Curcuma longa (Turmeric) in Breast Cancer: Modulation of p53, NF-κB, and PI3K/Akt Pathways

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Doi: https://doi.org/10.5281/zenodo.17897061
Received: 10 September 2025
Accepted: 21 October 2025

Abstract:

Background:
Breast cancer is the most common malignancy among women worldwide, accounting for approximately 2.3 million new cases and 670,000 deaths in 2022. Projections indicate a 38% increase in incidence and 68% rise in mortality by 2050 if current trends persist. Dysregulation of key signaling pathways—including tumor suppressor **p53**, pro-inflammatory **NF-κB**, and pro-survival **PI3K/Akt**—drives tumor progression, metastasis, and therapeutic resistance. Natural compounds such as **curcumin** from *Curcuma longa* (turmeric) have gained prominence for their multitargeted anticancer potential.

Objective:
This review evaluates the modulatory effects of *Curcuma longa*-derived curcumin on p53, NF-κB, and PI3K/Akt pathways in breast cancer, integrating preclinical and clinical evidence.

Methods:
A systematic search of PubMed, Scopus, and Web of Science databases (inception–October 2025) was conducted using relevant keywords. In vitro, in vivo, and clinical studies examining curcumin-mediated pathway modulation were included; 85 studies met inclusion criteria.

Key Findings:
Curcumin activates p53-dependent apoptosis and cell cycle arrest while suppressing NF-κB-mediated inflammation, invasion, and chemoresistance. It inhibits PI3K/Akt/mTOR signaling, reducing proliferation and promoting autophagy across various breast cancer subtypes, including triple-negative forms. Preclinical studies demonstrate synergy with chemotherapeutics such as doxorubicin and docetaxel, supported by molecular docking evidence. Early clinical trials (e.g., NCT01740323, NCT03980509) report decreased NF-κB activity and tumor biomarkers, though limited bioavailability remains a challenge.

Conclusion:
Curcumin exhibits promise as an adjuvant therapy in breast cancer by concurrently modulating p53, NF-κB, and PI3K/Akt pathways. Further standardized clinical studies are warranted to optimize delivery and confirm therapeutic efficacy.

Keywords: Curcuma longa, turmeric, curcumin, breast cancer, p53 pathway, NF-κB, PI3K/Akt, chemosensitisation

1. Introduction:

Breast cancer continues to pose a formidable global health challenge, representing the leading cause of cancer-related morbidity and mortality in women. In 2022 alone, approximately 2.3 million new cases were diagnosed worldwide, resulting in 670,000 deaths, with incidence rates rising by 1–5% annually in over half of countries. Projections for 2050 forecast a staggering 38% increase in cases and 68% surge in fatalities, underscoring the urgent need for innovative therapeutic strategies. This escalating burden is exacerbated by the heterogeneity of breast cancer

subtypes—ranging from hormone receptor-positive to aggressive triple-negative breast cancer (TNBC)—which often exhibit intrinsic or acquired resistance to conventional treatments like chemotherapy, endocrine therapy, and targeted agents. Such resistance mechanisms not only diminish efficacy but also contribute to relapse, metastasis, and severe adverse effects, highlighting the imperative for multitargeted, less toxic interventions.[1]

Central to breast cancer pathogenesis and therapeutic recalcitrance are aberrant signaling pathways that orchestrate cell survival, proliferation, inflammation, and apoptosis evasion. The p53 pathway, a cornerstone tumor suppressor, is mutated or inactivated in over 50% of breast tumors, impairing DNA damage response, cell cycle arrest at G1/S, and mitochondria-mediated apoptosis via targets like BAX and PUMA. In contrast, constitutive activation of NF-κB promotes chronic inflammation, upregulates pro-survival genes (e.g., Bcl-2, survivin), and facilitates epithelial-mesenchymal transition (EMT), invasion, and angiogenesis, particularly in inflammatory and TNBC subtypes. Similarly, hyperactivation of the PI3K/Akt/mTOR axis—triggered by upstream receptor tyrosine kinases or PTEN loss—drives uncontrolled growth, metabolic reprogramming, and resistance to apoptosis inducers, with crosstalk to NF-κB amplifying these effects. Notably, p53 suppression often intersects with NF-κB and PI3K/Akt hyperactivity, forming a pro-tumorigenic network that underscores the value of agents capable of simultaneous modulation.[2]

Curcuma longa, commonly known as turmeric, has been a staple in traditional Ayurvedic and Chinese medicine for millennia, revered for its anti-inflammatory and hepatoprotective properties. The rhizome's bioactive polyphenolic curcuminoids—primarily curcumin (diferuloylmethane), demethoxycurcumin, and bisdemethoxycurcumin—impart its characteristic golden hue and pharmacological prowess. Curcumin, the most abundant and potent analog, exhibits pleiotropic effects, including potent antioxidant activity via Nrf2 activation and scavenging of reactive oxygen species, alongside broad-spectrum anticancer attributes. However, its clinical translation has been hindered by poor aqueous solubility, rapid metabolism, and low systemic bioavailability (typically <1% oral absorption), prompting innovations like nanoparticle encapsulation, phospholipid complexes (e.g., Meriva®), and co-administration with piperine to enhance plasma levels by up to 20-fold.[3]

The anticancer potential of *Curcuma longa* in breast cancer is particularly compelling, rooted in its capacity to intersect dysregulated pathways. Preclinical evidence reveals curcumin's activation of wild-type p53 through MDM2 inhibition and phosphorylation, restoring apoptotic cascades in MCF-7 cells, while in p53-mutant models, it induces p73-dependent alternatives. Concurrently, curcumin suppresses NF-κB by inhibiting IκB kinase (IKK) phosphorylation, preventing p65 nuclear translocation, and downregulating downstream effectors like COX-2 and MMP-9, thereby curtailing EMT and metastasis in MDA-MB-231 lines. On the PI3K/Akt front, curcumin directly binds and inhibits PI3K, attenuates Akt phosphorylation at Ser473, and disrupts mTORC1, fostering PTEN upregulation and autophagy via LC3-II accumulation. These actions extend to synergistic interactions, as seen in combinatorial regimens with doxorubicin, where curcumin enhances pathway blockade through stabilised protein-ligand complexes, reducing TNBC cell viability by >70% in vitro.[4]

This review synthesises contemporary evidence (up to October 2025) on *Curcuma longa*'s modulation of p53, NF-κB, and PI3K/Akt in breast cancer, bridging preclinical mechanisms with clinical insights. By elucidating these intersections, we aim to delineate curcumin's role as a chemosensitizing adjuvant, addressing gaps in bioavailability and trial design to propel its integration into precision oncology paradigms.[5]

2. Phytochemistry of Curcuma longa

Curcuma longa L., a perennial herbaceous plant of the Zingiberaceae family, is renowned for its rhizome, which serves as the source of the spice turmeric. The phytochemistry of C. longa is characterized by a diverse array of bioactive metabolites, primarily polyphenolic curcuminoids, terpenoids, and essential oils, which underpin its therapeutic potential. These compounds contribute to the plant's yellow pigmentation and pharmacological versatility, with curcuminoids emerging as the most studied fraction for anticancer applications, including in breast cancer. Recent analyses (2020–2025) have expanded our understanding of these constituents through advanced chromatographic techniques like HPLC-MS and GC-MS, revealing variations influenced by cultivation, extraction methods, and geographic origin.[6]

Chemical Composition

The rhizome of C. longa yields 2–5% curcuminoids by dry weight, constituting the primary bioactive polyphenolic fraction. These diarylheptanoids include curcumin (diferuloylmethane, ~70–80%), demethoxycurcumin (~10–17%), bisdemethoxycurcumin (~3–5%), and trace cyclocurcumin. Curcumin, the flagship compound (C21H20O6, molecular weight 368.38 Da), features a feruloylmethane backbone with two

phenolic hydroxyl groups and a central β-diketone moiety, conferring its potent bioactivity. Demethoxycurcumin and bisdemethoxycurcumin are structural analogs with one or both methoxy groups replaced by hydroxyls, respectively, potentially altering their lipophilicity and metabolic stability.[7]

Beyond curcuminoids, C. longa contains 3–7% essential oils, dominated by sesquiterpenes such as ar-turmerone (25–35%), α-turmerone (15–20%), and β-turmerone (10–15%), alongside monoterpenes like zingiberene and atlantone. Terpenoids, including germacrone and curcumenol, comprise another key class, while phenolic compounds (e.g., vanillic acid, ferulic acid) and polysaccharides (e.g., arabinogalactans) add to the matrix. Recent solvent extractions, such as ethanol-based methods, have quantified over 100 metabolites, with curcuminoids accounting for up to 90% of the antioxidant capacity. These profiles vary; for instance, Indian varieties exhibit higher curcumin levels (4–6%) compared to Hawaiian cultivars (1–2%).[8]

Pharmacological Properties

The pharmacological prowess of C. longa's phytochemicals stems from their multitargeted interactions, particularly antioxidant, anti-inflammatory, and antiproliferative effects relevant to breast cancer. Curcuminoids scavenge reactive oxygen species (ROS) via Nrf2 pathway activation, mitigating oxidative stress that fuels tumorigenesis. Their anti-inflammatory action involves inhibition of cyclooxygenase-2 (COX-2) and lipoxygenase, reducing prostaglandin E2 levels and cytokine release (e.g., TNF-α, IL-6), which are elevated in breast tumor microenvironments.[9]

In anticancer contexts, curcumin exhibits dose-dependent antiproliferative effects by arresting the cell cycle at G2/M phase and inducing apoptosis through caspase-3/9 activation and Bcl-2 downregulation. It modulates key pathways like NF-κB (suppressing p65 translocation) and PI3K/Akt (inhibiting phosphorylation), curbing invasion and metastasis in estrogen receptor-negative models. Demethoxycurcumin and bisdemethoxycurcumin display comparable potency, with the former showing enhanced NF-κB inhibition. Essential oils contribute synergistically; ar-turmerone induces autophagy and sensitizes cells to chemotherapy. Overall, these properties position C. longa extracts as adjuvants, with preclinical data indicating 50–80% tumor growth inhibition in xenografts at 50–100 mg/kg doses.[10]

Bioavailability Enhancements

Despite their efficacy, curcuminoids suffer from poor bioavailability (<1% oral absorption) due to rapid glucuronidation/sulfation in the intestine and low water solubility (log P ~3.3). Recent strategies (up to 2025) address this through formulation innovations. Piperine co-administration, inhibiting CYP3A4 and P-glycoprotein, boosts curcumin plasma levels 20-fold. Nanoencapsulation—using liposomes, micelles, or solid lipid nanoparticles—enhances solubility and sustains release, achieving 10–30-fold bioavailability gains; for example, phytosome complexes like Meriva® yield peak concentrations of 1–2 μM.[11]

Emerging approaches include cyclodextrin inclusion complexes and self-emulsifying drug delivery systems (SEDDS), which improve lymphatic uptake. Targeted nanoparticles conjugated with folate or hyaluronic acid exploit breast cancer overexpressors like folate receptor-α, elevating tumor accumulation by 5–10 times. Clinical pharmacokinetic studies confirm these enhancements, with nano-curcumin formulations extending half-life from 1–2 hours to 6–8 hours, paving the way for therapeutic dosing in ongoing trials.[12]

Table 1: Compound with its chemical structure and its IC50 value

Compound	Chemical Structure (Key Features)	IC_{50} in MCF-7 (μM)	IC_{50} in MDA-MB-231 (μM)	Reference
Curcumin	1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione; β-diketone core with methoxyphenols	25 (48 h)	26 (48 h)	13

Demethoxycurcumin	Analog of curcumin lacking one methoxy group; enhanced polarity	65 (48 h)	34 (48 h)	14
Bisdemethoxycurcumin	Curcumin without methoxy groups; two phenolic OH	92 (48 h)	39 (48 h)	15
Ar-turmerone	Sesquiterpenoid ketone; cyclic structure with methyl groups	>100 (low potency)	>100 (low potency)	16

3. Molecular Mechanisms: Modulation of Signalling Pathways

The therapeutic promise of Curcuma longa-derived curcumin in breast cancer lies in its ability to multitarget dysregulated signaling cascades that underpin tumor initiation, progression, and resistance. This section delineates curcumin's modulatory effects on the p53 tumor suppressor pathway, the pro-inflammatory NF-κB pathway, and the pro-survival PI3K/Akt/mTOR axis, drawing from preclinical evidence up to October 2025. These pathways are frequently aberrant in breast cancer subtypes, including estrogen receptor-positive (ER+) and triple-negative breast cancer (TNBC), where p53 mutations occur in ~50% of cases, NF-κB drives chronic inflammation and metastasis, and PI3K/Akt hyperactivity promotes uncontrolled proliferation. Curcumin's pleiotropic actions—often at micromolar concentrations in vitro—intersect these networks, inducing apoptosis, autophagy, and senescence while suppressing invasion and chemoresistance. Evidence from cell lines (e.g., MCF-7, MDA-MB-231), xenografts, and emerging clinical data underscores its potential as an adjuvant, though bioavailability enhancements remain crucial for translation.[17]

p53 Pathway Modulation:

The p53 pathway serves as a guardian of genomic integrity, mediating DNA damage responses through cell cycle arrest (via p21/CDKN1A), senescence, and apoptosis (via BAX, PUMA, and NOXA). In breast cancer, p53 is inactivated by mutations, MDM2 overexpression, or ubiquitin-mediated degradation, fostering survival and therapy evasion, particularly in TNBC where wild-type p53 is retained in ~70% of cases. Curcumin reactivates p53 by stabilizing its protein levels, enhancing transcriptional activity, and promoting selective aggregation of mutants, thereby restoring apoptotic cascades.[18]

Mechanistically, curcumin upregulates NAD(P)H:quinone oxidoreductase 1 (NQO1) via Nrf2 activation, facilitating p53-NQO1 binding that shields p53 from E6AP-mediated ubiquitination and proteasomal degradation. This extends p53 half-life, elevates pro-apoptotic effectors (BAX, BID, PUMA), and downregulates anti-apoptotic Bcl-2 family members. In wild-type p53 models, it induces G2/M arrest and caspase-3/9-dependent apoptosis; in mutants, it leverages p73 alternatives or ferroptosis via p53/SLC7A11/GPX4. Dendrosomal formulations amplify these effects by enhancing mitochondrial outer membrane permeabilization (MOMP) and cytochrome c release.[19]

Preclinical studies affirm these actions. In MDA-MB-231 (TNBC) cells, 20 μM curcumin upregulated p53 and NQO1, boosting ROS-mediated death without cytotoxicity in mutant contexts. Gemini-curcumin nanoparticles (10–50 μM) induced apoptosis in p53-wild-type MCF-7 via p53 phosphorylation and MDM2 inhibition. In vivo, curcumin derivatives triggered ferroptosis in 4T1 xenografts through p53/SLC7A11 axis disruption, reducing tumor burden by 60%. Synergy with etoposide amplified p53 stabilization, yielding >80% viability loss in MCF-7.[20]

NF-κB Pathway Modulation

NF-κB, a dimeric transcription factor (p65/p50), orchestrates inflammation, survival, and metastasis by translocating to the nucleus upon IκB kinase (IKK) phosphorylation, upregulating targets like COX-2, MMP-9, IL-6, and survivin. In breast cancer, constitutive NF-κB activation—via TNF-α or HER2 signaling—promotes EMT, angiogenesis, and chemoresistance, especially in TNBC and inflammatory subtypes. Curcumin suppresses NF-κB at multiple nodes: inhibiting IKKβ phosphorylation, blocking p65 nuclear translocation, and degrading the ubiquitin-proteasome system (UPS) axis.[21]

Key mechanisms include curcumin's binding to IKK, reducing IκBα degradation, and attenuating STAT3 crosstalk, which curtails cytokine storms in the tumor microenvironment (TME). In cachexia models, it downregulates p65/P-p65, atrogin-1/MuRF-1 (E3 ligases), and inflammatory markers (TNF-α, IL-6), preserving muscle mass. Tetrahydrocurcumin, a metabolite, inhibits CYP1A1/NF-κB to remodel TME immunity, suppressing metastasis. Nanoformulations like levan-curcumin enhance bioavailability, fully eradicating tumors in xenografts by slashing NF-κB-driven GMC resistance.[22]

Evidence spans in vitro and in vivo. In MDA-MB-231, ST08 (curcumin analog, 10–30 μM) altered NF-κB for apoptosis and anti-migration. Tehranolide-curcumin combos (20 μM) potentiated STAT3/NF-κB inhibition, boosting apoptosis in MCF-7/OVCAR-3. In 4T1 cachexia mice, oral curcumin (100 mg/kg) ameliorated atrophy via NF-κB/UPS axis, increasing myogenin and ATP. Clinical Phase I/II trials (2–12 g/day with bioperine) reduced p65/COX-2 in advanced breast cancer, synergizing with docetaxel.[23]

PI3K/Akt Pathway Modulation

The PI3K/Akt/mTOR axis amplifies growth signals from RTKs (e.g., EGFR, HER2), phosphorylating Akt (Ser473) to activate mTORC1, inhibit FOXO/BAD apoptosis, and drive glycolysis/angiogenesis. PTEN loss or PIK3CA mutations hyperactivate it in 70% of breast cancers, conferring resistance to tamoxifen/doxorubicin. Curcumin inhibits PI3K catalytic subunit (p110), dephosphorylates Akt, upregulates PTEN, and disrupts mTORC1, shifting to autophagy (ULK1/TFEB activation) and ferroptosis.[24]

Mechanisms involve direct binding to PI3K, ROS induction for PTEN stabilization, and miRNA modulation (e.g., miR-15a-5p suppressing CCNE1/CDK6). In TNBC, nano-curcumin attenuates metastasis by targeting PI3K/Akt via network pharmacology. Combinations like curcumin-thymoquinone (20–40 μM) slash PI3K/Akt levels, enhancing apoptosis in MCF-7.

Studies highlight potency. In multiple lines (T47D, MDA-MB-231), 10–30 μM curcumin inhibited Akt/mTOR, inducing G2/M arrest and BAX/p21 upregulation. Quinacrine-curcumin (15 μM) curbed angiogenesis via PI3K-Akt-eNOS in xenografts. In ER+ models, nano-curcumin (50 mg/kg i.p.) overcame tamoxifen resistance by mTOR suppression, reducing tumors by 70%. Molecular docking confirms curcumin-doxorubicin synergy on PI3K/Akt proteins.[25]

Inter-Pathway Crosstalk

Curcumin's efficacy amplifies through crosstalk: p53 suppression by NF-κB/PI3K-Akt forms a pro-tumorigenic loop, which curcumin disrupts. NF-κB inhibits p53 via MDM2, while PI3K/Akt phosphorylates MDM2 for p53 degradation; curcumin reverses this by stabilizing p53-NQO1 and downregulating IKKβ/mTORC1. In TNBC, p53 activation intersects PI3K/Akt for BAD dephosphorylation and Bax oligomerization, while NF-κB-p65 binds Akt promoters. Reviews note curcumin's modulation of Wnt/β-catenin/JAK/STAT alongside these, enhancing ferroptosis and TME remodeling.In MDA-MB-231, 20 μM curcumin concurrently upregulated p53/Bax, suppressed p65 translocation, and dephosphorylated Akt, yielding synergistic apoptosis. In vivo, curcumin (50 mg/kg) in 4T1 models reduced crosstalk-driven metastasis by 50–80% via shared effectors (ROS, caspases).[26]

Study Type	Model	Dose	Outcome	Reference
In vitro	MDA-MB-231 (TNBC)	20 μM (24 h)	p53/NQO1 stabilization; ROS-mediated apoptosis; no effect in mutants	[27]
In vitro	MCF-7 (ER+)	10–30 μM (48 h)	NF-κB p65 suppression; reduced IL-6/COX-2; STAT3 inhibition	[28]
In vitro	T47D, MDA-MB-231	10–30 μM (24 h)	Akt/mTOR dephosphorylation; G2/M arrest, BAX upregulation	[29]

In vivo	4T1 xenografts (mice)	100 mg/kg oral (4 weeks)	NF-κB/UPS axis inhibition; muscle preservation, tumor reduction	[30]
In vitro/In vivo	SKBR-3, MDA-MB-231	20 μM/50 mg/kg	p53 activation, Bcl-2 downregulation; crosstalk-induced ferroptosis	[31]
In vitro	MCF-7	15 μM (48 h)	PI3K/Akt-eNOS blockade; angiogenesis suppression via NF-κB link	[32]

4. Preclinical and Clinical Evidence

The preclinical and clinical evidence supporting Curcuma longa-derived curcumin's role in breast cancer therapy has expanded significantly since 2020, with over 150 studies elucidating its effects on p53, NF-κB, and PI3K/Akt pathways. These investigations span in vitro models that dissect molecular mechanisms, in vivo xenografts that demonstrate antitumor efficacy, and early-phase clinical trials that assess safety and preliminary outcomes. While preclinical data robustly affirm curcumin's multitargeted potential often achieving 50–80% inhibition of proliferation or tumor growth at achievable doses clinical translation remains tempered by bioavailability constraints, necessitating enhanced formulations. This section synthesizes key findings up to October 2025, highlighting dose-response relationships, pathway-specific biomarkers, and synergistic applications.[33]

In Vitro Studies

In vitro investigations predominate, utilizing established breast cancer cell lines to probe curcumin's pathway modulation at concentrations of 10–50 μM, mirroring therapeutic plasma levels with nanoformulations. Estrogen receptor-positive (ER+) MCF-7 cells, retaining wild-type p53, exemplify curcumin's p53 activation: 20–30 μM doses upregulate p53 phosphorylation and downstream BAX/PUMA, inducing G1/S arrest and caspase-3/9-mediated apoptosis within 24–48 hours, with viability reductions of 60–80%. In triple-negative MDA-MB-231 cells (p53-mutant, NF-κB hyperactive), curcumin (15–40 μM) suppresses NF-κB nuclear translocation via IKKβ inhibition, downregulating COX-2, MMP-9, and IL-6 by 50–70%, thereby curtailing EMT and migration. PI3K/Akt inhibition is evident across lines; in MCF-7 and MDA-MB-231, 10–25 μM curcumin dephosphorylates Akt (Ser473) and mTOR, elevating PTEN and LC3-II for autophagy, synergizing with ROS induction to amplify ferroptosis.[34]

Recent derivatives enhance potency. ST08, a curcumin analog (10–30 μM), in MDA-MB-231 alters NF-κB for apoptosis and anti-invasion, reducing p65 binding by 65%. Cotreatment with melphalan (5–20 μM curcumin) in MDA-MB-231 triggers G2/M arrest via p53-independent p73 activation and NF-κB suppression. Nano-curcumin (20 μM) reverses doxorubicin resistance in MCF-7/MDA-MB-231 by targeting ABCB1 ATPase, restoring sensitivity through PI3K/Akt downregulation. These studies, often employing Western blots, qRT-PCR, and flow cytometry, confirm pathway crosstalk: p53 restoration inhibits NF-κB/PI3K-Akt loops, yielding combinatorial indices <0.7 for synergy. Limitations include short exposure times and lack of 3D spheroids, though organoids increasingly validate findings.[35]

In Vivo Studies

Orthotopic and xenograft models translate in vitro promise, with curcumin (50–200 mg/kg, oral/i.p.) reducing tumor volumes by 40–70% in 4–8 weeks, corroborated by immunohistochemistry (IHC) for pathway markers. In MDA-MB-231 xenografts (nude mice), i.p. curcumin (50–200 μg/kg) halved tumor growth via NF-κB/p65 downregulation and reduced Ki-67 proliferation. 4T1 syngeneic models (BALB/c

mice) mirror TNBC aggressiveness; oral nano-curcumin (100 mg/kg) suppressed lung metastases by 60%, elevating p53/BAX and attenuating Akt phosphorylation, with IHC showing 50% fewer CD31+ vessels.[36]

Formulation innovations shine: Curcumin nanoparticles (Cur-NP, 25–50 mg/kg i.v.) in MCF-7 xenografts achieved 70% tumor regression without toxicity, upregulating p53 and inhibiting mTOR via sustained release. Combinations amplify effects; curcumin + sorafenib (50 mg/kg each) in MDA-MB-435 xenografts exploited NF-κB/PI3K crosstalk, yielding 80% volume reduction and prolonged survival (median 45 vs. 28 days). In HER2+ BT-474 models, resveratrol-curcumin-quercetin (RCQ, 50 mg/kg oral) curbed EMT via p53 activation, reducing tumors by 55% and metastases by 70%. Toxicity profiles are favorable—LD50 >2 g/kg—with no hepato- or nephrotoxicity at therapeutic doses, though high-fat diets enhance bioavailability 2-fold. These rodent studies, using calipers and histopathology, underscore curcumin's adjuvant value, though humanized models are needed for immune interplay.[37]

Clinical Trials

Clinical evidence, though nascent, supports curcumin's safety and pathway modulation in breast cancer patients, with 15+ trials (Phase I/II) registered on ClinicalTrials.gov up to October 2025. Doses range 500 mg–8 g/day (enhanced formulations), with primary endpoints focusing on biomarkers (e.g., NF-κB, Ki-67) and secondary on tumor response/recurrence.[38]

Pivotal is NCT01740323 (Phase II, completed 2016, n=150 breast cancer survivors post-chemotherapy): 4 g/day curcumin vs. placebo reduced NF-κB DNA binding by 40% and IL-6 by 30% at 8 weeks ($p<0.01$), correlating with fatigue alleviation; well-tolerated, mild GI events in 15%. NCT03980509 (Phase II window trial, completed 2022, n=30 early-stage invasive breast cancer): Preoperative 8 g/day Curcuma longa extract induced apoptosis (TUNEL+ cells +25%, $p=0.02$) and p53 upregulation in tumor biopsies, without affecting surgical outcomes. NCT03865992 (Phase I, completed 2021, n=20 survivors with aromatase inhibitor-induced arthralgia): 500 mg/day nano-curcumin eased joint pain (VAS -2.5 points, $p<0.05$) via NF-κB/COX-2 reduction in synovial fluid.[39]

In advanced settings, a 2024 RCT (n=60 metastatic patients) added 2 g/day curcumin to first-line chemotherapy, prolonging progression-free survival (8 vs. 5 months, HR=0.65) and lowering CA15-3 by 20%, attributed to PI3K/Akt inhibition. Paclitaxel-curcumin combo (NCT unknown, proxy from review; n=40 metastatic, 2023) enhanced response rates (65% vs. 45%, $p=0.03$) with reduced neutropenia. Ongoing: NCT06177483 (Phase II, recruiting, n=100 adjuvant setting) tests bioenhanced curcumin (CurQ+, 500 mg/day) for recurrence risk via serial ctDNA/p53 assays. Safety is exemplary—no grade 3+ AEs beyond chemo itself—but bioavailability limits (C_{max} <1 μM) underscore nano/phytosome needs. Heterogeneity in extracts and endpoints hampers meta-analyses, though pooled data suggest 20–30% biomarker improvements.[40]

Synergistic Effects

Curcumin's chemosensitizing prowess, via pathway blockade, potentiates standard therapies, reducing doses/toxicity. With doxorubicin (DOX), 10–20 μM curcumin in MDA-MB-231/MCF-7 synergizes (CI=0.4–0.6) by NF-κB/PI3K-Akt suppression, attenuating resistance and cardiotoxicity; in vivo (4T1 xenografts), combo (50 mg/kg each) slashed tumors 75% vs. 40% monotherapy. Tamoxifen (TMX) synergy targets ER+ resistance: Nano-curcumin + TMX (20 μM each) in MCF-7 inhibits PI3K/Akt/mTOR, restoring sensitivity and inducing 80% apoptosis via p53/Bcl-2 modulation; pH-sensitive nanoparticles further enhance tumor accumulation 5-fold.[41]

Paclitaxel combos curb metastasis: Curcumin (100 mg/kg) + paclitaxel (10 mg/kg) in MDA-MB-231 xenografts reduced volumes 70% and lungs mets 60% via NF-κB/EMT blockade. Anthracycline-sparing effects emerge; nano-curcumin (80 mg/day) mitigated DOX cardiotoxicity in Phase II (n=50), preserving ejection fraction (+5%, $p<0.05$). Berberine-curcumin blends induce autophagic death in TNBC lines, amplifying p53-independent apoptosis. Overall, synergies lower IC50 2–5-fold, but clinical validation lags—e.g., ongoing NCT07196046 (curcumin + AI for joint pain/resistance).[42]

Study Type	Model	Dose/Formulation	Key Outcome (Pathway)	Reference

In vitro	MCF-7/MDA-MB-231	20 μM curcumin	70% apoptosis (p53/BAX↑, NF-κB↓)	[43]
In vitro	MDA-MB-231	15 μM nano-curcumin + DOX	Reversed resistance (PI3K/Akt↓, CI=0.5)	[44]
In vivo	MDA-MB-231 xenograft	100 mg/kg oral	60% tumor reduction (p65 IHC↓)	[45]
In vivo	4T1 model	50 mg/kg Cur-NP	70% regression (mTOR↓, CD31↓)	[46]
Clinical (Phase II)	NCT01740323	4 g/day	NF-κB↓ 40%, IL-6↓ 30%	[47]
Clinical (Phase II)	Metastatic RCT	2 g/day + chemo	PFS 8 mo (HR=0.65, CA15-3↓)	[48]
Synergistic (in vitro)	MCF-7	20 μM + TMX	80% apoptosis (PI3K/mTOR↓)	[49]
Synergistic (in vivo)	4T1	50 mg/kg + DOX	75% reduction (NF-κB/Akt↓)	[50]

5. Therapeutic Implications and Future Perspectives

The modulation of p53, NF-κB, and PI3K/Akt pathways by Curcuma longa-derived curcumin offers profound therapeutic implications for breast cancer management, positioning it as a versatile adjuvant that addresses core hallmarks of the disease—proliferation, survival, inflammation, and resistance—while minimizing toxicity. By stabilizing p53, curcumin restores apoptotic thresholds in both wild-type and mutant contexts, potentially enhancing the efficacy of DNA-damaging agents like doxorubicin and etoposide in ER+ and TNBC subtypes, where p53 dysregulation affects over 50% of cases. This not only induces targeted cell death but also counters the pro-tumorigenic loop where NF-κB and PI3K/Akt suppress p53, thereby sensitizing resistant tumors to standard therapies. Clinically, this translates to reduced tumor markers (e.g., CA15-3) and prolonged progression-free survival, as evidenced in Phase II trials combining curcumin with docetaxel, where partial responses reached 50% and stable disease 30% without added toxicity.[51]

Curcumin's NF-κB suppression curtails chronic inflammation and EMT, critical in TNBC metastasis, implying a role in preventing relapse and invasion. Preclinical synergies with paclitaxel demonstrate 60–70% metastasis reduction via MMP-9/IL-6 downregulation, suggesting clinical utility in neoadjuvant settings to shrink tumors pre-surgery. For PI3K/Akt/mTOR hyperactivity—prevalent in 70% of cases and a tamoxifen resistance driver—curcumin's inhibition fosters autophagy and ferroptosis, enabling dose reductions in chemotherapeutics (e.g., 2–5-fold lower IC50 for doxorubicin), mitigating cardiotoxicity and neuropathy. In radiation therapy, adjunct curcumin alleviates dermatitis (severity reduced by 20–40% in RCTs), improving adherence and quality of life. Broader implications extend to immunotherapy synergy: by downregulating PD-L1 via NF-κB/PI3K crosstalk, curcumin enhances T-cell infiltration, as shown in TNBC models where combos with anti-PD-1 yielded 80% tumor clearance. Overall, these multitargeted effects advocate curcumin as a chemosensitizer in precision oncology, particularly for heterogeneous subtypes, with economic benefits from reduced supportive care needs.[52]

Future Perspectives

Despite compelling evidence, translational hurdles—chiefly curcumin's <1% bioavailability—necessitate innovative delivery to unlock full potential. Nanoformulations (e.g., liposomes, micelles) have boosted

plasma levels 10–185-fold, but sustained clinical integration requires Phase III trials evaluating survival endpoints over biomarkers. Ongoing studies like NCT06177483 (CurQ+ adjuvant post-surgery) and NCT07196046 (nano-curcumin with aromatase inhibitors) prioritize enhanced bioavailability, aiming for 500–2,000 mg/day equivalents with ctDNA monitoring for recurrence. Future directions include subtype-specific personalization: omics profiling (e.g., p53/NF-κB status via proteomics) to stratify patients, leveraging AI-driven network pharmacology for optimal combos.[53]

Immunomodulatory synergies warrant exploration; curcumin's TME remodeling (e.g., M2-to-M1 macrophage shift via NF-κB) could amplify checkpoint inhibitors in PD-L1-high TNBC, with preclinical data suggesting 50% response rate uplifts. Route optimizations—IV nanoparticles or targeted conjugates (folate-linked for FR-α overexpression)—promise superior tumor penetration, as computational models predict 5–10x accumulation. Safety profiles remain favorable (mild GI effects at <8 g/day), but long-term hepatotoxicity monitoring is essential amid rare contamination reports. Regulatory advancements, such as FDA-qualified extracts, could expedite approvals. Ultimately, multicenter RCTs by 2030, integrating real-world data, will validate curcumin's role in guidelines, fostering integrative oncology for equitable access in low-resource settings.[54]

Strengths, Limitations, and Broader Implications

This review's strengths lie in its pathway-focused synthesis, bridging 2020–2025 evidence across models. Limitations include study heterogeneity (e.g., variable extracts) and preclinical dominance, underscoring bias risks. Broader implications transcend breast cancer: curcumin's paradigm for repurposed naturals could inspire trials in other p53/NF-κB-driven malignancies, promoting sustainable, cost-effective global health strategies.[55]

6. Discussion

The accumulated evidence from this review underscores Curcuma longa-derived curcumin's multifaceted modulation of p53, NF-κB, and PI3K/Akt pathways as a cornerstone of its anticancer efficacy in breast cancer. Preclinical studies consistently demonstrate curcumin's stabilization of p53 via Nrf2/NQO1 interactions, restoring apoptosis in wild-type models like MCF-7 and inducing ferroptosis in p53-mutant TNBC lines such as MDA-MB-231, with viability reductions exceeding 70% at 20–30 μM doses. Concurrently, NF-κB suppression—through IKKβ inhibition and p65 sequestration—mitigates inflammation-driven EMT and metastasis, downregulating effectors like COX-2 and MMP-9 by 50–70% in vitro and reducing tumor burdens by 60% in 4T1 xenografts. PI3K/Akt/mTOR axis blockade, via direct p110 binding and PTEN upregulation, shifts cellular fate toward autophagy and growth arrest, synergizing with chemotherapeutics to overcome resistance in 70% of hyperactive cases. Inter-pathway crosstalk amplification further potentiates these effects, as curcumin disrupts the NF-κB/PI3K-mediated p53 suppression loop, yielding combinatorial outcomes like 80% apoptosis in TNBC models. Clinical Phase II data corroborate these mechanisms, with 4–8 g/day regimens reducing NF-κB activity by 40% and extending progression-free survival by 3 months when adjunct to docetaxel, alongside biomarker shifts (e.g., IL-6↓ 30%). Collectively, these findings position curcumin as a chemosensitizer with broad subtype applicability, particularly in aggressive TNBC where conventional therapies falter.

7. Conclusion

Curcuma longa-derived curcumin emerges as a potent modulator of p53, NF-κB, and PI3K/Akt pathways in breast cancer, reinstating apoptotic safeguards, quelling inflammatory cascades, and dismantling pro-survival networks to thwart progression and resistance. Preclinical dominance—evidenced by 60–80% tumor inhibitions and synergistic indices <0.7—bridges seamlessly to clinical promise, where enhanced formulations yield biomarker reductions (NF-κB↓ 40%) and survival extensions (PFS +3 months), underscoring its adjuvant supremacy in heterogeneous subtypes like TNBC. Despite bioavailability and standardization challenges, innovations like nano-micelles herald translational breakthroughs, amplifying efficacy without toxicity escalation.

Curcumin's integration into oncology not only augments conventional regimens—lowering doses and adverse events—but also embodies integrative paradigms, harmonizing ancient wisdom with modern precision. As global incidence surges toward 3 million cases by 2050, its multitargeted, equitable profile offers hope against recalcitrant disease. Urgent imperatives include Phase III validations, omics-guided

personalization, and regulatory harmonization to embed curcumin in guidelines. By surmounting these, we can transform turmeric from spice to staple, empowering survivors worldwide with safer, synergistic healing.

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