Curcumin Suppresses Breast Cancer Stem Cells via Mitochondrial Remodeling, Redox Stress, and Oncogenic Pathway Inhibition; A Review

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Submitted 2026/5/11

Revised 2026/7/18

Accepted 2026/7/20

Abstract

Breast cancer stem cells (BCSCs) represent a highly aggressive subpopulation responsible for tumor initiation, recurrence, metastasis, and therapeutic resistance. Mitochondria play a central role in maintaining BCSC stemness through enhanced oxidative phosphorylation (OXPHOS), redox adaptation, and metabolic plasticity. Dysregulated mitochondrial dynamics and elevated reactive oxygen species (ROS) levels tightly modulate survival pathways, contributing to stemness maintenance. Curcumin, a pleiotropic phytochemical, has emerged as a promising agent capable of disrupting the ROS–mitochondria

axis and modulating oncogenic signaling. Evidence indicates that curcumin alters mitochondrial biogenesis, suppresses OXPHOS, induces ROS-mediated mitochondrial dysfunction, and downregulates multiple pathways associated with BCSC maintenance, including PI3K/Akt/mTOR, Wnt/β-catenin, Ras, and p53. Despite its extensive anticancer potential, curcumin's limited bioavailability has restricted its translation into clinical settings. Novel nanoformulations and targeted delivery approaches may enhance its therapeutic efficacy. This review provides a comprehensive analysis of the multimodal mechanisms through which curcumin targets BCSCs, with an emphasis on mitochondrial remodeling and ROS-driven vulnerabilities, offering a framework for future therapeutic development.

Keywords: Breast Neoplasms, Cancer Stem Cells, Curcumin, Mitochondria, Reactive Oxygen Species, Signal Transduction

Introduction

Breast cancer (BC) is the most frequently diagnosed malignancy among women and remains a leading cause of cancer-related mortality worldwide.[1,2] It accounts for more than half a million deaths annually, with certain regions, including Iran, notably experiencing an earlier age of onset, approximately a decade younger than the global average.[3,4]Histologically, BC arises from epithelial cells lining the mammary ducts or lobules, manifesting clinically as a painless mass, changes in breast shape or size, nipple discharge, skin dimpling, nipple retraction, or persistent localized pain.Advanced stages may present with regional lymphadenopathy and systemic symptoms.[5,6]

The etiology of BC is multifactorial, incorporating genetic predispositions and environmental influences. Key risk factors include prolonged estrogen exposure, obesity, delayed menopause, oral contraceptive or hormone replacement therapy use, and a family history of breast malignancy.[7,8] These factors drive genetic mutations and the dysregulation of critical oncogenic pathways, such as RAS/RAF/MEK/ERK, PI3K/Akt/mTOR, estrogen receptor (ER), and cyclin-dependent kinase (CDK) signaling.

Diagnosis typically involves clinical breast examination, mammography, ultrasonography, and confirmation by histopathological biopsy. Advances in gene expression profiling have enabled the molecular classification of BC into four intrinsic subtypes, luminal A, luminal B, HER2-enriched, and basal-like, each with distinct clinical behaviors and therapeutic implications. Despite its utility, this framework oversimplifies tumor heterogeneity, as variations persist within each subtype. In routine clinical settings, immunohistochemistry (IHC) remains a practical surrogate for molecular classification.[9]

Therapeutic strategies are tailored according to tumor biology and stage, and may include surgery, radiotherapy, endocrine therapy for hormone receptor–positive disease, chemotherapy, HER2-targeted agents such as trastuzumab, and emerging immunotherapies.[10-12]These treatments are often associated with significant adverse effects: surgery may lead to pain, infection, lymphedema, or reduced arm mobility; chemotherapy commonly causes fatigue, nausea, alopecia, and myelosuppression; radiotherapy may induce skin irritation, fatigue, and breast texture changes; and endocrine therapies are linked to hot flashes, mood disturbances, thrombotic risk, and bone loss.[13,14]

Growing interest has centered on phytochemicals, bioactive plant-derived compounds, as potential adjuncts or alternatives with lower toxicity profiles in BC management. Compounds such as curcumin, resveratrol, epigallocatechin gallate (EGCG), genistein, and sulforaphane demonstrate anticancer activity by modulating multiple hallmarks of cancer. Curcumin, a natural polyphenol from Curcuma longa, exhibits potent anti-inflammatory and anticancer properties. In BC models, it targets several key signaling pathways, including NF-κB, PI3K/Akt, and MAPK,thereby inhibiting tumor growth, reducing proliferation, promoting apoptosis, and suppressing metastasis (Figure 1).[6,15-19]

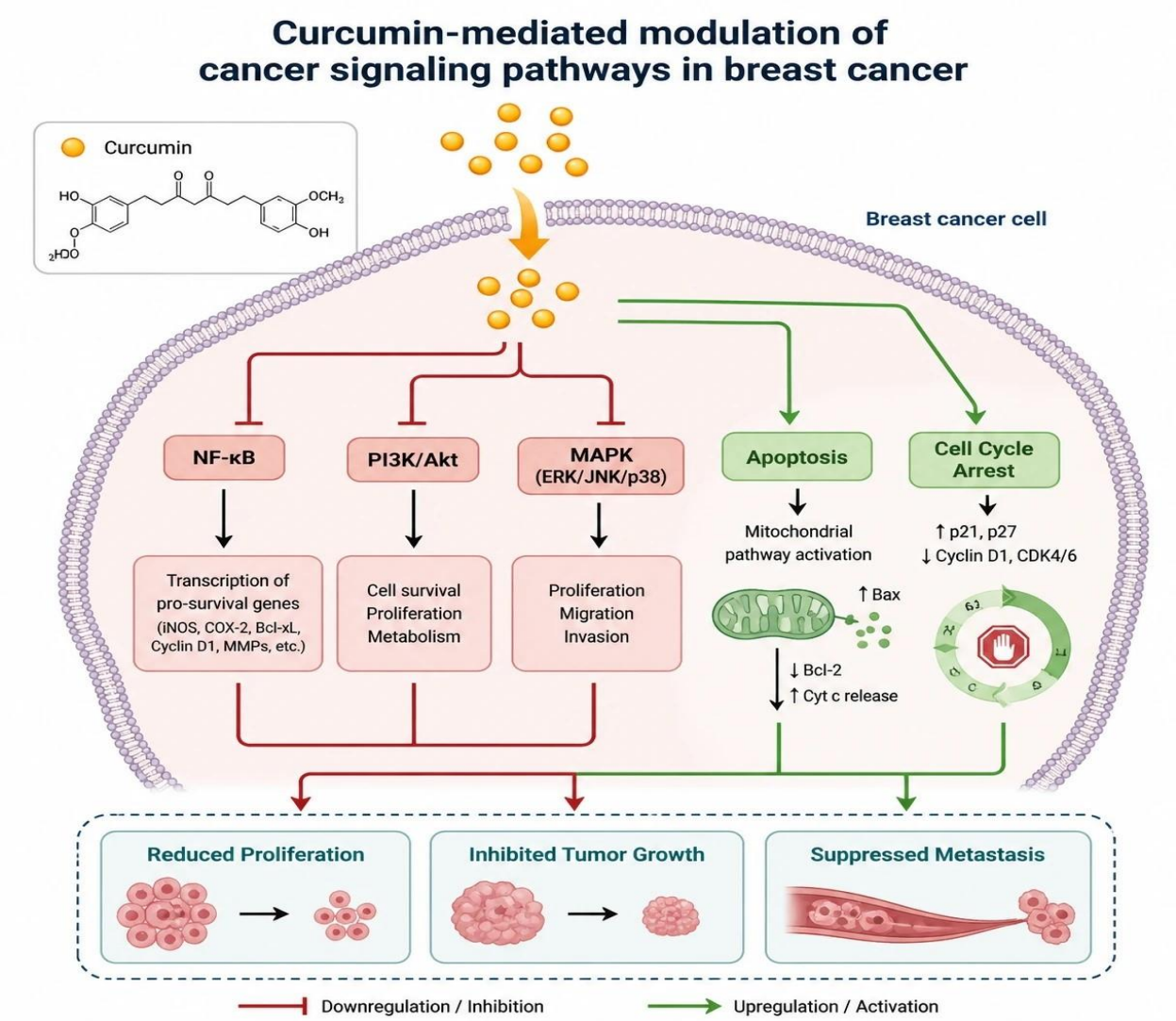

Figure 1. Curcumin modulates major oncogenic signaling pathways in breast cancer, including NF-κB, PI3K/Akt, and MAPK, resulting in reduced proliferation, enhanced apoptosis, and suppression of metastatic potential.

This review provides an updated synthesis of curcumin's inhibitory effects on breast cancer, with particular emphasis on mitochondria-related signaling pathways.

1. Methodology (Literature Search Strategy)

A structured literature search was performed using PubMed, Scopus, Web of Science, and Embase to identify relevant studies published between January 2000 and Apr 2026. The search combined MeSH, Emtree, and free-text terms including "Curcumin", "Breast Neoplasms", "Cancer Stem Cells", "Mitochondria", "Oxidative Stress", "ROS", and "Signal Transduction". Boolean operators (AND/OR), truncations, and field tags were applied.

Inclusion criteria encompassed original experimental studies, mechanistic investigations, and preclinical research on curcumin; studies examining BCSCs or breast cancer cells with stem-like features; articles evaluating mitochondrial function, oxidative stress, or related signaling pathways; and English-language publications. Exclusion criteria included non-cancer or non-breast cancer studies; clinical studies not evaluating mechanistic endpoints; reviews, commentaries, and case reports (used only for background); and studies lacking mitochondrial or ROS-related outcomes. Two independent reviewers screened titles and abstracts, with disagreements resolved through discussion; full texts were then evaluated using predefined criteria. This review is classified as a narrative review with structured search elements, not a systematic review.

2. Heterogeneity in Tumor Mass

Breast cancer exhibits pronounced heterogeneity across genomic, epigenomic, transcriptomic, and proteomic levels, collectively shaping fundamental tumor characteristics such as proliferation, cell death, metastatic potential, and therapeutic response. This diversity manifests in two principal forms: intertumoral heterogeneity, which refers to differences between tumors from different patients or metastatic sites, and intratumoral heterogeneity, which captures the coexistence of distinct cellular subpopulations within a single tumor in the same patient.[20]

Heterogeneity further extends across both spatial and temporal dimensions. Temporal heterogeneity describes the molecular evolution of tumors as they progress or are exposed to therapeutic pressures.[4]Spatial heterogeneity arises from the uneven distribution and interactions of unique cellular subclones within the complex architecture of the tumor microenvironment. Collectively, these layers of variability complicate early detection, challenge precision therapeutic strategies, and limit prognostic accuracy.[21]

3. Breast Cancer Stem Cells

The cancer stem cell (CSC) paradigm gained prominence in the early 2000s, particularly through studies of breast malignancies.[22] Within the tumor mass, three principal cellular compartments are typically recognized: bulk cancer cells, progenitor populations, and cancer stem cells (CSCs). Studies using MCF7 cells show that bulk tumor cells constitute approximately 85–95% of the neoplasm and possess limited tumor-initiating capacity, whereas progenitor cells, which make up less than 5% of the population, display intermediate phenotypes with moderate proliferative and differentiation potential. In contrast, CSCs, although exceedingly rare (less than 1%), exert a disproportionately significant influence due to their strong self-renewal ability, potent tumor-initiating capacity, and heightened propensity for metastatic dissemination. Phenotypically, breast cancer stem cells (CSCs) recapitulate essential attributes of normal stem cells through a balanced regulation of self-renewal and differentiation, thereby sustaining tumor growth while maintaining a reservoir of stem-like cells. Functionally, CSCs evade conventional therapies through quiescence, enhanced DNA damage repair, and multidrug resistance mechanisms, all of which contribute to disease persistence, therapeutic failure, and relapse. Notably, CSCs exhibit considerable metabolic plasticity allowing them to adapt to microenvironmental stresses and therapeutic pressures.

The origins of breast cancer stem cells (BCSCs) appear to be multifactorial and context-dependent. Evidence suggests that BCSCs may arise through lineage continuity with mammary stem cells (MaSCs), supported by overlapping surface markers such as CD44 and PROCR, and dependence on key developmental pathways including NOTCH, Wnt, and Hedgehog. Alternatively, oncogenic mutations in normal stem or progenitor compartments, such as those occurring in luminal or basal progenitors, can initiate distinct tumor phenotypes; for instance, PIK3CA mutations have been associated with divergent BC subtypes, while BRCA1 loss promotes stem-cell expansion and malignant transformation. The presence of markers such as CD133 and CD49f (integrin α6) further supports the heterogeneity of potential cells of origin within the mammary epithelium. In addition, epithelial–mesenchymal transition (EMT) contributes to the generation or enrichment of BCSCs by conferring stem-like traits on non-stem cancer cells through EMT-associated plasticity and metabolic reprogramming. Collectively, these findings highlight a hierarchical yet dynamic tumor architecture in which rare, therapy-resistant CSCs orchestrate growth, relapse, and metastatic spread, underscoring their relevance in risk stratification and CSC-targeted therapeutic strategies.

Accumulating evidence indicates that partial EMT or hybrid epithelial/mesenchymal (E/M) states are strongly associated with increased stemness, heightened tumorigenic potential, and unfavorable clinical outcomes.[23] These hybrid phenotypes allow cells to retain epithelial properties needed for adhesion while acquiring mesenchymal traits that enhance motility and invasiveness, thereby promoting tumor progression and metastatic dissemination. Metabolically, CSCs differ markedly from bulk tumor cells, which predominantly rely on aerobic glycolysis (the Warburg effect). CSCs, by contrast, demonstrate significant metabolic flexibility, alternating between glycolysis and oxidative phosphorylation (OXPHOS) according to environmental and energetic demands. This adaptive metabolic reprogramming enables survival under hypoxia, nutrient deprivation, or therapeutic stress, thereby supporting their persistence and tumor-initiating capacity.[24-26]

Recognition of CSCs as major contributors to recurrence and treatment resistance has catalyzed efforts to develop targeted strategies that disrupt CSC-associated pathways governing self-renewal, drug

resistance, and differentiation.[27,28] Combining CSC-targeted approaches with standard therapies has been proposed as a means to enhance therapeutic efficacy and improve patient survival, At the same time, advances in stem cell biology emphasize the importance of precise regulation to prevent aberrant activation and malignant transformation.[29,30] Recent studies have further underscored the central role of mitochondria in CSC physiology. Compared with non-stem cancer cells, CSCs display distinctive mitochondrial features, including elevated reactive oxygen species (ROS), increased mitochondrial biogenesis, higher mitochondrial DNA content, and altered regulation of mitophagy and mitochondrial membrane potential.[31,32] These mitochondrial adaptations support energy production, redox homeostasis, and biosynthetic requirements essential for CSC maintenance. Importantly, breast cancer stem cells exhibit increased mitochondrial mass and metabolic activity, which facilitate self-renewal, differentiation, and metastatic progression. Their contribution to the aggressiveness and persistence of metastatic lesions highlights the therapeutic potential of targeting mitochondrial pathways in BCSCs to inhibit breast cancer progression and enhance treatment outcomes.[33,34]

4. The Role of Mitochondria in Cancer Stem Cells

Mitochondria are central regulators of cellular bioenergetics and survival, generating ATP through oxidative phosphorylation (OXPHOS) while coordinating redox balance, apoptotic pathways, and metabolic adaptation in response to environmental stressors. [35-37] In cancer, these organelles play a decisive role in tumor progression and therapy resistance, with particularly prominent impacts on cancer stem cells (CSCs).

Extensive evidence shows that CSCs possess a distinct mitochondrial profile characterized by increased mitochondrial mass and heightened oxidative metabolism. CSC enriched spheroids exhibit upregulation of key nuclear encoded mitochondrial proteins compared with differentiated monolayer cultures derived from the same breast cancer cell lines. [36,38,39] This pattern suggests enhanced mitochondrial biogenesis or diminished mitophagic turnover, leading to the mitochondrial enrichment now recognized as a hallmark of the CSC phenotype. [40] Functionally, CSCs depend heavily on OXPHOS for energy production and survival; inhibition of ATP synthase (Complex V) using oligomycin markedly reduces spheroid formation, confirming OXPHOS reliance. Increased mitochondrial content in CSCs has also been associated with elevated telomerase (hTERT) activity, linking mitochondrial abundance with self-renewal and cellular immortality. [26,40]

Morphologically and functionally, CSC mitochondria differ from those of differentiated tumor cells. CSC mitochondria are often smaller, rounded, and perinuclearly clustered, whereas differentiated cells typically exhibit elongated, interconnected networks. Altered cristae organization, reductions in mitochondrial DNA content, and decreased TFAM expression have all been reported in CSCs, contributing to tightly regulated electron transport activity and controlled reactive oxygen species (ROS) generation. [41-44]Such moderated ROS levels promote stabilization of hypoxia-inducible factor-1α (HIF-1α) and activation of pathways such as MAPK, ultimately sustaining stemness, survival, and tumorigenicity. A defining feature of CSCs is their high metabolic plasticity. These cells can switch between glycolysis and OXPHOS depending on environmental constraints such as hypoxia or nutrient limitation. During these

transitions, mitochondria generate oncometabolites including fumarate, succinate, lactate, and 2-hydroxyglutarate, which act as signaling mediators that reinforce tumor progression. These metabolites contribute to HIF 1α stabilization, STAT3 driven VEGF expression, and NF κB activation, promoting angiogenesis, invasion, and CSC maintenance.[45,46] Collectively, mitochondrial metabolism is integral to CSC survival, plasticity, and therapeutic resistance.

5. Mitochondrial Dysfunction in Cancer

Mitochondrial dysfunction is a major driver of tumor initiation, progression, and therapeutic resistance. This dysfunction encompasses impaired OXPHOS, disrupted tricarboxylic acid (TCA) cycle activity, and excessive reactive oxygen species (ROS) generation, resulting in chronic oxidative stress and widespread metabolic reprogramming in cancer cells. [47]

The conceptual link between mitochondrial impairment and aging originated from Harman's free radical theory, proposing that cumulative oxidative damage caused by ROS contributes to age related cellular decline.[48] Later studies identified mitochondria as both the predominant source and the primary target of ROS. Persistent oxidative stress can damage mitochondrial DNA (mtDNA), respiratory-chain proteins, and membrane lipids, creating a self-reinforcing cycle of mitochondrial injury that further elevates ROS production.[49] In cancer, mitochondrial dysfunction arises through mtDNA mutations, defects in electron transport chain complexes, and dysregulation of TCA cycle enzymes. These abnormalities alter bioenergetic balance and facilitate metabolic rewiring that supports unchecked proliferation. Oncogenic signaling and loss of tumor suppressors further reshape mitochondrial metabolism, enabling tumor cells to withstand metabolic stressors and maintain rapid growth.Beyond metabolic reprogramming, mitochondrial dysfunction critically impacts several hallmarks of cancer. Aberrant mitochondrial signaling disrupts ROS homeostasis, modifies calcium flux, and impairs apoptotic machinery, enabling tumor cells to evade programmed cell death. Such alterations promote treatment resistance and facilitate survival under harsh microenvironmental and therapeutic conditions. Collectively, these mitochondrial perturbations contribute to a pro-tumorigenic state that drives malignant transformation, progression, and resistance to standard therapies.[48]Given the central role of mitochondria in maintaining cancer stem cell (CSC) metabolism, redox balance, and resistance to apoptosis, mitochondrial dysfunction emerges as a strategic therapeutic vulnerability in breast cancer. CSCs rely heavily on tightly regulated OXPHOS activity, moderated ROS signaling, and metabolic plasticity to sustain self-renewal and survive environmental and therapeutic stressors.[35,36,42,43,46,47] At the same time, tumor cells exhibiting mitochondrial defects, including altered mtDNA integrity, dysregulated TCA cycle enzymes, and disrupted apoptotic signaling, develop a heightened dependence on compensatory redox pathways and metabolic adaptations that reinforce malignancy.[48-50] This convergence of mitochondrial dependence in CSCs and mitochondrial dysfunction in cancer cells positions mitochondria as an especially attractive therapeutic target. In this context, curcumin is of particular interest due to its multi targeted ability to modulate mitochondrial bioenergetics, induce ROS mediated stress beyond CSC tolerance thresholds, and disrupt OXPHOS dependent survival pathways. These properties suggest that curcumin may selectively compromise CSC viability by exploiting their mitochondrial liabilities while simultaneously counteracting

tumor-associated mitochondrial defects. This mechanistic alignment provides the biological rationale for exploring curcumin as a mitochondrial-targeting agent in breast cancer stemness.

6. ROS-Mediated Regulation of Mitochondrial Function in Cancer Stem Cells

Recent studies have shown that the mitochondrial features of cancer stem cells (CSCs) differ significantly from those of non-stem cancer cells. Notable variations have been observed in mitochondrial DNA (mtDNA) content, mitochondrial biogenesis, membrane potential, reactive oxygen species (ROS) production, and mitophagic activity.[50-52] These findings highlight the crucial role of mitochondrial integrity and function in regulating CSC behavior, maintaining their stemness, and supporting tumor progression. In cells, ROS are primarily generated by several enzymatic systems, including NADPH oxidases, nitric oxide synthases (NOS), xanthine oxidases, and the mitochondrial electron transport chain (ETC).[53,54] When ROS production exceeds the capacity of cellular antioxidant defenses, oxidative stress occurs, leading to cellular damage and pathological changes. Among reactive free-radical species, ROS are particularly significant because they arise directly from essential metabolic pathways, especially aerobic metabolism within the mitochondrial respiratory chain. Therefore, ROS plays a key role in the initiation and progression of various malignancies.[55-57]Beyond their damaging effects, ROS also act as critical regulators of intracellular signaling networks. They influence pathways related to growth factors, mitogenic responses, and stress responses that govern vital cellular processes, including proliferation, metabolism, gene expression, differentiation, and programmed cell death. However, persistent accumulation of ROS can promote abnormal cell growth, genomic instability, and carcinogenesis, particularly within the tumor microenvironment.[58,59] Elevated levels of ROS have been associated with numerous pathological conditions, including cancer, diabetes, atherosclerosis, stroke, and arthritis. Additionally, oxidative by-products are often used as biomarkers of tumor activity and systemic oxidative stress.[60-62]

Maintaining redox homeostasis is essential for normal cellular function and relies on a coordinated network of antioxidant defenses. Key components of this system include superoxide dismutase (SODs)[63], superoxide reductases, catalase (CAT), glutathione peroxidase (GPX), glutathione reductase, peroxiredoxins (Prdxs), and thioredoxins (Trx).[64-66] Together, these enzymes detoxify excess ROS and preserve both mitochondrial and cellular integrity. The generation of mitochondrial ROS is regulated by tightly controlled interactions among redox-active molecules, metabolic intermediates, ETC complexes, making mitochondria both a major source and a primary target of oxidative signaling. The dynamic balance between ROS production and antioxidant activity ultimately determines cellular fate under both physiological and pathological conditions.[67]

A growing body of evidence underscores the central role of mitochondria in carcinogenesis, with mitochondrial dysfunction manifested as excessive ROS generation, impaired oxidative metabolism, altered mitochondrial dynamics, or disrupted bioenergetic signaling emerging as a hallmark of many cancers.[48,68-70] These abnormalities contribute to tumor initiation, progression, metabolic adaptation, and resistance to apoptosis. Collectively, these findings emphasize the dual role of ROS as both vital signaling mediators and pathological agents, highlighting the importance of mitochondrial redox regulation in cancer development and progression. Given the reliance of CSCs on mitochondrial homeostasis and redox adaptation, these pathways present attractive therapeutic targets. Among the agents that can exploit

such vulnerabilities, curcumin has emerged as a promising modulator of mitochondrial function and ROS-dependent signaling.

7. Strategies to Target Breast Cancer Stem Cells

A wide range of therapeutic strategies has been developed to selectively eradicate breast cancer stem cells (BCSCs), reflecting their central role in tumor initiation, metastatic progression, and resistance to therapy. One major approach targets surface markers highly expressed on BCSCs, including CD44, CD24, and ALDH1. These markers not only facilitate the identification and isolation of CSC subpopulations but also serve as entry points for monoclonal antibodies and ligand-directed drug delivery systems designed to eliminate these cells.Another key strategy involves the inhibition of signaling pathways essential for CSC maintenance and self-renewal. The Notch, Wnt/β-catenin, Hedgehog, and PI3K/Akt/mTOR pathways represent critical regulators of stemness, and their pharmacologic inhibition, using smallmolecule inhibitors or RNA-based therapeutics, has shown promising results in preclinical models by reducing CSC viability and tumor-initiating capacity.[71-73]Epigenetic regulation has also emerged as a compelling therapeutic avenue. Agents targeting DNA methylation or histone modifications can reactivate silenced tumor suppressor genes and promote CSC differentiation or apoptosis, thereby diminishing their contribution to tumor persistence.[74,75] In parallel, the tumor microenvironment (TME), which provides structural and biochemical support for CSC survival, has become a focal point of CSC-directed therapies. Strategies aimed at disrupting stromal signaling, hypoxic niches, or extracellular matrix (ECM) interactions can weaken the protective niche that shields CSCs from immune surveillance and therapeutic interventions.[76]Given the metabolic plasticity of CSCs, metabolic targeting has gained increasing attention. Inhibiting glycolysis, oxidative phosphorylation (OXPHOS), or other key metabolic pathways can selectively impair CSC energy production and reduce their survival under stress conditions.[77] Furthermore,recent advancements in immunotherapy have expanded the therapeutic landscape for CSC targeting. Immune checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell therapies engineered to recognize CSC-specific surface antigens are being explored to enhance immune-mediated eradication of CSC populations.[78-80]

Combination therapies integrating conventional modalities, such as chemotherapy or radiation, with CSC-specific interventions hold significant promise for mitigating therapeutic resistance and preventing disease relapse. Collectively, these strategies illustrate the multifaceted nature of CSC targeting and highlight the substantial progress made toward translating these findings into clinical applications.[81]In parallel, renewed interest has emerged in plant-derived compounds as safer and more widely accepted therapeutic alternatives. Among these, curcumin, a natural polyphenol with broad anticancer activity, has gained particular attention as a leading candidate for targeting BCSCs (Table 1).

Table 1. The Therapeutic Role of Curcumin in Different Cancers

Cancer Type	Cell Line	Curcumin Conc.	Finding/Mechanisms	Ref.
Colon	HT-29 cells	50 and 75 μM	Regulating the expression of apoptosis-related proteins and activating p53.	82
Renal	RCC	58 μM	Upregulation of YAP/p53.	83
Gastric	SGC-7901 and BGC-823	0, 10, 20, and 40 μm	Affecting P53 and PI3K signaling.	84
Colorectal	HCT-15 cells	30 and 50 μM	Regulation of p53 and Prp4expression.	85
Glioma	U251 cells	–	Upregulation of ING4 expression and induces G2/M cell cycle arrest in a p53-dependent manner.	86
Hepatic	HSCs	20 μM	Activation of PPARγ/P53 signaling pathway.	87
MM	RPMI 8226 cells	20 and 40 μmol/l	Promotion of the apoptosis of MM cells by upregulating p53 protein expression.	88
Lung	A549 and NCI-H1299	400 nmol/L	Induction of p53 reactivation and NF-κB inhibition in human lung cancer cells.	89
Colon	HCT-116	2.5–160 lM	Activation of the p53-independent apoptosis and superoxide anion production in human colon cancer cells.	90
Colorectal	HCT-15 cells	-	Increasing of p53 molecules expression in tumor cells, subsequent in accelerated apoptosis of tumor cells.	91
Ovarian	HO-8910	42	↓Cell growth, ↑apoptosis	92

*Human renal cell carcinoma (RCC), Multiple myeloma (MM).

8. Bioactivity of Curcumin and Its Cyto-Protective Action

Curcumin (CURC) is a naturally occurring polyphenol derived from the rhizome of Curcuma longa.[93,94] Recognized for its ability to modulate free radical–mediated cellular injury, curcumin exhibits potent antioxidant and anti-inflammatory properties.it can reprogram gene expression by influencing key transcription factors that regulate cell survival and metabolic homeostasis.[95,96] In addition to its cytoprotective effects, CURC demonstrates broad antitumor activity and has been shown to impact cancer stem cell (CSC) populations across several malignancies, including colon, pancreatic, brain, breast, and head-and-neck cancers, thereby suppressing tumor growth and progression. Notably, CURC enhances the cytotoxic effects of chemotherapeutic agents while simultaneously mitigating drug resistance, ultimately improving overall therapeutic efficacy.[97,98] Owing to these properties, curcumin has gained significant attention in oncology, and evidence from in vitro, in vivo, and clinical studies indicates that it modulates multiple molecular pathways involved in tumor initiation and progression.[99]

Mechanistically, curcumin inhibits cancer cell proliferation by disrupting the cell cycle disruption, typically inducing arrest at the G1/S or G2/M checkpoints by downregulating cyclins and cyclin-dependent kinases.

This arrest is accompanied by the suppression of growth-promoting oncogenes and the induction of tumor suppressors such as p21 and p53.[100] Concurrently, curcumin promotes apoptosis via both intrinsic (mitochondrial) and extrinsic (death receptor–mediated) pathways. It upregulates pro-apoptotic proteins, including Bax, Bad, and p53, while decreasing the expression of anti-apoptotic mediators such as Bcl-2 and Bcl-xL, thereby shifting the balance toward caspase activation and programmed cell death.[101,102]

Curcumin also exhibits robust antiinflammatory activity primarily through suppression of the nuclear factor-κB (NF-κB) signaling pathway. NF-κB is a master regulator of inflammatory cytokines, chemokines, and adhesion molecules. By inhibiting NF-κB, curcumin reduces the expression of pro-inflammatory mediators such as TNF-α, IL-6, COX-2, and iNOS, thereby attenuating inflammatory signaling and microenvironmental activation.[103]

Angiogenesis, a critical process for tumor growth and metastasis, is another target of curcumin. Curcumin exerts anti-angiogenic effects by downregulating vascular endothelial growth factor (VEGF) and its receptor-associated signaling, which inhibits extracellular matrix degradation and tumor invasiveness. This effect is reinforced by its suppression of matrix metalloproteinases MMP-2 and MMP-9, key proteolytic enzymes involved in extracellular matrix breakdown and metastatic spread.[104]

Beyond these actions, curcumin broadly modulates several oncogenic signaling networks, including PI3K/Akt, MAPK, JAK/STAT, and Wnt/β-catenin pathways, thereby restraining proliferative, survival, and metastatic programs.[104,105] As depicted in (Figure 2), curcumin's pleiotropic effects further include inhibition of NF-κB and AP-1 signaling, suppression of lipoxygenase (LOX) and cyclooxygenase (COX) enzymatic activity, interference with sarcoplasmic reticulum Ca^{2+}-ATPase function, and blockade of drug-induced NF-κB activation. Collectively, these multifunctional properties strengthen curcumin's antitumor, anti-inflammatory, and chemosensitizing potential.

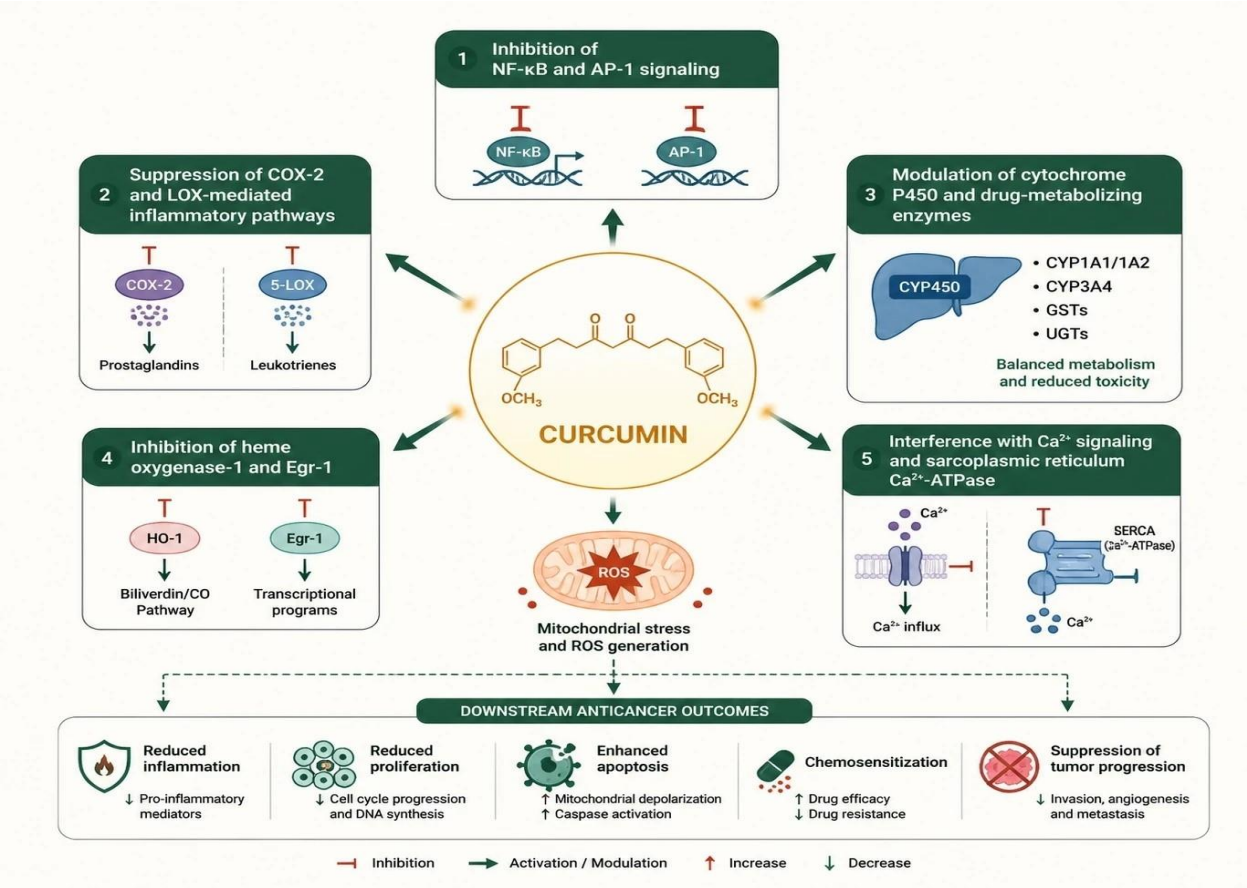

Figure 2. The Role of Curcumin on Various Cell Signaling Pathways.

9. Curcumin Effects on Mitochondrial Dynamics and Biogenesis in Tumorigenesis

Building on the mitochondrial vulnerabilities outlined earlier, curcumin demonstrates multifaceted anti-cancer stem cell (CSC) effects by coordinating the disruption of mitochondrial structure, bioenergetics, and redox balance. One of its main mechanisms involves the inhibition of the electron transport chain (ETC) complexes, leading to decreased oxidative phosphorylation and ATP production. This metabolic impairment is coupled with the modulation of Bcl-2 family proteins, causing an increased Bax/Bcl-2 ratio, mitochondrial outer membrane permeabilization (MOMP), cytochrome-c release, and the subsequent activation of caspase-dependent apoptotic pathways in CSCs.[106]

Additionally, curcumin promotes the accumulation of reactive oxygen species (ROS) in CSCs, enhancing oxidative stress and triggering apoptotic signaling. This pro-oxidant activity in malignant cells contrasts with curcumin's antioxidant effects in non-transformed tissues, where it can bolster endogenous antioxidant defenses and minimize oxidative damage. Through this dual action, curcumin selectively induces cytotoxicity in CSCs while preserving normal cellular integrity, partly by limiting oxidative injury and facilitating mitochondrial DNA (mtDNA) repair, thus maintaining mitochondrial genome stability and countering the metabolic reprogramming that supports breast cancer stem cell (BCSC) survival.Moreover,

curcumin disrupts mitochondrial calcium homeostasis by modulating the mitochondrial calcium uniporter (MCU) complex. Increased uptake of calcium by the mitochondria leads to calcium overload, loss of mitochondrial membrane potential (ΔΨm), and activation of apoptotic signaling pathways. Curcumin further impairs mitochondrial function by inhibiting mitochondrial ribosomal activity, which reduces the synthesis of ETC subunits and compromises respiratory capacity and energy production. These combined effects diminish the bioenergetic flexibility necessary for the maintenance and tumorigenicity of CSCs.

In summary, Figure 3 illustrates the interconnected mitochondrial mechanisms that contribute to the maintenance and aggressiveness of breast cancer stem cells (CSCs). These pathways include ROS-driven PI3K/AKT/NF-κB signaling, resistance to apoptosis, metabolic reprogramming (the Warburg effect), and metastatic programming. Together, they represent crucial mitochondrial dependencies. Targeting these processes such as with agents like curcumin could help suppress CSC survival, self-renewal, and tumor growth.[107-119]

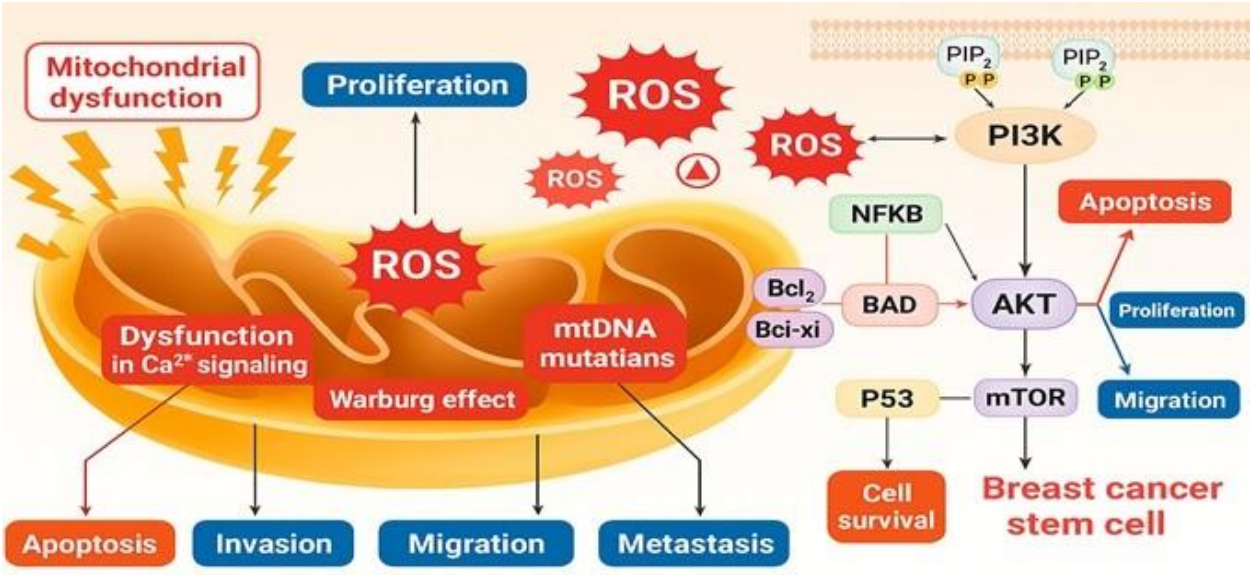

Figure 3. The Signaling Pathways Related to Mitochondrial Dysfunction in Breast Cancer Stem Cells.

9.1. CUR-mediated Regulation of Tumor Protein P53 Pathway

The tumor suppressor p53 plays a central role in governing apoptosis, cell-cycle progression, and genomic stability. In response to DNA damage, p53 acts as a transcription factor that activates a network of pro-apoptotic genes, leading to cell-cycle arrest or programmed cell death. Conversely, mutations or loss of p53 function are among the most common abnormalities in human cancers, highlighting its essential role in tumor suppression. In breast cancer (BC), reduced p53 expression is frequently associated with elevated cyclin-dependent kinase (CDK) levels, reflecting a breakdown in cell-cycle checkpoints and impaired DNA repair fidelity[120-122]. More broadly, TP53 deregulation disrupts DNA damage responses, checkpoint control, and genomic maintenance, thereby accelerating malignant transformation.[123]

Curcumin (CUR) interacts with this pathway at multiple regulatory nodes. Numerous studies have shown that CUR activates p53 signaling in malignant cells, thereby promoting apoptosis and suppressing proliferation. In breast cancer models, CUR induces both p53-dependent and p53-independent cell death mechanisms.[123,124] In MCF-7 cells, CUR disrupts cell-cycle progression and triggers intrinsic (mitochondrial) apoptosis through p53-dependent pathways, characterized by Bax upregulation and mitochondrial outer membrane permeabilization.[125-127] Even in contexts where p53 is mutated or functionally inactivated, CUR remains effective by modulating alternative signaling cascades, including downregulation of MAPK p38 and suppression of the anti-apoptotic protein Bcl-2, thereby attenuating tumorigenesis.[128] Beyond classical apoptosis regulators, CUR influences additional molecular components implicated in BC progression, further broadening its mechanistic scope.[129]Mechanistically, CUR has been shown to elevate p53 expression and enhance serine phosphorylation of p53, resulting in p53 hyperactivation and subsequent inhibition of Akt signaling via dephosphorylation.[130,131] CUR also suppresses tumor growth by reducing mutant p53 expression and activating caspase-3-mediated apoptosis. Notably, cells harboring mutant p53 may exhibit increased sensitivity to CUR compared to wild-type counterparts. In models overexpressing cyclin D1, CUR selectively enhances wild-type p53 levels, thereby inducing arrest in the S and G2/M phases and limiting tumor expansion.[124,130]

Collectively, these findings highlight curcumin as a potent, multifaceted regulator of the p53 network in breast cancer. By modulating both wild-type and mutant p53 states and engaging multiple apoptotic pathways, CUR offers significant therapeutic promise for overcoming resistance and improving treatment outcomes.

9.2. CUR-mediated Regulation of Ras Signaling

Rat sarcoma virus (Ras) GTPases are membrane-anchored small GTP-binding oncoproteins that regulate a broad array of intracellular signaling pathways essential for proliferation, survival, and differentiation. Constitutive activation of Ras or its downstream effectors is a well-established oncogenic driver in numerous malignancies, positioning Ras pathway modulation as an important therapeutic target.[132,133]

Curcumin (CUR) has been shown to interact with this axis through mechanisms involving reactive oxygen species (ROS) signaling. CUR elevates intracellular ROS levels, triggering apoptotic cascades characterized by the activation of caspase-9 and caspase-3, upregulation of the pro-apoptotic protein Bax, and suppression of the anti-apoptotic effector Bcl-2.[134] In breast cancer models exhibiting Ras-driven signaling, CUR-induced ROS has been reported to suppress tumorigenic potential by downregulating MMP-9 and Bcl-2 while upregulating Bax and caspase-3, thereby reinforcing its pro-apoptotic and anti-metastatic effects.[135]

Beyond apoptosis, CUR also affects cell-cycle progression. Notably, CUR has been observed to induce G2/M arrest, in part by modulating extracellular signal-regulated kinases 1 and 2 (ERK1/2), which are canonical downstream mediators of Ras signaling. This supports the concept that suppression of Ras-ERK pathway activity contributes to CUR's antitumor efficacy in breast cancer.[135]

Collectively, these findings indicate that curcumin exerts potent anti-Ras effects through integrated modulation of ROS generation, apoptotic regulators, and ERK-mediated cell-cycle signaling, highlighting its promise as a multi-targeted therapeutic agent in Ras-dependent breast cancer.

9.3. CUR-mediated Regulation of PI3K/Akt/mTOR Signaling

The mammalian target of rapamycin (mTOR) complexes play a central role in cancer metabolism by directly regulating mitochondrial activity. Through the regulation of electron transport chain (ETC) protein expression, mTOR helps sustain mitochondrial membrane potential and modulate oxygen consumption,thereby supporting the bioenergetic demands of rapidly proliferating cancer cells.[136] Consistent with these functions, the PI3K–Akt–mTOR signaling cascade is frequently hyperactivated across malignancies and drives tumorigenesis by coordinating angiogenesis, apoptosis resistance, and enhanced proliferation.[137,138] This pathway integrates upstream cues from receptor tyrosine kinases (RTKs), Ras GTPases, and integrins, making it a critical regulator of tumor progression and treatment resistance.[139] Therapeutically, the PI3K–Akt–mTOR axis is notable for its strategic position downstream of multiple activated RTKs, enabling it to orchestrate diverse cellular programs, including growth, survival, migration, and metabolic reprogramming. Within this network, phosphoinositide 3-kinases (PI3Ks) phosphorylate membrane phospholipids to generate phosphatidyl-3,4,5-trisphosphate (PIP3), a key second messenger that initiates downstream signaling.[140,141] PIP3 accumulation promotes PDK1-dependent activation of Akt, a serine/threonine kinase that regulates cell-cycle progression, metabolic adaptation, and anti-apoptotic responses.[142] Hyperactivation of the PI3K/Akt pathway is a hallmark of many cancers, including breast cancer (BC), and contributes to oncogenesis partly by suppressing tumor-inhibitory proteins such as glycogen synthase kinase-3β (GSK3β). Conversely, the tumor suppressor PTEN antagonizes this signaling cascade by dephosphorylating PIP3, thereby restraining oncogenic signaling.[143,144] Downstream, Akt-mediated activation of mTOR amplifies proliferative and survival programs.[145] Dysregulation of PI3K/Akt/mTOR signaling is observed in more than 50% of human cancers, underscoring its relevance as a therapeutic target in BC and related malignancies.[146] Beyond promoting proliferation, this axis enhances survival by modulating anti-apoptotic regulators, including members of the Bcl-2 family. Preclinical evidence indicates that curcumin (CUR) interacts with this pathway: in BC models, CUR enhances apoptosis induced by the PI3K inhibitor LY294002, suggesting synergistic suppression of the PI3K/Akt/mTOR network[145]. The importance of this pathway is especially pronounced in triple-negative breast cancer (TNBC), an aggressive subtype lacking targeted therapies, where PI3K/Akt/mTOR hyperactivation contributes to tumor progression and chemoresistance.[147,148] Li et al. reported that CUR inhibits doxorubicin-induced epithelial–mesenchymal transition (EMT) in TNBC cells by simultaneously suppressing PI3K/Akt and TGF-β signaling, thereby counteracting a major mechanism of drug resistance.[149]

Collectively, these findings support PI3K/Akt/mTOR modulation as a key mechanism underlying CUR's antitumor activity in BC, particularly in TNBC. Nonetheless,further mechanistic and translational studies are needed to refine dosing parameters, contextual effects, and combinatorial regimens that maximize the therapeutic value of CUR in targeting this critical signaling hub.

9.4. CUR-mediated Regulation of Wnt/-catenin Signaling

Extensive research over the past two decades has established the Wnt/β-catenin signaling pathway as a key regulator of tumor initiation, progression, metastasis, and apoptosis.[150] The pathway is driven by a family of secreted glycoproteins and it operates through both βcatenin–dependent (canonical) and βcatenin–independent (non-canonical) mechanisms to regulate cellular proliferation, differentiation, and survival. Dysregulation of this pathway contributes significantly to cancer stem cell (CSC) maintenance and immune evasion, particularly in solid tumors such as breast cancer (BC).[151] Thus, therapeutic modulation of Wnt/βcatenin signaling has emerged as a promising approach for BC management.Curcumin (CUR) has shown considerable efficacy in modulating this pathway. In both MCF-7 (ER-positive) and MDA-MB-231 (triple-negative) BC cell lines, CUR induces G2/M cell-cycle arrest and reduces nuclear β-catenin accumulation, thereby suppressing oncogenic Wnt signaling.[152] This suppression is accompanied by upregulation of GSK3β, a central inhibitor of β-catenin stability, and increased expression of E-cadherin, an epithelial marker whose restoration counteracts metastatic transition.[153] Moreover, CUR-mediated inhibition of Wnt and Sonic Hedgehog signaling has been shown to diminish stemness traits in BC cells such as MCF7 and SUM159. These effects include reduced expression of CSC-associated markers (ALDH1A1, CD44, Oct4, Nanog), decreased spheroid formation, attenuated proliferation, and increased apoptosis.[154] Collectively, these findings illustrate that CUR attenuates Wnt/β-catenin signaling, disrupts CSC maintenance, and limits BC progression.Beyond Wnt pathway regulation, Curcumin exerts broader modulatory effects on BC cells. CUR induces apoptosis and inhibits proliferation by downregulating Bcl-2, suppressing Akt/mTOR phosphorylation, and enhancing Bax expression, thereby shifting the intracellular balance toward programmed cell death[112]. Combination therapies further enhance these therapeutic effects. For instance, co-administration of CUR with mitomycin C (MMC) has been shown to potentiate MMC's tumoricidal activity while reducing its toxicity.[155] This protective action is mediated in part by CUR-induced inhibition of GRP58-mediated DNA cross-linking in MCF-7 xenografts.[156] Clinical evaluations of intravenous CUR combined with paclitaxel in patients with advanced or metastatic BC have yielded favorable outcomes, confirming both safety and therapeutic efficacy.[157]Metal–Curcumin complexes, including boron–Curcumin [$B(Cur)_2$] and iron–Curcumin [$Fe(Cur)_3$], further enhance the anticancer potency of CUR. Both complexes inhibit cell invasion, while CUR and $B(Cur)_2$ additionally suppress migration, demonstrating synergistic anti-metastatic activity.[158] CUR also exerts dose-dependent cytotoxic effects in BC cell lines such as MCF-7 and MDA-MB-453, underscoring its broad spectrum antitumor efficacy.[159]At the epigenetic level, CUR reactivates tumor suppressor genes (TSGs) silenced by DNA methylation and induces hypermethylation-driven downregulation of oncogenes, thereby modulating multiple intracellular pathways. In a BC xenograft model, dietary CUR significantly reduced pulmonary metastasis and suppressed MMP-9, NF-κB, and COX-2 expression.[160] In triple-negative breast cancer (TNBC), CUR inhibits epithelial–mesenchymal transition (EMT), reducing metastasis.[161] In MDA-MB-231 cells specifically, CUR suppresses migration and proliferation by decreasing NF-κB p65 expression and increasing the Bax/Bcl-2 ratio, thereby enhancing apoptosis.[162,163] Additionally, CUR reduces inflammatory signaling by inhibiting chemokines CXCL1 and CXCL2 via NF-κB inhibition.[164] It also decreases Akt protein levels in a time- and dose-dependent manner, accompanied by inhibition of the ubiquitin–proteasome system (UPS) and activation of autophagy, indicating an alternative route of cell death.[165]

The mechanisms underlying these effects are summarized (in Table 2 and depicted in Figure 4). These findings highlight Curcumin's broad anti-cancer, anti-metastatic, anti-inflammatory, and epigenetic reprogramming activities, reinforcing its potential as a multifunctional therapeutic and adjuvant agent in breast cancer management.

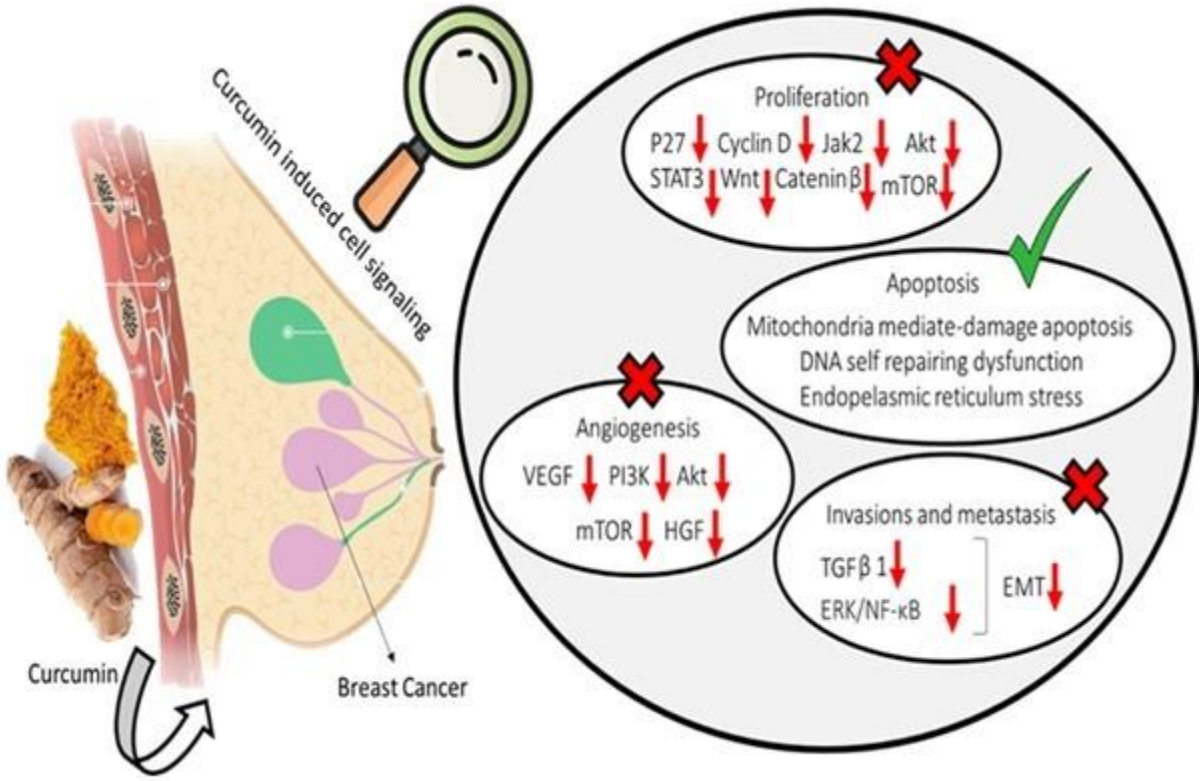

Figure 4. Schematic Illustration of the CUR-induced Pathways in BC Treatment.

Table 2. The Therapeutic Role Curcumin in Breast Cancer

Cancer Type	Cell Line	Curcumin Conc.	Finding/Mechanisms	Ref.
Breast	MCF10A cells	-	Affecting DNA methylation.	75
Breast	T47D, MCF7, MDA-MB-415, SK-BR-3, MDA-MB-231, MDA-MB-468 and BT-20	10 μg/ml	Increasing expression of P21, inducing cell cycle arrest at the G2/M phase, likely mediated by the decreased expression of CDC25 and CDC2.	112
Breast	MB-231 cells	40 μM	Both MMC and CUR synergistically enhanced apoptosis in MCF-7 cells, and apoptosis was most likely due to both activation of caspases and regulation of bcl-2/bax expression.	155
Breast	MCF-7 cells	150 μL	Preventing GRP58-mediated DNA cross-linking by the ERK/p38 MAPK pathway.	156
Breast	H-Ras MCF10A	15 mg/ml	-	157
Breast	MDA-MB-231	5, 10, 15, 20, 25 and 30 μM	Used complex inhibited cell invasion, but only CUR and B(Cur)2 inhibited cell migration.	158
Breast	MDA-MB-453 and MCF-7	0, 1, 2, 5, 10, 20, and 50 μM	Dose-dependently suppression of the viability of both MCF-7 and cells MDA-MB-453.	159
Breast	MDA-MB-435	50 μmol/L	Inhibition of the expression of matrix metalloproteinase-9 and NF-κB, cyclooxygenase 2.	160
Breast	TNBC cells	-	Modulation of the epithelial-mesenchymal transition (EMT) signaling pathways.	161
Breast	MDA-MB-231 cells	150 μL	Reduction of NF-κBp65 expression and growing the Bax to Bcl-2 ratio in breast cancer MDA-MB-231 cells.	162
Breast	MDA-MB-231	25 μM	CUR decreases breast cancer metastasis via NFκB-mediated expression of the two pro-metastatic cytokines, CXCL1 /2.	164
Breast	MB-231	25 μM	Reduction of Akt protein expression in a time and dose-dependent manner.	165

10. Promises and Challenges of Curcumin Usage in Cancer

Curcumin displays broad anticancer activity by modulating multiple molecular targets that regulate proliferation, survival, inflammation, and immune responses. It can sensitize therapy-resistant tumor cells to chemotherapy and radiotherapy and may reduce treatment-related toxicity through synergistic interactions. Immunologically, curcumin has been reported to enhance natural killer (NK) cell function and to attenuate regulatory T cells (Tregs), thereby supporting antitumor immune responses. Overall, curcumin is considered relatively safe and well-tolerated, even at comparatively high doses, which is an advantage over many conventional cytotoxic agents.[166,167]However, translation into clinical practice

remains restricted. Curcumin demonstrates extremely low aqueous solubility, limited intestinal absorption, rapid first-pass metabolism, and fast systemic clearance. These limitations prevent achieving pharmacologically meaningful concentrations with conventional oral dosing. Furthermore, inconsistency in formulations, purity, and bioavailability across studies complicates interpretation. Potential interactions with drug-metabolizing enzymes also require careful evaluation.Advanced formulations, including liposomes, polymeric nanoparticles, micelles, solid lipid nanoparticles, and phospholipid complexes, show improved absorption and stability, yet most remain in preclinical stages. Synthetic analogs with enhanced potency and pharmacokinetics are under active investigation.

Combination strategies that integrate curcumin with other natural products or with standard anticancer regimens have shown additive or synergistic effects in preclinical models, suggesting a role as an adjuvant rather than a stand-alone therapy.[168,169] As precision oncology evolves, curcumin based interventions may be better tailored to tumor genomic and microenvironmental features; however, rigorous clinical trials are required before routine incorporation into evidence based cancer management.

11. Critical View

This review provides an integrative framework for the emerging role of curcumin in modulating breast cancer stem cells (BCSCs) through mitochondria-centered mechanisms, a dimension underrepresented in recent literature.[170,171] Unlike general reviews of curcumin's anticancer properties that treat mitochondrial pathways and stemness regulation as separate domains[172], our analysis synthesizes their mechanistic convergence: ROS signaling, metabolic reprogramming, mitochondrial dynamics disruption (fusion/fission/mitophagy), and CSC survival. This framework positions mitochondrial vulnerabilities as a tractable therapeutic axis for curcumin-based interventions.

The scope is distinguished by its emphasis on mitochondrial bioenergetics, oxidative stress responses, and CSC-driven tumor propagation. We comprehensively discuss curcumin-mediated modulation of p53, PI3K/Akt/mTOR, Ras, and Wnt/β-catenin pathways within the context of mitochondrial dynamics, an approach absent in prior summaries.[173] By consolidating preclinical evidence from molecular to cellular to functional outcomes (Table 1, Figures 1-3), we clarify curcumin's multimodal inhibitory effects on BCSCs and therapy resistance.

Future Directions: Targeting mitochondrial dependencies (e.g., ROS-mediated mitophagy) may complement conventional therapies, particularly in aggressive subtypes like TNBC. Recommendations include: 1) Phase II trials with curcumin nanocarriers [166]; 2) Genomic studies for BCSC biomarkers (CD44+/CD24-); 3) 3D organoid models for synergy with PARP inhibitors. These insights inform optimized delivery systems and mechanistically grounded applications of curcumin as an adjuvant in breast cancer management.

12. Conclusion

In conclusion, this review highlights the pivotal role of mitochondrial metabolism in maintaining breast cancer stem cell (BCSC) stemness, driving tumor progression, and mediating therapeutic resistance. Curcumin, by virtue of its ability to disrupt mitochondrial membrane potential, induce toxic levels of reactive oxygen species, and impair electron transport chain activity, represents a compelling multi-target agent that can simultaneously dismantle the metabolic underpinnings of BCSC self-renewal and epithelial–mesenchymal transition. However, the clinical potential of curcumin remains constrained by its poor bioavailability and rapid systemic clearance, challenges that have thus far prevented its translation from bench to bedside. The advent of nanotechnology-based delivery platforms, particularly mitochondria-targeted nanocarriers, offers a paradigm shift, providing a means to enhance tumor accumulation, overcome pharmacokinetic limitations, and deliver synergistic payloads. Looking forward, the most impactful therapeutic strategies will likely involve the rational design of nanocarrier systems that co-deliver curcumin with established chemotherapeutics or novel metabolic inhibitors to exploit mitochondrial vulnerabilities in BCSCs with precision. Realizing this goal demands a concerted multidisciplinary effort, integrating nanomedicine, mitochondrial pharmacology, and systems biology approaches such as metabolomics and single-cell sequencing. By addressing both the molecular target and the delivery challenge simultaneously, curcumin-based strategies hold the potential to transition from a promising natural compound to a cornerstone of next-generation breast cancer therapies aimed at eliminating the root of tumor recurrence.

CRediT authorship contribution statement

Sonya Mahabadi: Conceptualization, Investigation, Methodology, Visualization, Writing – original draft. Arta Armani: Data Curation, Methodology, Validation, Writing – review & editing. Ahmed Alsaidi: Visualization, Writing – review & editing. Nosratollah Zarghami: Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Funding

The authors declare that no funding, grants, or other financial support were received for the preparation of this manuscript.

AI-assisted technology declaration

During the preparation of this work, the authors used GapGPT, an AI-assisted image-generation tool, to create two illustrative images. These images were used solely for illustrative purposes and do not represent or alter the research data or results. The authors reviewed the generated content and take full responsibility for the final images.

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