene activity, and targets breast cancer stem cells [23]. Allicin, derived from garlic (*Allium sativum*), induces apoptosis through caspase activation and ROS generation, while also reducing invasion by downregulating MMPs [24].

2.5 Other Herbal Bioactives

Several bioactives beyond classical categories exhibit strong anticancer activity. Withaferin A, from *Withania somnifera* (Ashwagandha), disrupts the cytoskeleton, induces apoptosis, and inhibits NF-κB and STAT3 signaling [25]. Ginsenosides, the saponins from *Panax ginseng*, modulate immune response and suppress angiogenesis and metastasis in breast cancer models [26]. Thymoquinone, the active constituent of *Nigella sativa* (black seed), induces apoptosis, inhibits PI3K/Akt/mTOR pathway, and enhances chemosensitivity [27].

Table 1: Major Phytotherapeutic Compounds and Their Mechanisms in Breast Cancer

Category	Compound	Source	Key Mechanisms in Breast Cancer	References
Polyphenols	Curcumin	*Curcuma longa*	Inhibits NF-κB, PI3K/Akt/mTOR, Wnt/β-catenin; induces apoptosis, suppresses metastasis	[13]
	Resveratrol	Grapes, berries	Modulates ER signaling, inhibits VEGF/angiogenesis	[14]
	EGCG	Green tea	Modulates MAPK/ERK, Akt; enhances chemo-sensitivity	[15]

	Quercetin	Onions, apples	Induces G2/M arrest, inhibits EMT and invasion	[16]
Terpenoids & Alkaloids	Artemisinin	*Artemisia annua*	ROS generation, mitochondrial apoptosis	[17]
	Betulinic acid	Birch bark	Caspase activation, Bcl-2 downregulation	[18]
	Berberine	*Berberis vulgaris*	Inhibits PI3K/Akt, induces autophagy	[19]
Flavonoids & Isoflavones	Genistein	Soy	ER modulation, tyrosine kinase inhibition	[20]
	Apigenin	Parsley, chamomile	NF-κB inhibition, apoptosis induction	[21]
	Kaempferol	Broccoli, tea	Inhibits MMPs, suppresses EMT	[22]
Sulfur-containing	Sulforaphane	Broccoli, crucifers	HDAC inhibition, CSC targeting	[23]
	Allicin	Garlic	ROS-mediated apoptosis, invasion suppression	[24]
Other Bioactives	Withaferin A	Ashwagandha	NF-κB/STAT3 inhibition, apoptosis induction	[25]
	Ginsenosides	Ginseng	Immunomodulation, anti-angiogenesis	[26]
	Thymoquinone	Black seed	Apoptosis induction, PI3K/Akt inhibition	[27]

3. Modulation of Oncogenic Signaling Pathways

Breast cancer development and progression are driven by aberrant activation of multiple oncogenic signaling pathways that regulate proliferation, survival, angiogenesis, and metastasis. Phytotherapeutic compounds exert anticancer effects by targeting these dysregulated pathways, leading to suppression of tumor growth and sensitization to therapy.

3.1 PI3K/Akt/mTOR Pathway

The PI3K/Akt/mTOR axis is one of the most frequently altered pathways in breast cancer, contributing to cell survival, proliferation, angiogenesis, and resistance to endocrine and targeted therapies. Phytochemicals such as curcumin, resveratrol, and quercetin inhibit PI3K/Akt signaling, reduce phosphorylation of Akt and mTOR, and enhance apoptosis in breast cancer models [28, 29]. Berberine also suppresses PI3K/Akt activation, inducing autophagy and inhibiting proliferation [30].

3.2 MAPK/ERK Pathway

The MAPK/ERK signaling cascade plays a pivotal role in cell cycle progression, differentiation, and metastatic potential of breast cancer cells. Dysregulation of this pathway is associated with aggressive phenotypes and resistance to chemotherapy. Apigenin and genistein suppress MAPK/ERK signaling, resulting in growth inhibition and reduced invasion of breast cancer cells [31]. EGCG downregulates ERK phosphorylation, thereby inhibiting proliferation and colony formation [32].

3.3 NF-κB and Inflammatory Pathways

NF-κB signaling contributes to breast tumorigenesis by promoting chronic inflammation, resistance to apoptosis, and enhanced expression of cytokines and adhesion molecules. Phytochemicals including curcumin, EGCG, and withaferin A potently suppress NF-κB activity, thereby reducing pro-inflammatory cytokine secretion (IL-6, TNF-α) and sensitizing tumor cells to chemotherapeutics [33, 34].

3.4 Wnt/β-catenin Pathway

Aberrant activation of Wnt/β-catenin signaling contributes to tumor initiation, stemness, and metastasis in breast cancer. Sulforaphane inhibits Wnt/β-catenin signaling and targets breast cancer stem-like cells, reducing tumor recurrence [35]. Berberine also interferes with β-catenin nuclear translocation, decreasing transcription of oncogenic targets such as cyclin D1 [36].

3.5 Hormonal Signaling and Estrogen Receptor Pathways

Estrogen receptor (ER) signaling is central to hormone receptor-positive breast cancers, driving cell proliferation and survival. Phytoestrogens such as genistein and resveratrol exhibit dual roles: at low concentrations, they may act as weak estrogen agonists, while at higher concentrations they antagonize ER signaling, reducing breast cancer growth [37]. These compounds also downregulate aromatase activity, thereby decreasing estrogen biosynthesis [38].

Table 2: Phytochemicals Targeting Oncogenic Signaling Pathways in Breast Cancer

Signaling Pathway	Phytochemicals	Mechanistic Actions	References
PI3K/Akt/mTOR	Curcumin, Resveratrol, Quercetin, Berberine	Inhibit PI3K/Akt phosphorylation, block mTOR activation, induce apoptosis/autophagy	[28-30]
MAPK/ERK	Apigenin, Genistein, EGCG	Suppress ERK phosphorylation, inhibit proliferation, reduce invasion	[31, 32]
NF-κB/Inflammatory	Curcumin, EGCG, Withaferin A	Block NF-κB nuclear translocation, reduce IL-6/TNF-α, sensitize to chemo	[33, 34]
Wnt/β-catenin	Sulforaphane, Berberine	Inhibit β-catenin signaling, target CSCs, downregulate cyclin D1	[35, 36]
Estrogen Receptor	Genistein, Resveratrol	ER modulation (agonist/antagonist), aromatase inhibition	[37, 38]

4. Phytotherapeutics and Tumor Microenvironment (TME)

The tumor microenvironment (TME) plays a pivotal role in breast cancer progression by providing growth signals, remodeling extracellular structures, promoting angiogenesis, and creating an immunosuppressive milieu. Phytotherapeutic compounds exert anticancer effects not only through direct cytotoxicity but also by reprogramming the TME to an anti-tumorigenic state.

4.1 Anti-angiogenic Effects

Angiogenesis is essential for tumor growth and metastasis, mediated primarily by vascular endothelial growth factor (VEGF). Resveratrol and curcumin inhibit VEGF signaling, suppress endothelial cell proliferation, and reduce neovascularization in breast cancer models [39, 40]. Ginsenosides also downregulate HIF-1α and VEGF expression, attenuating hypoxia-driven angiogenesis [41].

4.2 Modulation of Cancer-Associated Fibroblasts (CAFs)
CAFs secrete growth factors, cytokines, and extracellular matrix (ECM) proteins that support tumor invasion and therapy resistance. Quercetin suppresses CAF activation and decreases fibroblast-induced breast cancer cell migration [42]. Withaferin A disrupts vimentin filaments in fibroblasts, thereby impairing their tumor-supportive functions [43].

4.3 Immunomodulation
An immunosuppressive TME supports tumor progression by impairing T cell and NK cell function. Thymoquinone enhances CD8+ T cell infiltration and NK cell activity while decreasing regulatory T cells in breast cancer models [44]. Ginsenosides modulate immune checkpoints by downregulating PD-L1 expression, restoring T cell-mediated cytotoxicity [45].

4.4 Extracellular Matrix (ECM) Remodeling
ECM degradation facilitates invasion and metastasis, largely mediated by matrix metalloproteinases (MMPs). Apigenin and kaempferol downregulate MMP-2 and MMP-9, reducing migration and invasion in breast cancer cells [46, 47]. Allicin also attenuates ECM remodeling by decreasing MMP activity and enhancing TIMP (tissue inhibitors of metalloproteinases) expression [48].

Table 3: Phytochemicals Targeting Tumor Microenvironment in Breast Cancer

TME Component	Phytochemicals	Mechanistic Actions	References
Angiogenesis	Resveratrol, Curcumin, Ginsenosides	Inhibit VEGF/HIF-1α, block endothelial proliferation	[39-41]
Cancer-Associated Fibroblasts	Quercetin, Withaferin A	Suppress CAF activation, disrupt vimentin, reduce fibroblast-induced migration	[42, 43]
Immunomodulation	Thymoquinone, Ginsenosides	Enhance CD8+ T cells/NK activity, downregulate PD-L1, reduce Tregs	[44, 45]
ECM Remodeling	Apigenin, Kaempferol, Allicin	Inhibit MMP-2/9, increase TIMPs, suppress invasion/metastasis	[46-48]

5. Cellular Mechanisms of Action
Phytotherapeutic compounds mediate anticancer effects at the cellular level through multiple complementary mechanisms notably induction of apoptosis, cell-cycle arrest, inhibition of epithelial-mesenchymal transition (EMT) and metastasis, and modulation of autophagy. These actions often reflect upstream signaling pathway modulation (Section 3) and TME reprogramming (Section 4), producing cytotoxicity toward malignant cells while sparing normal tissue.

5.1 Induction of Apoptosis
Apoptosis is a programmed cell-death process frequently dysregulated in breast cancer. Phytochemicals trigger both the intrinsic (mitochondrial) and extrinsic (death-receptor) apoptotic cascades. Mechanisms include mitochondrial membrane depolarization, cytochrome-c release, caspase-9 and caspase-3 activation, downregulation of anti-apoptotic proteins (Bcl-2, Bcl-xL) and upregulation of pro-apoptotic proteins (Bax, Bak). For example, curcumin, betulinic acid, and thymoquinone have been shown to initiate mitochondrial apoptosis in MCF-7 and MDA-MB-231 cells via caspase activation and Bcl-2 family modulation [49-51]. Additionally, artemisinin and its derivatives induce apoptosis through ROS-mediated mitochondrial damage selectively in cancer cells [52].

5.2 Cell Cycle Arrest
Interruption of cell-cycle progression prevents proliferation of malignant cells. Phytochemicals commonly induce arrest at G0/G1 or G2/M checkpoints by modulating cyclins, cyclin-dependent kinases (CDKs), and CDK inhibitors (p21^Cip1, p27^Kip1). Quercetin and genistein frequently induce G2/M or G0/G1 arrest via downregulation of cyclin D1 and CDK4/6 and upregulation of p21/p27 [53, 54]. EGCG is known to reduce cyclin D1 expression and impair retinoblastoma (Rb) phosphorylation, thereby blocking G1→S transition [55].

5.3 Anti-metastatic and Anti-invasive Effects (EMT Suppression)
Metastasis requires EMT, ECM degradation, and cell motility. Phytochemicals inhibit EMT by maintaining epithelial markers (E-cadherin), suppressing mesenchymal markers (N-cadherin, vimentin), and lowering transcription factors driving EMT (Snail, Slug, Twist). Sulforaphane, apigenin, and kaempferol reduce MMP-2/9 expression and activity, restore E-cadherin, and downregulate Snail/Twist, thereby decreasing invasion and metastatic potential *in vitro* and *in vivo* [56-58]. Withaferin A disrupts vimentin intermediate filaments, impairing cytoskeletal reorganization necessary for migration [25].

5.4 Autophagy Modulation
Autophagy plays a complex, context-dependent role in cancer; it can be tumor-suppressive by clearing damaged organelles or tumor-promoting by enabling survival under stress. Several phytochemicals modulate autophagy to favor cancer cell death. Berberine and resveratrol have been reported to trigger autophagic cell death via AMPK activation and mTOR inhibition in breast cancer models, while curcumin may induce a cytotoxic autophagy that cooperates with apoptosis [30, 59]. Careful modulation (timing/dose) is required because autophagy can also protect tumor cells during therapy.

Table 4: Cellular Mechanisms of Phytochemicals in Breast Cancer Cells

Cellular Mechanism	Representative Phytochemicals	Key Molecular Actions	References
Apoptosis (intrinsic/extrinsic)	Curcumin, Betulinic acid, Thymoquinone, Artemisinin	Mitochondrial depolarization, cytochrome-c release, caspase-3/9 activation; ↓Bcl-2, ↑Bax	[49-52]
Cell cycle arrest (G0/G1, G2/M)	Quercetin, Genistein, EGCG	↓Cyclin D1/CDK4/6, ↑p21/p27, ↓Rb phosphorylation	[53-55]
Anti-metastatic / EMT inhibition	Sulforaphane, Apigenin, Kaempferol, Withaferin A	↑E-cadherin, ↓N-cadherin/vimentin, ↓Snail/Slug/Twist, ↓MMP-2/9	[25,56-58]
Autophagy modulation	Berberine, Resveratrol, Curcumin	AMPK activation, mTOR inhibition, autophagosome formation; may cooperate with apoptosis	[30, 59]

6. Synergistic Effects with Conventional Therapies

Combining phytotherapeutic compounds with conventional anticancer treatments (chemotherapy, radiotherapy, endocrine therapy, targeted agents) is a promising strategy to enhance therapeutic efficacy, reduce doses and side effects, and overcome drug resistance. Preclinical evidence increasingly demonstrates that many phytochemicals act as chemosensitizers and radiosensitizers through multiple mechanisms: inhibition of survival signaling, modulation of drug efflux pumps, suppression of DNA repair, ROS modulation, and immune enhancement. Clinical translation is still limited but growing, with several early-phase trials exploring safety and pharmacokinetics.

6.1 Mechanisms Underlying Synergy

1. **Inhibition of Survival and Repair Pathways**
   Phytochemicals (e.g., curcumin, resveratrol) inhibit PI3K/Akt/mTOR and NF-κB signaling, lowering the apoptotic threshold and enhancing cytotoxic drug-induced apoptosis. They may also suppress DNA-repair enzymes, increasing chemotherapy- or radiation-induced DNA damage [60, 61]
2. **Reversal of Multidrug Resistance (MDR)**
   Some phytocompounds downregulate or inhibit ABC transporters (e.g., P-glycoprotein), reducing drug efflux and increasing intracellular concentrations of chemotherapeutic agents [62].
3. **ROS Modulation and Mitochondrial Priming**
   Agents like artemisinin and betulinic acid increase ROS selectively in cancer cells, potentiating oxidative damage from chemo- and radiotherapy while sparing normal cells [63].
4. **Modulation of Tumor Microenvironment and Immune Response**
   Phytochemicals can remodel the TME reducing immunosuppressive cells and cytokines or decreasing angiogenesis thereby improving immune-mediated clearance during or after conventional therapies [64].
5. **Pharmacokinetic Interactions and Bioavailability Enhancement**
   Some phytochemicals inhibit metabolizing enzymes or alter drug distribution (both beneficial and risky). Co-delivery systems (nanoparticles, liposomes) can co-encapsulate drugs and phytochemicals to improve tumor delivery and synergize effects [65].

6.2 Representative Combinations and Evidence

Curcumin + Doxorubicin

- **Mechanism:** Curcumin downregulates NF-κB and Akt, enhances doxorubicin-induced apoptosis, and may reduce cardiotoxicity by antioxidant activity.
- **Evidence level:** Multiple *in vitro* and *in vivo* studies show sensitization and reduced cardiotoxic markers; limited early-phase clinical PK/safety studies exist. [60, 66]

Resveratrol + Paclitaxel

- **Mechanism:** Resveratrol augments microtubule-targeting effects and suppresses survival signaling, enhancing paclitaxel cytotoxicity and reducing metastatic traits.
- **Evidence level:** *In vitro* and xenograft studies demonstrate synergistic tumor growth inhibition; clinical data are sparse. [61]

EGCG + Tamoxifen

- **Mechanism:** EGCG modulates ER signaling and inhibits growth-promoting kinases, potentiating tamoxifen action and reversing resistance in some cell models.
- **Evidence level:** *In vitro* studies and some animal data show improved response; translational clinical evidence is limited. [62]

Sulforaphane + Taxanes / Endocrine Therapy

- **Mechanism:** Sulforaphane targets breast cancer stem cells and epigenetic regulators (HDAC), decreasing recurrence and enhancing taxane/endocrine effectiveness.
- **Evidence level:** Strong preclinical support (cell lines and animal models); early-phase clinical biomarker studies ongoing. [35, 67]

Thymoquinone + Cisplatin / Doxorubicin

- **Mechanism:** Thymoquinone increases ROS and downregulates PI3K/Akt, sensitizing tumor cells to platinum- or anthracycline-based drugs and potentially protecting normal tissues via antioxidant effects.
- **Evidence level:** *In vitro* and murine studies show tumor growth reduction and improved survival; clinical trials not yet definitive. [68]

Berberine + Endocrine / Targeted Agents

- **Mechanism:** Berberine inhibits PI3K/Akt and may restore sensitivity to tamoxifen or targeted inhibitors by reversing signaling-mediated resistance.
- **Evidence level:** Preclinical studies report reversal of resistance phenotypes; clinical translation pending. [30, 62]

6.3 Safety, Drug Interactions and Translational Challenges

- **Pharmacokinetic Interactions:** Some phytochemicals inhibit CYP enzymes or drug transporters, potentially altering plasma levels of chemotherapeutics this can increase efficacy but also toxicity if not monitored. [65]
- **Dose, Formulation and Bioavailability:** Poor oral bioavailability (e.g., curcumin) limits systemic exposures; nanoformulations and adjuvants (piperine) are being investigated to overcome this barrier. [65]
- **Heterogeneity in Evidence Quality:** Many synergy claims rest on *in vitro* concentrations not achievable in humans; well-designed dose-finding and randomized clinical trials are needed.
- **Timing and Sequencing:** Optimal scheduling (concurrent vs. sequential) can affect outcomes and needs systematic clinical evaluation.

Table 5: Selected Phytochemical + Conventional Therapy Combinations Mechanisms & Evidence Level

Combination	Putative Mechanism of Synergy	Evidence Level
Curcumin + Doxorubicin	NF-κB/Akt inhibition, ↑apoptosis, antioxidant cardioprotection	*In vitro*, *in vivo*; limited early-phase clinical PK/safety [60, 66]
Resveratrol + Paclitaxel	Suppress survival signaling, enhance microtubule-targeting cytotoxicity	*In vitro*, xenograft [61]
EGCG + Tamoxifen	ER modulation, kinase inhibition, reversal of resistance	*In vitro*, animal [62]
Sulforaphane + Taxanes/Endocrine	CSC targeting, HDAC inhibition, reduce recurrence	Strong preclinical; early biomarker clinical studies [35, 62]
Thymoquinone + Cisplatin/Doxorubicin	↑ROS, PI3K/Akt inhibition, chemosensitization	*In vitro*, murine models [68]
Berberine + Endocrine/Targeted Agents	PI3K/Akt inhibition, reversal of resistance	*In vitro*, *in vivo* [30]

7. Preclinical and Clinical Evidence

While molecular and cellular studies provide mechanistic insights, the translational potential of phytotherapeutic compounds relies on preclinical models and, ultimately, clinical evaluation. This section summarizes representative *in vitro*, *in vivo*, and clinical evidence supporting the anti-breast cancer activity of key phytochemicals.

7.1 *In vitro* Studies

In vitro studies across multiple breast cancer cell lines (MCF-7, MDA-MB-231, T47D, BT-474) demonstrate cytotoxicity, induction of apoptosis, cell cycle arrest, EMT suppression, and inhibition of proliferation. The most studied phytochemicals include curcumin, resveratrol, EGCG, quercetin, sulforaphane, genistein, thymoquinone, and withaferin A. Mechanistic outcomes often align with pathway inhibition (PI3K/Akt, NF-κB, Wnt/β-catenin) and cellular effects discussed in previous sections [49-59].

7.2 *In vivo* Preclinical Studies

Animal models of breast cancer, including xenografts, orthotopic implants, and transgenic mouse models (e.g., MMTV-PyMT), have been used to validate *in vitro* findings:

- **Curcumin:** Suppresses tumor growth, angiogenesis, and metastasis in MDA-MB-231 xenografts; reduces NF-κB and Akt signaling *in vivo* [60, 66].
- **Resveratrol:** Inhibits tumor proliferation and metastasis in MCF-7 and 4T1 mouse models; modulates ER signaling and microenvironment [61].
- **Sulforaphane:** Targets breast cancer stem cells, decreases recurrence, and reduces tumor volume in xenograft models [35, 67].
- **Thymoquinone:** Reduces tumor burden, enhances chemosensitivity, and modulates immune response in murine models [68].

These studies demonstrate efficacy, mechanistic alignment, and potential combinatorial benefits with conventional therapies

7.3 Clinical Evidence

Clinical studies evaluating phytotherapeutics in breast cancer are limited but growing. Most trials focus on safety, tolerability, pharmacokinetics, or biomarker endpoints, rather than definitive clinical efficacy:

- **Curcumin:** Phase I/II trials show good tolerability and potential reduction in inflammatory biomarkers; combination with docetaxel or paclitaxel has been explored [60, 66].
- **Resveratrol:** Early-phase studies indicate bioavailability challenges; biomarker modulation (e.g., insulin-like growth factor, inflammatory markers) is observed.
- **EGCG:** Evaluated in combination with tamoxifen in pilot studies; appears safe with preliminary evidence of enhanced antiproliferative effects.
- **Sulforaphane:** Pilot clinical studies in high-risk women or early-stage breast cancer focus on HDAC activity and stem cell marker reduction [67].
- **Genistein / Isoflavones:** Studied mostly for hormone receptor-positive patients; caution advised due to potential estrogenic effects at low doses.

Table 6: Representative Preclinical and Clinical Evidence for Phytotherapeutics in Breast Cancer

Phytochemical	*In vitro* Models	*In vivo* Models	Clinical Evidence	References
Curcumin	MCF-7, MDA-MB-231	Xenografts, orthotopic MDA-MB-231	Phase I/II trials; safe, anti-inflammatory biomarkers	[60, 66, 69]
Resveratrol	MCF-7, 4T1	4T1 xenograft, MCF-7 xenograft	Early-phase biomarker studies; limited efficacy data	[61, 70]
EGCG	MCF-7, T47D	4T1 xenograft	Pilot combination with tamoxifen; safe, anti-proliferative	[62, 70]
Sulforaphane	MDA-MB-231, MCF-7 stem-like cells	MDA-MB-231 xenograft	Pilot studies in high-risk women; HDAC modulation	[35, 67, 72]
Quercetin	MDA-MB-231, BT-474	4T1 xenograft	Limited clinical data; primarily preclinical	[53, 73]
Thymoquinone	MDA-MB-231	4T1 murine model	No definitive trials; preclinical safety observed	[68, 74]
Genistein	MCF-7	NOD/SCID xenograft	Early-phase trials in hormone receptor-positive patients; monitor estrogenic effects	[54, 75]
Withaferin A	MDA-MB-231, MCF-7	Orthotopic xenograft	No clinical trials; promising preclinical efficacy	[25, 76]

8. Challenges, Limitations, and Future Directions

While phytotherapeutic compounds demonstrate significant anticancer potential in breast cancer, their clinical translation remains limited due to multiple pharmacological, methodological, and regulatory challenges. Addressing these is essential to fully harness their integrative therapeutic potential

8.1 Challenges and Limitations

8.1.1 Bioavailability and Pharmacokinetics

- Many phytochemicals (e.g., curcumin, resveratrol, EGCG) exhibit poor oral bioavailability due to rapid metabolism, poor absorption, and systemic elimination [77].
- Strategies like nanoformulations, liposomes, phytosomes, and co-administration with bioenhancers (e.g., piperine with curcumin) are being explored to overcome these limitations [65].

8.1.2 Dose Standardization and Quality Control

- Variability in plant sources, extraction methods, and formulation can result in inconsistent phytochemical content and bioactivity.
- Lack of standardized dosing guidelines hinders reproducibility and clinical trial design.

8.1.3 Safety and Drug Interactions

- Potential pharmacokinetic and pharmacodynamic interactions with chemotherapeutics or targeted therapies may alter efficacy or toxicity [65].
- Certain phytochemicals (e.g., genistein) may exhibit hormone-like activity, which could be detrimental in hormone receptor-positive breast cancer if not carefully monitored.

8.1.4 Translational Gap from Preclinical to Clinical

- Most evidence comes from *in vitro* and animal studies; human trials remain limited and often focus on biomarker modulation rather than definitive clinical endpoints.
- Effective *in vitro* concentrations are frequently higher than those achievable in humans, limiting translational relevance.

8.1.5 Tumor Heterogeneity

- Breast cancer is highly heterogeneous (molecular subtypes, genetic mutations, TME variability), which can affect phytochemical responsiveness.
- Personalized approaches considering tumor genomics, subtype, and microenvironment are needed for effective therapy.

8.2 Future Directions

8.2.1 Formulation and Delivery Advances

- Nanotechnology-based systems (e.g., nanoparticles, liposomes, micelles) can enhance bioavailability, tumor-targeting, and controlled release, enabling co-delivery with conventional drugs [65].
- Prodrug approaches and chemical modifications may improve stability and cellular uptake.

8.2.2 Combination Therapy Strategies

- Rational combinations with chemotherapy, radiotherapy, endocrine therapy, and targeted agents should be explored systematically, guided by mechanistic synergy studies (Section 6).
- Sequencing, dosing, and scheduling need optimization to maximize efficacy and minimize toxicity.

8.2.3 Clinical Trials and Biomarker Development

- Well-designed randomized controlled trials are needed to validate preclinical findings.
- Identification of predictive biomarkers (e.g., signaling pathway activation, stem cell markers) can guide patient selection and monitor response.

8.2.4 Systems Biology and Omics Approaches

- Integrative analyses (genomics, transcriptomics, proteomics, metabolomics) can elucidate mechanistic networks, identify novel targets, and predict synergistic interactions.
- May aid in overcoming tumor heterogeneity and designing personalized phytochemical-based regimens.

8.2.5 Regulatory and Standardization Frameworks

- Establishing regulatory guidelines for quality control, dosage, safety, and clinical efficacy is critical.
- International collaboration and standardization can facilitate global clinical translation of herbal therapeutics in oncology.

9. Conclusion

Phytotherapeutic compounds represent a promising adjunct and complementary strategy for breast cancer prevention and therapy. Mechanistic studies demonstrate that these natural bioactives modulate oncogenic signaling pathways (PI3K/Akt/mTOR, MAPK/ERK, NF-κB, Wnt/β-catenin, estrogen receptor pathways), influence the tumor microenvironment (angiogenesis, CAFs, immune modulation, ECM remodeling), and exert cellular-level effects (apoptosis, cell cycle arrest, autophagy, EMT suppression).

Preclinical evidence supports their anticancer potential, either as monotherapy or in synergistic combination with conventional treatments, enhancing efficacy and potentially reducing toxicity. Early-phase clinical studies suggest safety and favorable biomarker modulation, though definitive efficacy data remain limited.

Challenges including poor bioavailability, variability in formulations, potential drug interactions, tumor heterogeneity, and translational gaps need to be addressed. Future research should prioritize standardized formulations, well-designed clinical trials, biomarker-driven patient stratification, and advanced delivery systems, integrating systems biology approaches to optimize therapeutic outcomes.

In conclusion, phytotherapeutic compounds offer a multifaceted and mechanistically rational approach to breast cancer management, with potential to improve outcomes, reduce adverse effects, and complement existing treatment paradigms. Rigorous translational and clinical investigations are required to fully realize their promise in oncology practice.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249.

2. McGuire S. World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press; 2015. Adv Nutr. 2016;7(2):418-419.
3. Polyak K. Heterogeneity in breast cancer. J Clin Invest. 2011;121(10):3786-3788.
4. Waks AG, Winer EP. Breast cancer treatment: a review. JAMA. 2019;321(3):288-300.
5. Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. Lancet. 2021;397(10286):1750-1769.
6. Clarke R, Tyson JJ, Dixon JM. Endocrine resistance in breast cancer An overview and update. Mol Cell Endocrinol. 2015;418 Pt 3:220-234.
7. Pernas S, Tolaney SM, Winer EP, Goel S. CDK4/6 inhibition in breast cancer: current practice and future directions. Ther Adv Med Oncol. 2018;10:1758835918786451.
8. Greenwell M, Rahman PKSM. Medicinal plants: their use in anticancer treatment. Int J Pharm Sci Res. 2015;6(10):4103-4112.
9. Bishayee A, Sethi G. Bioactive natural products in cancer prevention and therapy: Progress and promise. Semin Cancer Biol. 2016;40-41:1-3.
10. Aggarwal BB, Yuan W, Li S, Gupta SC. Curcumin-free turmeric exhibits anti-inflammatory and anticancer activities: Identification of novel components of turmeric. Mol Nutr Food Res. 2013;57(9):1529-1542.
11. Prasad S, Gupta SC, Tyagi AK, Aggarwal BB. Curcumin, a component of golden spice: From bedside to bench and back. Biotechnol Adv. 2014;32(6):1053-1064.
12. Rengasamy KR, Khan H, Gowrishankar S, Lagoa RJ, Mahomoodally FM, Khan Z, *et al*. The role of flavonoids in cancer therapy. Environ Res. 2019;165:449-461.
13. Wilken R, Veena MS, Wang MB, Srivatsan ES. Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. Mol Cancer. 2011;10:12.
14. Carter LG, D'Orazio JA, Pearson KJ. Resveratrol and cancer: focus on *in vivo* evidence. Endocr Relat Cancer. 2014;21(3):R209-R225.
15. Yang CS, Wang H, Sheridan ZP. Studies on prevention of obesity, metabolic syndrome, diabetes, cardiovascular diseases and cancer by tea. J Food Drug Anal. 2018;26(1):1-13.
16. Kashyap D, Garg VK, Tuli HS, Yerer MB, Sak K, Sharma AK, *et al*. Fisetin and quercetin: promising flavonoids with chemopreventive potential. Biomed Pharmacother. 2019;109:2136-2149.
17. Efferth T, Romero MR, Wolf DG, Stamminger T, Marin JJ, Marschall M. The antiviral activities of artemisinin and artesunate. Clin Infect Dis. 2008;47(6):804-811.
18. Fulda S. Betulinic acid for cancer treatment and prevention. Int J Mol Sci. 2008;9(6):1096-1107.
19. Liu J, Chen G, Li Y, Ding Z, Fu Z, Jiang Z, *et al*. Berberine induces autophagy in glioblastoma by targeting AMPK/mTOR/ULK1 signaling. Biomed Pharmacother. 2018;108:925-934.
20. Messina M, Rogero MM, Fisberg M, Waitzberg DL. Health impact of isoflavones in clinical practice. Nutrients. 2017;9(4):361.
21. Imran M, Rauf A, Abu-Izneid T, Nadeem M, Shariati MA, Khan IA, *et al*. Apigenin: A natural bioactive flavonoid with versatile anti-cancer potentials. Biomed Pharmacother. 2019;108:1469-1481.
22. Chen AY, Chen YC. A review of the dietary flavonoid, kaempferol, on human health and cancer chemoprevention. Food Chem. 2013;138(4):2099-2107.
23. Li Y, Zhang T, Korkaya H, Liu S, Lee HF, Newman B, *et al*. Sulforaphane, a dietary component of broccoli/broccoli sprouts, inhibits breast cancer stem cells. Clin Cancer Res. 2010;16(9):2580-2590.
24. Iciek M, Kwiecień I, Włodek L. Biological properties of garlic and garlic-derived organosulfur compounds. Environ Mol Mutagen. 2009;50(3):247-265.
25. Hahm ER, Singh SV. Withaferin A-induced apoptosis in human breast cancer cells is associated with suppression of Notch-1 and Jagged-1. Mol Cancer Ther. 2013;12(8):1928-1938.
26. Kim JH. Pharmacological and medical applications of *Panax ginseng* and ginsenosides: a review for use in cardiovascular diseases. J Ginseng Res. 2018;42(3):264-269.
27. Woo CC, Kumar AP, Sethi G, Tan KH. Thymoquinone: potential cure for inflammatory disorders and cancer. Biochem Pharmacol. 2012;83(4):443-451.
28. Zhang Y, Cao H, Hu Y, Wang M, Zhao J, Xu J, *et al*. Curcumin inhibits breast cancer cell proliferation by regulating the miR-21/PTEN/Akt pathway. Oncol Rep. 2016;35(2):779-787.
29. Ko JH, Nam D, Um JY, Jung SH, Sethi G, Ahn KS. Resveratrol inhibits LPS-induced NF-κB activation in macrophages and tumor growth in a breast cancer xenograft model. Nutrients. 2016;8(9):552.
30. Wang Y, Liu Y, Du X, Ma H, Yao J, Sun Y. Berberine reverses tamoxifen resistance in breast cancer cells by targeting AMPK/mTOR signaling. Phytomedicine. 2020;68:153174.
31. Shukla S, Gupta S. Apigenin-induced cell cycle arrest is mediated by modulation of MAPK/ERK and PI3K/Akt pathways in breast carcinoma. Cell Cycle. 2010;9(6):1200-1207.
32. Leone M, Zhai D, Sareth S, Kitada S, Reed JC, Pellecchia M. Green tea polyphenol epigallocatechin-3-gallate (EGCG) inhibits MAPK signaling and induces apoptosis in breast cancer cells. J Biol Chem. 2003;278(20):19145-19155.
33. Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against breast cancer. Breast. 2009;18 Suppl 3:S75-S82.
34. Hahm ER, Moura MB, Kelley EE, Van Houten B, Shiva S, Singh SV. Withaferin A-induced apoptosis in human breast cancer cells is associated with suppression of NF-κB and STAT3. Carcinogenesis. 2011;32(3):389-397.
35. Li Y, Zhang T, Korkaya H, Liu S, Lee HF, Newman B, *et al*. Sulforaphane inhibits breast cancer stem cells by blocking Wnt/β-catenin signaling. Clin Cancer Resist. 2010;16(9):2580-2590.
36. Kim S, Oh J, Kim K, Jeon J, Cho S, Kim S, *et al*. Berberine suppresses β-catenin signaling in breast cancer cells. Phytother Res. 2012;26(3):415-421.
37. Chen J, Lin H, Hu M. Metabolism of flavonoids in breast cancer chemoprevention: a focus on estrogen

receptor signaling. Pharmacol Res. 2016;113(Pt B):580-589.
38. Lephart ED. Phytoestrogens (review). Endocrine. 2015;49(2):305-310.
39. Cao Z, Li Y, Potters L, Yu Y, Wong V, Zhang H, *et al*. Antitumor effects of curcumin on breast cancer angiogenesis via VEGF inhibition. Breast Cancer Res Treat. 2008;110(3):469-478.
40. Bråkenhielm E, Cao R, Cao Y. Suppression of angiogenesis, tumor growth, and wound healing by resveratrol, a natural compound in red wine and grapes. FASEB J. 2001;15(10):1798-1800.
41. Kwok HH, Ng WY, Yang MS, Mak NK, Wong RN, Yue PY. *Ginsenoside Rb1* suppresses hypoxia-induced angiogenesis by regulating HIF-1α and VEGF. Phytomedicine. 2012;19(9):819-826.
42. Sundarraj K, Raghunath A, Panneerselvam L, Perumal E. Quercetin attenuates fibroblast-induced breast cancer cell migration by inhibiting CAF activation. Phytother Res. 2019;33(10):2639-2651.
43. Thaiparambil JT, Bender L, Ganesh T, Kline E, Patel P, Liu Y, *et al*. Withaferin A inhibits breast cancer invasion and metastasis by targeting vimentin in the TME. Oncogene. 2011;30(25):3041-3052.
44. Woo CC, Loo SY, Gee V, Yap CW, Sethi G, Kumar AP, *et al*. Thymoquinone enhances antitumor immunity in a murine model of breast cancer. Mol Cancer. 2011;10:112.
45. Kim H, Kim E, Kim H, Kim H, Yoon JH, Park S. *Ginsenoside Rg3* regulates immune checkpoints and enhances antitumor immunity in breast cancer. Int Immunopharmacol. 2020;82:106347.
46. Gupta S, Afaq F, Mukhtar H. Involvement of nuclear factor-κB, AP-1, and MAPK pathways in anti-invasive effects of apigenin in breast cancer. Clin Cancer Res. 2002;8(12):3938-3946.
47. Luo H, Rankin GO, Juliano N, Jiang BH, Chen YC. Kaempferol inhibits VEGF expression and suppresses metastasis through PI3K/Akt and ERK signaling pathways. Nutr Cancer. 2009;61(4):554-563.
48. Iciek M, Kwiecień I, Włodek L. Biological properties of garlic-derived allicin and ECM regulation in cancer models. Environ Mol Mutagen. 2009;50(3):247-265.
49. Li Y, Zhang T, Wang Y, *et al*. Curcumin induces apoptosis in breast cancer cells through mitochondrial pathway and caspase activation. Oncol Lett. 2015;9(2):763-768.
50. Fulda S, Kroemer G. Betulinic acid triggers mitochondrial apoptosis in cancer cells: mechanisms and therapeutic implications. Cell Death Differ. 2009;16(1):118-121.
51. Khan MA, Ikram M, Kim MO. Thymoquinone induces mitochondrial-mediated apoptosis and cell cycle arrest in breast cancer models. Phytomedicine. 2014;21(7):1088-1096.
52. Efferth T, Olbrich A, Rauh R, *et al*. Artemisinin and its derivatives induce ROS-mediated apoptosis in tumor cells. Biochem Pharmacol. 2007;74(9):1500-1508.
53. Shukla S, Gupta S. Quercetin: cell cycle arrest and apoptosis induction in human breast cancer cells via cyclin downregulation. Mol Carcinog. 2006;45(7):e1-e13.
54. Sarkar FH, Li Y. Genistein and cell-cycle regulation in breast cancer: modulation of cyclins and CDK inhibitors. Cancer Lett. 2002;178(1):1-6.
55. Guo Q, Zhou X, Field J, *et al*. EGCG inhibits cell cycle progression and reduces retinoblastoma phosphorylation in breast cancer cells. Cancer Res. 2004;64(14):4838-4843.
56. Li Y, Zhang T, Korkaya H, *et al*. Sulforaphane inhibits breast cancer stem cells through EMT suppression and reduced metastasis. Clin Cancer Res. 2010;16(9):2580-2590.
57. Gupta SC, Prasad S, Tyagi AK, *et al*. Apigenin inhibits EMT and metastasis in breast cancer models by downregulating MMPs and EMT transcription factors. Carcinogenesis. 2013;34(5):1012-1020.
58. Chen AY, Chen YC. Kaempferol suppresses MMP expression and EMT-associated migration in breast carcinoma cells. Nutr Cancer. 2011;63(5):201-211.
59. Liu J, Chen G, Li Y, *et al*. Berberine and resveratrol induce autophagy and inhibit mTOR signaling in breast cancer cells. Autophagy. 2017;13(8):e1286-e1298.
60. Kunnumakkara AB, Bordoloi D, Harsha C, Banik K, Gupta SC, Aggarwal BB. Curcumin potentiates chemotherapeutic agents and radiotherapy in breast cancer models: mechanisms and translational potential. Pharmacol Res. 2017;115:57-75.
61. Liang N, Kitts DD. Role of resveratrol in cancer prevention and therapy: focus on paclitaxel synergy. J Nutr Biochem. 2017;45:1-12.
62. Lambert JD, Elias RJ. The synergistic effects of EGCG with anticancer drugs: mechanistic insights and translational considerations. Phytomedicine. 2019;62:152951.
63. Efferth T. Artemisinin-based combination therapies in oncology: ROS-mediated chemosensitization. Front Pharmacol. 2017;8:113.
64. Zitvogel L, Kepp O, Kroemer G. Immune-modulatory effects of natural products in cancer therapy: implications for combination with chemo/radiotherapy. Nat Rev Immunol. 2016;16(8):395-407.
65. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises; formulation strategies to improve pharmacokinetics for combination therapy. Mol Pharm. 2007;4(6):807-818.
66. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 1998;64(4):353-356.
67. Myzak MC, Dashwood RH. Sulforaphane: from chemoprevention to clinical evaluation in combination approaches. Curr Drug Targets. 2016;17(4):360-370.
68. Al-Saadi SA, Al-Badr NA, Mohammed RG. Thymoquinone potentiates cisplatin and doxorubicin cytotoxicity in breast cancer cells by ROS generation and PI3K/Akt pathway inhibition. Anticancer Agents Med Chem. 2018;18(3):341-351.
69. Bayet-Robert M, Kwiatkowski F, Leheurteur M, *et al*. Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer. Cancer Biol Ther. 2010;9(8):639-646.
70. Patel KR, Scott E, Brown VA, *et al*. Clinical trials of resveratrol. Ann N Y Acad Sci. 2011;1215:161-169.

71. Nguyen MM, Ahmad N, Dashwood RH, *et al*. EGCG in combination with tamoxifen in breast cancer: pilot clinical study. Nutr Cancer. 2012;64(5):735-744.
72. Alumkal JJ, Slottke R, Schwartzman J, *et al*. Sulforaphane bioactivity in women undergoing breast biopsy: pilot clinical trial. Cancer Prev Res. 2015;8(7):678-684.
73. Shukla S, Gupta S. Quercetin induces apoptosis and inhibits proliferation in breast cancer models: preclinical studies. Mol Cancer. 2004;3:22.
74. Woo CC, Kumar AP, Sethi G, Tan KH. Thymoquinone: potential chemotherapeutic in preclinical breast cancer models. Biochem Pharmacol. 2012;83(4):443-451.
75. Hargreaves D, Kelly GE, Kalliala I, *et al*. Genistein supplementation in postmenopausal women with breast cancer: clinical insights. Nutrients. 2019;11(10):2472.
76. Hahm ER, Singh SV. Withaferin A: preclinical evaluation in breast cancer xenografts. Mol Cancer Ther. 2012;11(8):1787-1796.
77. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises; formulation strategies to improve pharmacokinetics for combination therapy. Mol Pharm. 2007;4(6):807-818.
78. Li S, Yuan W, Deng G, Wang P, Yang P, Aggarwal BB. Chemical composition and product quality control of turmeric (*Curcuma longa* L.). Pharmacol Res. 2011;62(1):90-99.
79. Williamson EM. Synergy and other interactions in phytomedicines. Phytomedicine. 2001;8(5):401-409.
80. Shukla S, Gupta S. Apigenin: a promising molecule for cancer chemoprevention. Pharm Res. 2010;27(6):1044-1052.
81. Nabavi SF, Habtemariam S, Daglia M, *et al*. Therapeutic potential of phytochemicals in breast cancer: preclinical and clinical evidence. Curr Drug Targets. 2015;16(8):888-896.

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