

# Research Progress on the Effects and Mechanisms of Curcumin Against Breast Cancer

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**How to cite this paper:** Liu, J. R., & Yang, X. L. (2026). Research Progress on the Effects and Mechanisms of Curcumin Against Breast Cancer. *Health, Medicine and Therapeutics*, 2(1), 1–19. ISSN Print: 3079-5079; ISSN Online: 3079-5087.

<https://doi.org/10.63313/hmt.2001>

Published: 2026-04-20

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## Abstract

Curcumin is a natural lipophilic polyphenolic compound extracted and isolated from the dried rhizome of *Curcuma longa* L., a plant of the genus *Curcuma* in the family Zingiberaceae. It exhibits a variety of pharmacological activities, including anti-inflammatory, antioxidant, immunomodulatory, and antitumor effects, and has shown significant application value in the adjuvant treatment of various diseases. In recent years, the potential of curcumin in the field of oncology has attracted considerable attention. Studies have confirmed that curcumin possesses significant therapeutic potential against breast cancer, playing important roles in multiple key biological processes such as inhibiting cell proliferation, inducing apoptosis, blocking invasion and metastasis, suppressing angiogenesis, and regulating the tumor immune microenvironment. This article systematically reviews relevant domestic and international literature to summarize the research progress on the effects and mechanisms of curcumin against breast cancer, aiming to provide a reference for further research on curcumin and the development of novel anti-breast cancer drugs.

## Keywords

Curcumin; Breast Cancer; Antitumor Mechanism; Apoptosis; Angiogenesis; Tumor Immune Microenvironment

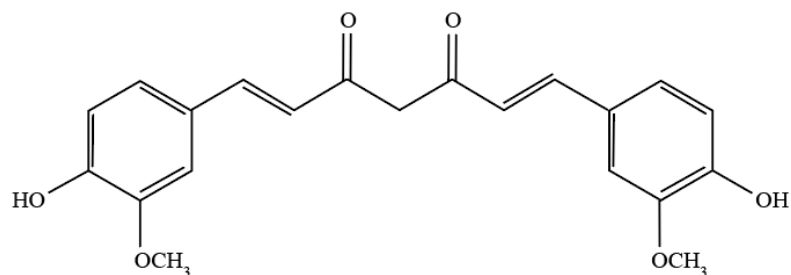
## 1. Introduction

Breast cancer is the most common primary malignant tumor among women worldwide. It originates from the epithelial tissue of the mammary gland, characterized by the malignant proliferation of ductal or lobular epithelial cells leading to mass formation, with the capacity for invasive growth and distant metastasis [1]. Based on molecular characteristics, breast cancer can be classified into four major subtypes: Luminal A, Luminal B, HER2-overexpressing, and triple-negative breast cancer (TNBC). The degree of malignancy and prognosis vary significantly among these subtypes, among which TNBC poses a major clinical challenge due to its high invasiveness and propensity for early metastasis [2]. Clinically, breast cancer typically manifests as a painless breast mass, nipple

discharge, peau d'orange skin changes, and axillary lymphadenopathy. According to World Health Organization statistics, breast cancer accounts for 24% of all female malignancies. The 5-year survival rate exceeds 90% for patients diagnosed at an early stage, but drops to approximately 27% for those with advanced metastasis. The disease shows a predilection for two age groups: 45–55 years (associated with hormonal fluctuations and reproductive factors) and over 65 years (associated with BRCA1/2 mutations, obesity, and other factors) [3]. Although conventional treatment modalities such as surgical resection, radiotherapy, chemotherapy, and endocrine therapy are widely used in clinical practice and have achieved certain therapeutic effects, challenges remain, including high risks of recurrence and metastasis, development of treatment resistance in some patients, and adverse effects such as bone marrow suppression, gastrointestinal reactions associated with chemoradiotherapy, and osteoporosis induced by endocrine therapy, all of which significantly impair patients' quality of life [4]. In this context, the exploration of active ingredients from natural products, their derivatives, and novel drug delivery systems has become a research hotspot in the field of breast cancer therapy [5]. Curcumin, a natural polyphenolic compound, has shown unique potential in anti-breast cancer research [6-7]. Existing evidence indicates that this compound can regulate multiple signaling pathways, including phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), nuclear factor- $\kappa$ B (NF- $\kappa$ B), and mitogen-activated protein kinase (MAPK) [8-9], inhibit breast cancer cell proliferation and migration [10-11], induce apoptosis [12], and to some extent reverse drug resistance induced by endocrine therapy and HER2-targeted agents [13-14]. Furthermore, curcumin can enhance the responsiveness of breast cancer to immunotherapy [15]. This article systematically reviews the mechanisms of action of curcumin against breast cancer, analyzes current challenges in research, and discusses future directions, aiming to provide new insights for the clinical treatment of breast cancer.

## **2. Overview of the Physicochemical Properties and Pharmacological Activities of Curcumin**

Curcumin is a natural lipophilic polyphenolic compound isolated from the dried rhizome of *Curcuma longa* L., a plant of the genus *Curcuma* in the family Zingiberaceae. It is the key active component responsible for the pharmacological effects of turmeric, with the chemical full name (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, molecular formula  $C_{21}H_{20}O_6$  (see Figure 1), and relative molecular mass of 368.39. The compound appears as an orange-yellow crystalline powder. Its chemical structure consists of two guaiacyl units linked by a conjugated diketone chain, which not only endows curcumin with its characteristic chromophoric properties but also serves as the structural basis for its diverse biological activities.



**Figure 1.** Chemical structure of curcumin.

In terms of physicochemical properties, curcumin has poor water solubility (its solubility in water at 25 °C is only approximately 11 ng/mL), while its lipid solubility is relatively good. This compound is sensitive to light, heat, and pH changes; it is prone to degradation in alkaline environments but remains relatively stable under acidic conditions. Furthermore, curcumin exhibits inherent drawbacks such as low absorption efficiency *in vivo*, rapid metabolism, and poor bioavailability, which are currently the main bottlenecks limiting its clinical development and application.

As one of the most extensively studied natural active ingredients, curcumin has been demonstrated to possess a variety of pharmacological activities, including anti-inflammatory, antioxidant, antitumor, antibacterial, and immunomodulatory effects [16-27]. Its mechanisms of action involve the regulation of signaling pathways such as NF- $\kappa$ B, PI3K/Akt, MAPK, and Wnt/ $\beta$ -catenin, thereby influencing key biological processes including cell proliferation, apoptosis, invasion, and metastasis. In the field of antitumor research, curcumin has gained widespread attention due to its unique advantages of "multi-targeting and low toxicity". Studies on breast cancer have shown that curcumin exhibits inhibitory activity against different molecular subtypes, including hormone receptor-positive, HER2-overexpressing, and triple-negative breast cancer, making it a highly promising candidate compound in the field of natural product-based antitumor research. At present, research focusing on the mechanisms of action of curcumin against breast cancer and strategies to optimize its application is gradually becoming a hotspot in the field of adjuvant therapy for breast cancer.

### 3. Main Mechanisms of Curcumin in the Treatment

#### 3.1. Inhibition of Breast Cancer Cell Proliferation

Uncontrolled cell proliferation is a core feature of breast cancer initiation and progression. The normal cell cycle depends on strict regulatory mechanisms, whereas in tumor cells, cell cycle-related molecules are often aberrantly expressed, leading to continuous division [28]. Curcumin can intervene in the expression of various cell cycle regulatory proteins, arresting breast cancer cells at specific phases of the cell cycle and thereby effectively inhibiting their proliferative capacity. Studies have shown that curcumin treatment significantly reduces the expression levels of Cyclin D1, cyclin-dependent kinase 4 (CDK4), and CDK6 in breast cancer

cells, resulting in cell cycle arrest at the G1/S checkpoint [29]. Cyclin D1 is a key regulator of the G1-to-S phase transition; its downregulation impairs CDK4/6-mediated phosphorylation of the retinoblastoma protein (Rb), thereby preventing the release of E2F transcription factors and ultimately inhibiting DNA replication initiation [30]. In MCF-7 (Luminal A) and MDA-MB-231 (triple-negative breast cancer) cells, curcumin reduces Cyclin D1 protein levels in a concentration-dependent manner, accompanied by an increase in the proportion of cells in the G0/G1 phase and a decrease in the S-phase fraction [31].

In addition to G1/S arrest, curcumin can also induce G2/M phase arrest in breast cancer cells. It has been reported that curcumin upregulates the expression of cyclin-dependent kinase inhibitors p21 and p27 and inhibits the activity of the Cyclin B1/CDK1 complex, thereby blocking entry into mitosis [32]. In HER2-overexpressing breast cancer cells, curcumin treatment significantly increases p21 expression, decreases Cyclin B1 levels, arrests cells in the G2/M phase, and markedly reduces proliferative activity [33].

The inhibitory effect of curcumin on breast cancer cell proliferation also involves cross-regulation of multiple signaling pathways. The phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway is a core signaling axis regulating cell survival and proliferation, and its aberrant activation is closely associated with breast cancer development and progression. Curcumin can inhibit the phosphorylation levels of PI3K and Akt, reduce the activity of downstream mammalian target of rapamycin (mTOR) and p70S6K, and thereby block the transmission of proliferative signals [34]. Furthermore, curcumin can suppress the activation of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway, reduce the expression of transcription factors c-Fos and c-Jun, and further weaken the proliferative capacity of breast cancer cells [35].

It is worth noting that the inhibitory effect of curcumin on proliferation differs among breast cancer molecular subtypes. Triple-negative breast cancer (TNBC), which lacks expression of estrogen receptor, progesterone receptor, and HER2, responds poorly to conventional endocrine therapy and targeted therapy. Studies have shown that the half-maximal inhibitory concentration ( $IC_{50}$ ) of curcumin against TNBC cells MDA-MB-231 and SUM159 is significantly lower than that against hormone receptor-positive cells, suggesting that curcumin may have stronger antiproliferative activity in this subtype [36]. This characteristic is related to the sustained activation of the NF- $\kappa$ B and STAT3 signaling pathways in TNBC cells, and curcumin can selectively kill TNBC cells by inhibiting the activity of these pathways [37].

### **3.2. Induction of Apoptosis in Breast Cancer Cells**

Apoptosis is a programmed cell death process that is essential for maintaining tissue homeostasis and eliminating damaged or excess cells. Curcumin induces apoptosis

in breast cancer cells through multiple mechanisms, primarily including the activation of apoptosis-related signaling pathways, upregulation of pro-apoptotic protein expression, and downregulation of anti-apoptotic protein expression [38]. Studies have shown that curcumin can activate the caspase cascade, one of the core mechanisms of apoptosis, leading to cell death by cleaving a series of substrates [39]. In addition, curcumin upregulates the expression of pro-apoptotic proteins such as Bax and Bid, while downregulating the expression of anti-apoptotic proteins such as Bcl-2 and Bcl-xL, thereby disrupting the balance between pro-apoptotic and anti-apoptotic proteins and promoting the apoptotic process. These findings reveal the potential mechanisms by which curcumin induces apoptosis in breast cancer cells [40].

### **3.3. Inhibition of Breast Cancer Cell Invasion and Metastasis**

Invasion and metastasis are the leading causes of poor prognosis and mortality in breast cancer patients. According to statistics, approximately 90% of breast cancer-related deaths are attributed to tumor metastasis rather than the primary tumor itself [41]. Breast cancer metastasis is a multi-step complex process involving the detachment of tumor cells from the primary site, invasion of the basement membrane and extracellular matrix (ECM), entry into the bloodstream, colonization of distant organs, and formation of metastatic foci. During this process, epithelial-mesenchymal transition (EMT), aberrant activation of matrix metalloproteinases (MMPs), and tumor angiogenesis all play critical roles. Curcumin can intervene in the above steps through various mechanisms, thereby effectively inhibiting the invasion and metastatic capacity of breast cancer cells [42].

Further studies have also shown that curcumin downregulates the expression of proteins associated with breast cancer cell invasion and metastasis, such as matrix metalloproteinases (MMPs), which play key roles in the migration and invasion of tumor cells. By inhibiting the activity of MMPs, curcumin effectively reduces the invasive and metastatic ability of breast cancer cells, thereby slowing malignant progression. Moreover, curcumin can influence the epithelial-mesenchymal transition (EMT) process, an important mechanism by which tumor cells acquire invasive and metastatic properties. By inhibiting the expression of EMT-related transcription factors such as Snail, Slug, and Twist, curcumin reduces the transition of breast cancer cells from an epithelial to a mesenchymal phenotype, thereby suppressing cell invasion and metastasis [43].

### **3.4. Inhibition of Tumor Angiogenesis**

Tumor angiogenesis is a critical process in the growth, invasion, and distant metastasis of breast cancer. Newly formed blood vessels not only provide tumor cells with adequate oxygen and nutrients but also create favorable conditions for hematogenous dissemination [44]. Therefore, inhibiting tumor angiogenesis has become an important strategy in breast cancer therapy. Curcumin, as a multi-target

natural active ingredient, exhibits significant potential in anti-angiogenesis.

Studies have shown that curcumin can inhibit tumor neovascularization by downregulating the expression of various pro-angiogenic factors. Among these, vascular endothelial growth factor (VEGF) and its receptor VEGFR constitute the core signaling axis regulating angiogenesis. Curcumin inhibits VEGF expression at both the transcriptional and translational levels, while interfering with VEGFR-mediated downstream signaling, thereby reducing endothelial cell proliferation, migration, and tube formation ability [45]. Further research has revealed that curcumin exerts anti-angiogenic effects by suppressing the hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ )/VEGF pathway. Within solid tumors, the hypoxic microenvironment activates HIF-1 $\alpha$ , which in turn promotes the transcriptional expression of target genes such as VEGF. Curcumin can inhibit the protein stability and transcriptional activity of HIF-1 $\alpha$ , thereby blocking hypoxia-induced angiogenic responses [46]. This mechanism is of great significance for inhibiting tumor angiogenesis in breast cancer, especially in highly hypoxic subtypes such as triple-negative breast cancer.

In addition to the VEGF pathway, curcumin can also intervene in other regulators involved in angiogenesis. For example, curcumin reduces the activity of matrix metalloproteinases (MMP-2 and MMP-9), decreases extracellular matrix degradation, and thus indirectly inhibits endothelial cell sprouting and the extension of new blood vessels [47]. At the same time, curcumin regulates the expression levels of other pro-angiogenic molecules, including basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and angiopoietin, synergistically exerting anti-angiogenic effects [48]. It is worth noting that the anti-angiogenic effect of curcumin is concentration-dependent and may vary among different breast cancer subtypes. Studies have shown that curcumin exhibits particularly prominent anti-angiogenic activity against triple-negative breast cancer, which may be related to the high dependence of TNBC on VEGF-driven angiogenesis [49]. Furthermore, curcumin demonstrates synergistic effects when combined with anti-VEGF monoclonal antibodies (e.g., bevacizumab) or other anti-angiogenic drugs, providing new insights for clinical combination therapy [50].

### **3.5. Regulation of the Tumor Immune Microenvironment**

The tumor microenvironment (TME) is a complex ecosystem composed of tumor cells, immune cells, fibroblasts, extracellular matrix, and various cytokines and signaling molecules. During tumor initiation and progression, the TME often exhibits an immunosuppressive state, characterized by polarization of tumor-associated macrophages toward the M2 phenotype, accumulation of myeloid-derived suppressor cells, increased infiltration of regulatory T cells, and exhaustion of effector T cells, thereby helping tumor cells evade immune surveillance, resist therapy, and promote distant metastasis. Therefore, remodeling the TME and reversing immunosuppression have become important strategies in cancer therapy

[51].

### 3.5.1. Inhibition of Inflammatory Response and Regulation

NF- $\kappa$ B/STAT3 Signaling Pathways Inflammatory response is a hallmark of the TME, and the NF- $\kappa$ B and STAT3 signaling pathways are central hubs in the regulation of inflammation. In breast cancer, especially triple-negative breast cancer, the NF- $\kappa$ B signaling pathway is aberrantly activated, which in turn promotes the release of chemokines such as CCL2, creating an immunosuppressive microenvironment conducive to tumor progression. Multiple reviews published in 2025 have clearly indicated that curcumin and other polyphenolic compounds can ameliorate the inflammatory state of the TME by inhibiting the activation of the NF- $\kappa$ B signaling pathway and reducing the release of inflammatory mediators [52].

Regarding the STAT3 signaling pathway, curcumin and its analogues have been demonstrated to effectively target this pathway. STAT3 plays a critical role in breast cancer progression. Curcumin blocks the phosphorylation of JAKs and STAT3, prevents STAT3 dimerization and nuclear translocation, thereby inhibiting the transcription of pro-inflammatory cytokines (such as IL-6 and IFN- $\gamma$ ) and significantly reducing the inflammatory response [37]. Furthermore, molecular docking studies have shown that curcumin exhibits good binding affinity to key proteins such as NF- $\kappa$ B, STAT3, and HIF-1 $\alpha$ , highlighting its potential as a low-toxicity therapeutic option [53].

### 3.5.2. Regulation of Tumor-Associated Macrophage Polarization

Tumor-associated macrophages (TAMs) are one of the most abundant immune cell populations in the TME. In the tumor microenvironment, they are mainly polarized toward the M2 phenotype, promoting tumor immune escape and progression by secreting immunosuppressive cytokines such as IL-10 and TGF- $\beta$ . A study published in *Cell Biology and Toxicology* in 2025 developed M2-targeting peptide-chitosan-curcumin nanoparticles (M2pep-Cs-Cur NPs) to achieve targeted delivery to TAMs in a TNBC model. The study found that these nanoparticles effectively inhibited the proliferation (approximately 70%) and invasion (approximately 70%) of TNBC cells, while modulating the polarization state of TAMs by influencing the expression of key genes such as COX-2, thereby reversing M2-type polarization and enhancing the tumor response to anti-PD-L1 therapy (approximately 50% increase in survival rate). This study demonstrates that curcumin can not only directly kill tumor cells but also remodel the immune landscape of the TME by regulating the functional state of TAMs [54].

### 3.5.3. Selective Regulation of Myeloid-Derived Suppressor Cells

Myeloid-derived suppressor cells (MDSCs) represent another important class of immunosuppressive cells in the TME. They play a critical role in tumor immune evasion by inhibiting T cell activation and proliferation. Studies have shown that curcumin, similar to docetaxel, can selectively target granulocytic MDSCs

(CD11b<sup>+</sup>Ly6G<sup>+</sup>Ly6C<sup>low</sup>) while preserving monocytic MDSCs (CD11b<sup>+</sup>Ly6G<sup>-</sup>Ly6C<sup>high</sup>) and promoting their polarization toward CCR7<sup>+</sup>Dectin-1<sup>-</sup>M1-type macrophages, accompanied by the production of IFN- $\gamma$  and enhanced T cell cytolytic function, ultimately leading to a significant reduction in tumor burden in 4T1-Neu tumor-bearing mice [55]. This selective regulatory mechanism suggests that curcumin can precisely target different types of immunosuppressive cells in the TME, thereby effectively reversing the immunosuppressive state.

### **3.5.4. Regulation of T Cell Function and the PD-1/PD-L1 Immune Checkpoint**

T cell-mediated adaptive immune response is the core defense line of the body against tumors. Studies have confirmed that curcumin can significantly inhibit the expression of PD-L1 protein and mRNA in MCF-7 and MDA-MB-231 breast cancer cells. Mechanistic studies have shown that curcumin exerts its regulatory effects by suppressing PD-L1 promoter activity and the downstream PI3K/AKT/mTOR signaling axis, and that the combination of curcumin with a PD-L1 inhibitor synergistically inhibits the proliferation of breast cancer cells and induces apoptosis [56]. This finding provides experimental evidence for the use of curcumin in combination with immune checkpoint inhibitors for the treatment of breast cancer.

## **3.6. Regulation of Multiple Immune-Related Signaling Pathways**

### **3.6.1. PI3K/Akt Signaling Pathway**

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway is one of the core signaling networks regulating cell growth, proliferation, survival, metabolism, and angiogenesis [57-59]. In breast cancer, aberrant activation of this pathway is closely associated with tumor initiation, progression, invasion, metastasis, and therapeutic resistance. Clinical studies have shown that in patients with HR-positive, HER2-negative advanced breast cancer, the combination of PI3K/AKT/mTOR inhibitors with endocrine therapy has demonstrated significant clinical benefits. In triple-negative breast cancer (TNBC), approximately 60% of cases exhibit aberrant activation of this pathway, making it a highly promising therapeutic target. However, due to feedback activation within the pathway and the emergence of compensatory signaling pathways, inhibitors that solely target PI3K/Akt are prone to inducing resistance, limiting their clinical application. Against this backdrop, curcumin, with its multi-target regulatory properties, shows unique advantages in targeting the PI3K/Akt pathway [60].

Studies have shown that curcumin can inhibit PI3K activity, thereby blocking Akt phosphorylation, leading to alterations in the expression and function of downstream signaling molecules, and ultimately suppressing the malignant behavior of breast cancer cells. Wali et al. systematically summarized the regulatory effects of curcumin and other phytochemicals on the PI3K/AKT/mTOR pathway, pointing out that curcumin exerts anti-breast cancer effects through multiple mechanisms, including inhibiting key kinase activities, inducing apoptosis,

suppressing angiogenesis, and reversing chemotherapy resistance [61]. Faysal et al. explicitly stated in their review that curcumin reduces AKT phosphorylation levels in TNBC models, thereby inhibiting tumor progression [62].

### 3.6.2. NF- $\kappa$ B Signaling Pathway

The NF- $\kappa$ B signaling pathway is an important regulatory target through which curcumin exerts its anti-breast cancer effects. In various malignant tumor cells, NF- $\kappa$ B is constitutively activated and extensively participates in malignant biological processes such as tumor cell proliferation, apoptosis resistance, invasion and metastasis, and chemotherapy resistance by transcriptionally regulating the expression of downstream target genes including Bcl-2, Cyclin D1, COX-2, and MMP-9 [63]. Curcumin can intervene in the NF- $\kappa$ B signaling axis at multiple levels: at the upstream level, curcumin blocks the activation of the MAPK and PI3K/Akt pathways, thereby inhibiting IKK complex activity; at the core level, curcumin significantly downregulates NF- $\kappa$ B/p65 protein expression and prevents nuclear translocation of the p65 subunit; at the downstream level, curcumin inhibits the DNA-binding ability of NF- $\kappa$ B, thereby downregulating the transcriptional activity of its downstream target genes. Ultimately, these regulatory effects act synergistically to effectively inhibit the proliferation, invasion, and metastasis of breast cancer cells [64].

Experimental studies using mouse breast cancer 4T1 cells as a model have shown that curcumin inhibits the proliferation of 4T1 cells in a dose-dependent and time-dependent manner, with curcumin at concentrations of 10  $\mu$ mol/L, 20  $\mu$ mol/L, and 40  $\mu$ mol/L all significantly suppressing cell viability. Western blot analysis revealed that curcumin treatment significantly downregulated NF- $\kappa$ B p65 protein expression in 4T1 cells and increased the Bax/Bcl-2 ratio. Transwell assays further confirmed that curcumin effectively inhibited the invasion and migration abilities of 4T1 cells, with the most significant inhibitory effect observed in the 40  $\mu$ mol/L high-dose group [65]. This study demonstrated, at both the protein expression and cellular function levels, that curcumin exerts anti-breast cancer effects by downregulating NF- $\kappa$ B p65 expression.

In human breast cancer MDA-MB-231 cells, curcumin also exhibits the ability to exert anti-tumor effects by inhibiting the NF- $\kappa$ B pathway. Studies have found that curcumin significantly inhibits the proliferation of MDA-MB-231 cells and induces G2/M phase arrest, while increasing the Bax/Bcl-2 ratio. Notably, this study also confirmed that curcumin inhibits cell migratory activity by downregulating NF- $\kappa$ B p65 protein expression, providing important experimental evidence for the role of curcumin in triple-negative breast cancer through the NF- $\kappa$ B pathway [66].

### 3.6.3. MAPK Signaling Pathway

The mitogen-activated protein kinase (MAPK) family mainly includes three major subfamilies: extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase

(JNK), and p38 MAPK. They play critical regulatory roles in various biological processes such as cell proliferation, differentiation, apoptosis, and stress responses. Aberrant activation of the MAPK signaling pathway is closely associated with the initiation, progression, and therapeutic resistance of breast cancer, and targeting this pathway has become an important strategy to overcome drug resistance and enhance therapeutic efficacy in breast cancer [67]. Studies have shown that curcumin can regulate the MAPK signaling pathway at multiple levels to inhibit the growth and metastasis of breast cancer cells. Specifically, with respect to the ERK signaling axis, curcumin significantly downregulates the phosphorylation level of ERK, blocks its downstream signal transduction, and thereby inhibits the proliferative capacity of breast cancer cells. In MCF-7 breast cancer cells, curcumin-induced ERK phosphorylation plays an important role in regulating vascular endothelial growth factor secretion, further supporting the key role of ERK signaling in the anti-breast cancer effects of curcumin [68]. Regarding the JNK signaling axis, curcumin activates the JNK pathway, thereby inducing apoptosis in breast cancer cells. In hormone receptor-negative breast cancer, curcumin targets multiple signaling molecules including TGF, EGFR, MKK4/7, and JNK, downregulates the expression levels of nuclear transcription factors such as c-Myc, c-Fos, and c-Jun, thereby effectively inhibiting cell proliferation and migration and inducing apoptosis. With respect to the p38 MAPK signaling axis, curcumin-mediated regulation of this pathway can further influence the invasion and metastatic abilities of breast cancer cells [69].

#### **3.6.4. STAT3 Signaling Pathway**

The signal transducer and activator of transcription 3 (STAT3) signaling pathway is one of the key signal transduction pathways regulating cell proliferation, survival, apoptosis, and immune responses [70]. Hyperactivation of STAT3 is closely associated with the progression of aggressive breast cancer subtypes, particularly triple-negative breast cancer (TNBC), and has become an important potential therapeutic target for breast cancer [71]. Curcumin can effectively inhibit the activation of the STAT3 signaling pathway through multiple mechanisms. At the molecular level, curcumin blocks the phosphorylation activity of upstream kinases of STAT3 (mainly the JAK kinase family), thereby reducing the phosphorylation level of STAT3 protein. Specifically, curcumin inhibits the phosphorylation of JAKs (Janus kinases) and STAT3, prevents STAT3 dimerization, and subsequently impedes its nuclear translocation and DNA-binding capacity [72]. Furthermore, curcumin derivatives such as FLLL31 and FLLL32 have been shown to directly target the Src homology 2 domain of JAK2 and STAT3, specifically inhibiting STAT3 phosphorylation and DNA-binding activity [73]. At the functional level, the inhibitory effect of curcumin on the STAT3 signaling pathway further downregulates the expression of STAT3 downstream target genes. Studies have found that curcumin significantly reduces the expression levels of key target

proteins such as Cyclin D1 and Bcl-2 in breast cancer cells while inducing apoptosis [74]. In MCF-7 breast cancer cells, curcumin treatment significantly decreases the protein expression levels of p-JAK2 and p-STAT3, as well as the expression of downstream target genes such as Cyclin D1 and Bcl-2, thereby effectively inhibiting cell viability and inducing apoptosis [75]. Other studies have confirmed that curcumin can also downregulate the expression of anti-apoptotic proteins downstream of STAT3, such as Bcl-xL and Survivin, thereby promoting the apoptotic process in breast cancer cells [76]. In addition, by inhibiting STAT3 activation, curcumin effectively weakens the migration and invasion abilities of breast cancer cells and suppresses tumor metastasis [73].

## **4. Curcumin Reverses Therapeutic Resistance in Breast Cancer**

### **4.1. Curcumin Reverses Chemotherapy Resistance in Breast Cancer Cells**

Chemotherapy is one of the most important modalities in the clinical treatment of breast cancer; however, long-term drug exposure tends to induce acquired resistance in tumor cells, significantly limiting therapeutic efficacy and leading to treatment failure. The development of multidrug resistance (MDR) involves multiple complex mechanisms, among which the overexpression of ATP-binding cassette (ABC) transporter family members (such as P-glycoprotein, MDR1, MRP2, and BCRP) is a key factor leading to reduced intracellular accumulation of chemotherapeutic agents. Owing to its multi-target regulatory properties, curcumin exhibits unique application value in reversing chemotherapy resistance in breast cancer. Studies have shown that curcumin effectively downregulates the expression levels of drug efflux pumps such as P-glycoprotein (P-gp) and MDR1 in drug-resistant breast cancer cells, reduces the efflux of chemotherapeutic drugs, increases intracellular drug accumulation, and thereby restores the sensitivity of resistant cells to chemotherapeutic agents. Poma et al. co-encapsulated curcumin and doxorubicin in a biocompatible clay-based nanomaterial constructed from halloysite nanotubes and laponite, and demonstrated in doxorubicin-resistant MCF-7R breast cancer cells that curcumin acts as a substrate for P-gp, competitively inhibiting P-gp efflux function, significantly increasing the intracellular accumulation of doxorubicin, and effectively overcoming P-gp-mediated multidrug resistance [77]. Furthermore, Brodzicka et al. systematically summarized the regulatory effects of dietary-derived phytochemicals (including curcumin) on MDR transporters (MRP2, BCRP, and P-gp), clearly indicating that curcumin inhibits the activity of P-glycoprotein and MRP1, thereby making cancer cells more sensitive to chemotherapeutic agents [78].

In addition to regulating drug efflux pumps, curcumin can also reduce the expression of anti-apoptotic proteins by inhibiting the NF- $\kappa$ B signaling pathway, thereby promoting chemotherapy-induced apoptosis. A review published by Momal et al. in 2026 pointed out that curcuminoids can inhibit the activation of various

signaling pathways, including NF- $\kappa$ B, thereby inducing apoptosis, suppressing proliferation, and enhancing the efficacy of conventional chemotherapy and radiotherapy [79]. Faysal et al. indicated that curcumin and other natural compounds can inhibit metastasis, induce apoptosis, suppress proliferation, and reverse chemotherapy resistance by modulating key pathways such as PI3K/AKT/mTOR, NF- $\kappa$ B, and JAK/STAT. Animal experiments further confirmed the synergistic anti-tumor effects of curcumin combined with chemotherapeutic agents [80]. Nugroho et al. used a rat mammary adenocarcinoma model to combine Curcuma plant extract with an adriamycin-cyclophosphamide chemotherapy regimen. The results showed that the Curcuma extract significantly increased the expression level of granzyme B (reaching  $51.83 \pm 19.66$  in the P3 group) and markedly reduced tumor diameter ( $10.55 \pm 2.33$  in the P3 group) in a dose-dependent manner [81].

#### **4.2. Curcumin Reverses Radiotherapy Resistance in Breast Cancer**

Radiotherapy is an important modality for breast cancer treatment. Although it can effectively kill tumor cells, some patients develop radiotherapy resistance, leading to treatment failure and disease recurrence. Curcumin enhances the sensitivity of breast cancer cells to radiotherapy by modulating intracellular oxidative stress responses, DNA damage repair mechanisms, and apoptotic pathways. Specifically, curcumin induces the production of higher levels of reactive oxygen species (ROS) in breast cancer cells, exacerbating the intracellular oxidative stress state, thereby damaging the DNA structure and increasing DNA damage induced by radiotherapy [82]. At the same time, curcumin inhibits the expression and function of DNA damage repair-related proteins, hindering the repair of radiation-induced damage and making the cells more prone to apoptosis. Moreover, curcumin promotes radiotherapy-induced apoptosis of breast cancer cells by regulating apoptosis-related molecules such as Bcl-2 family proteins and the caspase cascade, further enhancing the therapeutic effect of radiotherapy. These findings provide strong support for the application of curcumin as a radiosensitizer in breast cancer therapy [83].

Komar et al. systematically evaluated the impact of curcumin on the homologous recombination (HR) pathway in eight breast cancer cell lines and patient-derived xenograft (PDX) models. Their results showed that curcumin treatment significantly reduced the ability to form radiation-induced RAD51 foci and decreased BRCA2 protein levels, thereby inducing homologous recombination deficiency (HRD) and rendering breast cancer cells more sensitive to DNA damage. Notably, this study also suggested that curcumin might simultaneously affect HR function in normal cells, providing an important caution regarding the safety of clinical combination therapy [84]. Furthermore, Khanehzar et al. pointed out that curcumin not only induces DNA double-strand breaks but also simultaneously impairs multiple repair

pathways, including homologous recombination and non-homologous end joining (NHEJ), and disrupts the ATR-CHK1 checkpoint mechanism, creating a synthetic lethal effect with PARP inhibitors. This offers new strategies for overcoming radiotherapy resistance [85].

## 5. Summary and Future Perspectives

Curcumin, as the core active component of the traditional Chinese medicine turmeric, exhibits considerable potential and unique advantages in breast cancer research. Through a synergistic regulatory network involving multiple targets and pathways, curcumin not only acts directly on breast cancer cells—by arresting the cell cycle, activating mitochondria- and death receptor-mediated caspase cascades to induce apoptosis, and inhibiting aberrantly activated signaling pathways such as PI3K/Akt/mTOR, NF- $\kappa$ B, and MAPK to block proliferation signals—but also intervenes in key steps of breast cancer progression: downregulating EMT transcription factors and MMP activity to suppress invasion and metastasis, modulating immune cell functions in the tumor microenvironment, and reversing drug resistance phenotypes mediated by P-gp and other transporters, thereby enhancing the efficacy of existing chemotherapeutic agents. The extensive preclinical evidence from *in vitro* and animal model studies has laid a solid theoretical foundation for the clinical translation of curcumin. However, significant challenges still impede the clinical application of curcumin in breast cancer. On one hand, its inherent poor bioavailability severely limits its *in vivo* efficacy; on the other hand, most current studies remain at the cellular and animal model stages, with a lack of multicenter, large-scale clinical trial data in breast cancer patients, making it difficult to provide sufficient evidence-based medical support for its clinical use. Therefore, future research should focus on two major directions: first, to intensify the development of novel delivery systems (e.g., nanocarriers, liposomes) to overcome the bioavailability bottleneck and improve the targeting and stability of curcumin; second, to promote the implementation of multicenter, randomized controlled trials to systematically evaluate the safety and efficacy of curcumin alone or in combination with surgery, radiotherapy, chemotherapy, and targeted therapy. With the gradual resolution of these key issues, curcumin is expected to transition from a dietary supplement and basic research hotspot to an important adjuvant in comprehensive breast cancer therapy, providing new strategies and insights for improving patient outcomes.

### Conflicts of Interest

The authors declare that they have no conflict of interest.

### Funding

This study was supported by the 17th Batch of College Students' Innovation and

Entrepreneurship Training Program of Yangtze University (Grant No. 364)

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