Moringa oleifera in Breast Cancer: Targeting ROS, p53, and VEGF Pathways through Phytochemical Synergy

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Doi: https://doi.org/10.5281/zenodo.17896883
Received: 2 September 2025
Accepted: 25 October 2025

Abstract:

Background: Breast cancer remains a leading cause of cancer-related mortality worldwide, with dysregulation of reactive oxygen species (ROS), p53 tumour suppressor pathway, and vascular endothelial growth factor (VEGF)-mediated angiogenesis contributing to tumour progression, metastasis, and therapeutic resistance. Natural products like *Moringa oleifera* (MO), a nutrient-rich medicinal plant, exhibit promising anticancer properties through its diverse phytochemicals, including flavonoids, isothiocyanates, and phenolics, which may act synergistically to target these pathways.

Objective: This review evaluates the mechanistic role of *M. oleifera* in modulating ROS, p53, and VEGF pathways in breast cancer, emphasising phytochemical synergies for enhanced therapeutic efficacy.

Methods: A comprehensive literature search was conducted across PubMed, Scopus, and Web of Science databases using keywords such as "Moringa oleifera," "breast cancer," "ROS," "p53," "VEGF," and "phytochemical synergy," covering studies from 2000 to October 2025. Inclusion criteria focused on preclinical in vitro/in vivo evidence and computational modeling; 45 relevant articles were analyzed.

Key Findings: MO extracts and isolated compounds (e.g., glucomoringin, quercetin) reduce ROS accumulation in breast cancer cells (e.g., MCF-7, MDA-MB-231) by activating Nrf2 and antioxidant enzymes, mitigating oxidative stress-induced proliferation. They restore p53 function via upregulation of p53-Bax apoptosis cascades, inducing cell cycle arrest and tumor regression in xenograft models. Anti-angiogenic effects involve downregulation of HIF-1α-VEGF signaling, decreasing vascularization and metastasis potential. Synergistic interactions, such as flavonoids enhancing isothiocyanate bioavailability, amplify these effects, outperforming single agents in polyherbal formulations.

Conclusions: Phytochemical synergy in *M. oleifera* offers a multifaceted approach to targeting ROS, p53, and VEGF in breast cancer, positioning it as a potential adjuvant to conventional therapies. However, clinical trials are essential to validate efficacy, bioavailability, and safety in humans.

Keywords: *Moringa oleifera*, breast cancer, ROS modulation, p53 activation, VEGF inhibition, phytochemical synergy

Introduction:

Breast cancer stands as the most prevalent malignancy among women globally, exerting a profound socioeconomic burden on healthcare systems and affected populations. In 2022, an estimated 2.3 million new cases were diagnosed, accompanied by 670,000 deaths, underscoring its status as a leading cause of cancer-related mortality.[1]Projections indicate a stark escalation, with incidence rates anticipated to surge by 38% and mortality by 68% by 2050 if prevailing trends persist, particularly in low- and middle-income countries where access to early detection and treatment remains limited.[2] In the United States alone, approximately 313,510 new cases and 42,170 deaths are forecasted for 2025, highlighting the disease's persistent toll despite advances in screening and therapy.[3]Current

therapeutic modalities, including surgery, chemotherapy, radiotherapy, and targeted agents like tamoxifen or trastuzumab, have improved survival rates—evidenced by a 44% decline in breast cancer mortality since 1989—yet challenges abound. These include intrinsic and acquired resistance, severe adverse effects, and heterogeneity across subtypes such as hormone receptor-positive, HER2-enriched, and triple-negative breast cancer (TNBC), which collectively contribute to recurrence in up to 30% of cases and underscore the urgent need for novel, multifaceted interventions.[4]

Central to breast cancer pathogenesis and progression are dysregulated cellular signaling pathways that orchestrate tumor initiation, growth, invasion, and metastasis. Among these, reactive oxygen species (ROS)—encompassing superoxide anions, hydrogen peroxide, and hydroxyl radicals—play a dual-edged role. At physiological levels, ROS facilitate redox signaling essential for cell proliferation and survival; however, chronic elevation in the tumor microenvironment (TME) induces oxidative stress, DNA damage, and genomic instability, thereby accelerating malignant transformation and therapeutic resistance. In breast cancer, heightened ROS production by sources such as NADPH oxidases and mitochondrial dysfunction not only promotes epithelial-mesenchymal transition (EMT) and invasion but also fosters an immunosuppressive TME conducive to metastasis, particularly in aggressive subtypes like TNBC.[5]The p53 tumor suppressor pathway, often dubbed the "guardian of the genome," is another critical nexus frequently perturbed in breast cancer. Encoded by the TP53 gene, wild-type p53 orchestrates DNA repair, cell cycle arrest at G1/S checkpoints via p21 induction, and apoptosis through Bax/Bak activation in response to genotoxic stress. Dysregulation, primarily through missense mutations occurring in over 80% of cases, abrogates these protective functions, enabling unchecked proliferation and survival under chemotherapeutic assault.[6] Mutant p53 isoforms further gain-of-function properties, transactivating pro-metastatic genes like VEGF and MDM2, thereby exacerbating disease aggressiveness and correlating with poorer prognosis. Complementing these, the vascular endothelial growth factor (VEGF) pathway drives pathological angiogenesis, a hallmark enabling nutrient and oxygen supply to hypoxic tumors. VEGF-A, the predominant ligand, binds VEGFR-2 on endothelial cells to trigger endothelial proliferation, migration, and tube formation, culminating in neovascularization that sustains tumor expansion and distant dissemination. In breast cancer, VEGF overexpression—upregulated by hypoxia-inducible factor-1α (HIF-1α)—is evident in up to 70% of tumors, correlating with lymph node involvement and reduced relapse-free survival, while anti-VEGF agents like bevacizumab have yielded mixed results due to compensatory pathway activation.[7]

Amid these molecular complexities, natural products derived from medicinal plants have emerged as promising adjuncts, offering pleiotropic effects with potentially lower toxicity profiles. Moringa oleifera Lam., commonly known as the "drumstick tree" or "miracle tree," exemplifies this paradigm. Native to northern India and widely cultivated across tropical and subtropical regions of Africa and Asia, this fast-growing, drought-resistant perennial belongs to the Moringaceae family and thrives in diverse agroecological zones. Traditionally revered in Ayurvedic, Unani, and African folk medicine, its leaves, pods, seeds, and roots have been employed for millennia to treat ailments ranging from malnutrition and inflammation to infectious diseases and reproductive disorders.[8] Nutritionally, M. oleifera is a powerhouse, rich in vitamins (A, C, E), minerals (calcium, iron, potassium), and essential amino acids, rendering it a staple in combating undernutrition in resource-poor settings. Its anticancer potential, however, has garnered recent scientific scrutiny, rooted in epidemiological observations linking high dietary intake to reduced cancer incidence in indigenous populations. Preclinical investigations reveal that M. oleifera extracts exert antiproliferative, pro-apoptotic, and anti-metastatic effects across various malignancies, including breast cancer, through modulation of key oncogenic pathways. For instance, leaf and seed extracts inhibit proliferation in MCF-7 and MDA-MB-231 cell lines by arresting the cell cycle and inducing caspase-dependent apoptosis, while in vivo models demonstrate tumor volume reduction in xenograft-bearing mice without overt toxicity.[9]

The therapeutic prowess of M. oleifera stems from its rich phytochemical repertoire, encompassing over 40 bioactive compounds that operate via synergistic mechanisms rather than isolated actions. Major classes include glucosinolates (e.g., glucomoringin, yielding the isothiocyanate moringin), flavonoids (quercetin, kaempferol, rutin), phenolic acids (chlorogenic, caffeic), alkaloids (moringine), and terpenoids, alongside polysaccharides and sterols. These constituents confer antioxidant, anti-inflammatory, and immunomodulatory properties, but their anticancer efficacy is amplified through phytochemical synergy—a phenomenon where co-occurring compounds enhance bioavailability, overcome efflux pumps, and concurrently target multiple nodes in carcinogenic cascades.[10] Unlike synthetic monotherapies, which often elicit resistance by hitting singular targets, synergistic polypharmacology mimics physiological homeostasis, reducing dosage requirements and mitigating side effects. In cancer contexts, such interactions have been documented to potentiate apoptosis (e.g., flavonoids augmenting isothiocyanate-induced ROS modulation) and inhibit

angiogenesis (e.g., phenolics synergizing with terpenoids to suppress VEGF transcription). This holistic approach aligns with systems biology principles, where network perturbations yield emergent therapeutic benefits, as evidenced in combinatorial natural product formulations outperforming isolated phytochemicals in preclinical breast cancer models.[11]

This review synthesizes the burgeoning evidence on M. oleifera's role in breast cancer management, with a deliberate focus on its phytochemical-mediated targeting of ROS, p53, and VEGF pathways. By dissecting mechanistic insights from in vitro, in vivo, and computational studies spanning 2000–2025, we elucidate how synergistic interactions among M. oleifera bioactives restore redox balance, reinstate p53-mediated surveillance, and curtail VEGF-driven vascularization. While preclinical data are compelling, clinical translation remains nascent, hampered by standardization challenges and limited human trials. Herein, we delineate knowledge gaps, including subtype-specific responses and long-term safety, to guide future research toward integrating M. oleifera as an adjuvant in precision oncology. Ultimately, harnessing this "tree of life" could democratize breast cancer therapy, particularly in underserved regions where it grows abundantly.[12]

Phytochemical Profile of Moringa oleifera

Moringa oleifera Lam., a multipurpose tree revered in traditional medicine systems across Asia, Africa, and Latin America, owes its therapeutic versatility to a rich and diverse phytochemical arsenal. These bioactives, distributed variably across leaves, seeds, roots, bark, flowers, and pods, encompass secondary metabolites that confer antioxidant, anti-inflammatory, and anticancer attributes. Recent analytical advancements, including high-performance liquid chromatography (HPLC) coupled with electrospray ionization mass spectrometry (ESI-MS) and gas chromatography-mass spectrometry (GC-MS), have illuminated over 100 distinct compounds, with concentrations influenced by edaphic factors, harvest timing, and geographic origin. This profile not only underpins *M. oleifera*'s nutritional superiority—boasting higher protein, vitamin, and mineral densities than many conventional crops—but also its potential in modulating oncogenic pathways, as explored in subsequent sections.[13]

Major Classes of Bioactive Compounds

The phytochemical landscape of *M. oleifera* is dominated by polyphenols, sulfur-containing glycosides, and lipids, with flavonoids and phenolic acids comprising the bulk in aerial parts. Leaves, the most studied organ, harbour the highest polyphenol content (up to 40 mg gallic acid equivalents/g dry weight), while seeds are lipid-rich (30–40% oil).

Compound Class	Specific Examples	Plant Part(s) Predominant	Concentration (mg/g DW, unless noted)	Bioactivity Highlights	References
Flavonoids	Quercetin, rutin, kaempferol, myricetin, isorhamnetin, epicatechin	Leaves, seeds	Quercetin: 2.03 µmol/100 g; Rutin: 0.56; Myricetin: 5.80	Antioxidant, anti-proliferative	14
Phenolic Acids	Gallic acid, caffeic acid, ferulic acid, chlorogenic acid, ellagic acid	Leaves, flowers	Gallic: 1.03; Caffeic: 0.41; Ferulic: 0.08	Anti-inflammatory, ROS scavenging	15
Glucosinolates	Glucomoringin, 4-(α-L-rhamnopyranosyloxy)benzyl glucosinolate, sinalbin	Seeds, leaves	Glucomoringin: 21.84–59.4; Sinalbin: 2.36	Anticancer, anti-angiogenic	16
Isothiocyanates	Moringin (from glucomoringin hydrolysis)	Seeds, leaves	Not quantified; yields ~4–6% in extracts	p53 activation, VEGF inhibition	17

Carotenoids	β-Carotene, lutein, violaxanthin	Leaves	β-Carotene: 11,300–23,000 IU/100 g fresh	Provitamin A, immunomodulatory	18
Alkaloids	Moringinine, aurnatiamide acetate, marumoside A/B	Stem, roots	Trace (e.g., <0.1)	Cardioprotective, antimicrobial	19
Phytosterols	β-Sitosterol, β-sitosterol-3-O-β-D-galactopyranoside	Seeds, bark	β-Sitosterol: 26.67 in bark	Anti-cholesterol, anti-estrogenic	20
Terpenes/Diterpenes	Phytol, farnesylacetone, linalool oxide	Leaves	Phytol: Abundant (~5–10% volatiles)	Antimicrobial, anti-malarial	21
Tannins/Saponins	Condensed tannins, saponins (unspecified)	Leaves, seeds	Tannins: 20.7 in leaves; Saponins: 0.89 in seeds	Astringent, hemolytic/immune-modulating	22
Fatty Acids	Oleic acid (70% w/w), palmitic, linolenic	Seeds	Oleic: 70% of total lipids	Hypolipidemic, anti-hypertensive	23

This tabulation, derived from HPLC-ESI-MS and GC-MS analyses, reveals flavonoids as the most abundant class (up to 20% DW in leaves), followed by phenolics (10–15%). Seeds stand out for glucosinolates and oils, yielding moringin upon myrosinase hydrolysis, a key enzyme activated during mastication or processing. Variations are notable: Indian cultivars exhibit 1.5-fold higher quercetin than African ones, attributable to soil micronutrients.

Extraction and Bioavailability

Efficient extraction is pivotal for harnessing *M. oleifera*'s bioactives, with solvent polarity dictating yield and selectivity. Conventional methods like maceration and Soxhlet extraction predominate, employing methanol (18.56% yield) or ethanol (10.7–14.5%) at 30–60°C for 5–8 hours, ideal for polar flavonoids and phenolics. Ultrasound-assisted extraction (UAE) emerges as superior, enhancing yields by 20–30% via cavitation—e.g., 45°C, 30 min in 80:20 ethanol-water yields 14.3% phenolics with minimal degradation. Supercritical CO_2 suits non-polar lipids from seeds, preserving thermolabile terpenes. Emerging green techniques, such as enzyme-assisted extraction, target glucosinolates by mimicking gastrointestinal hydrolysis.[24]

Bioavailability, however, poses challenges; many compounds exhibit poor aqueous solubility and rapid first-pass metabolism. Quercetin bioavailability hovers at 40–50% in lozenges, hampered by P-glycoprotein efflux, while isothiocyanates like moringin achieve ~60% absorption but degrade swiftly (half-life <2 hours). Gut microbiota modulates this, converting glucosinolates to bioavailable metabolites. Nanoencapsulation and piperine co-administration boost quercetin uptake by 2–3-fold, as seen in rodent models. Formulation innovations, including thermo-reversible nasal gels from hydroalcoholic leaf extracts, circumvent hepatic metabolism, achieving 80% plasma levels versus 30% oral. These strategies are crucial for clinical translation, particularly for breast cancer adjuncts where sustained ROS modulation demands consistent delivery.[25]

Synergistic Interactions

Beyond isolated effects, *M. oleifera*'s phytochemicals exemplify synergy, where multi-compound matrices outperform monotherapies by targeting redundant pathways and enhancing pharmacokinetics. Flavonoids like quercetin potentiate glucosinolate hydrolysis, elevating moringin levels by 1.5-fold via myrosinase stabilization, amplifying p53-mediated apoptosis in MCF-7 cells. Phenolics and terpenes exhibit additive ROS quenching—e.g., caffeic acid-ferulic combinations yield 25% greater Nrf2 activation than alone. In polyherbal contexts, *M. oleifera* leaf extracts synergize with curcumin-piperine, attenuating beryllium-induced oxidative stress in rats by 40% more than individual agents, via upregulated SOD and catalase. Antagonism is rare but noted in high-tannin fractions inhibiting iron absorption; thus, low-dose leaf powders mitigate this. Computational docking corroborates these, showing flavonoid-isothiocyanate pairs binding VEGF receptors with higher affinity (ΔG -9.2 kcal/mol vs. -7.5 singly). Such

interactions underscore *M. oleifera*'s holistic efficacy, mirroring traditional decoctions and paving the way for standardized synbiotic formulations in oncology.[26]

In summary, *M. oleifera*'s phytochemical symphony—rich in flavonoids, phenolics, and sulfur glycosides—positions it as a pharmacognostic treasure. Optimizing extraction and bioavailability will unlock its full potential against breast cancer's multifaceted etiology.

Breast Cancer Pathophysiology: Focus on ROS, p53, and VEGF Pathways

Breast cancer's intricate pathophysiology is underpinned by aberrant signaling cascades that drive uncontrolled proliferation, evasion of apoptosis, and metastatic dissemination. Among these, reactive oxygen species (ROS), the p53 tumor suppressor pathway, and vascular endothelial growth factor (VEGF)-mediated angiogenesis emerge as pivotal regulators, often exhibiting dysregulated crosstalk that amplifies tumor heterogeneity and therapeutic recalcitrance. This section delineates their individual contributions and interdependencies, drawing on recent mechanistic insights to contextualize *Moringa oleifera*'s targeted interventions.[27]

ROS in Breast Cancer

Reactive oxygen species, including superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH), are highly reactive molecules generated endogenously via mitochondrial electron transport chain leaks, NADPH oxidases (NOX family), and xanthine oxidases, or exogenously from ionizing radiation and chemotherapeutic agents. In physiological contexts, low-to-moderate ROS levels serve as redox messengers, modulating protein phosphorylation, calcium signaling, and gene expression to support cellular homeostasis.[28] However, in breast cancer, a chronic imbalance—termed oxidative stress—tilts this equilibrium, with tumor cells sustaining elevated ROS (2–10-fold higher than normal) through upregulated NOX1/4 and mitochondrial dysfunction, fostering a pro-oncogenic milieu. This oxidative surge induces DNA lesions, such as 8-oxoguanine adducts, precipitating genomic instability and oncogenic mutations in genes like PIK3CA and BRCA1, thereby initiating carcinogenesis.[29] In established tumors, ROS paradoxically promotes survival by activating prosurvival pathways like PI3K/AKT and MAPK/ERK, while suppressing phosphatases via cysteine oxidation, thus enhancing proliferation and metabolic reprogramming toward glycolysis (Warburg effect). Metastasis is further propelled as ROS triggers epithelial-mesenchymal transition (EMT) via Snail/Slug upregulation and matrix metalloproteinase (MMP) activation, facilitating invasion through basement membranes. Subtype-specific dysregulation is pronounced in triple-negative breast cancer (TNBC), where ROS levels correlate with aggressive phenotypes and poor prognosis due to deficient antioxidant defenses like glutathione peroxidase. Therapeutic implications are dual: while ROS overload underlies chemotherapy-induced cytotoxicity (e.g., doxorubicin's quinone-mediated cycling), adaptive antioxidant upregulation confers resistance, highlighting the need for redox-modulating adjuvants.[30]

p53 Pathway Dysregulation

The TP53 gene, encoding the p53 protein, stands as the most frequently mutated tumor suppressor in human cancers, with alterations in 30–50% of breast tumors, rising to 80% in basal-like subtypes. Wild-type p53, a sequence-specific transcription factor stabilized by post-translational modifications (e.g., serine-15 phosphorylation in response to DNA damage), orchestrates a multifaceted guardian response: G1/S cell cycle arrest via p21^CIP1/WAF1 induction, DNA repair through GADD45, and intrinsic apoptosis via PUMA/NOXA-Bax mitochondrial outer membrane permeabilization.[31] In breast cancer, TP53 dysregulation—predominantly missense mutations in the DNA-binding domain (e.g., R175H, R248Q)—renders p53 transcriptionally inactive, abolishing these cytoprotective functions and permitting unchecked replication of damaged cells. Mutant p53 acquires gain-of-function (GOF) properties, transactivating pro-oncogenic targets like MDM2 (autoregulatory loop amplification) and c-Myc, while repressing antioxidants like TIGAR, thereby sustaining a redox-permissive environment for tumor outgrowth. This dysregulation intersects with hormonal signaling; estrogen receptor (ER)-positive tumors exhibit wild-type p53 dependency for growth, whereas mutant forms drive endocrine resistance by altering chromatin landscapes. Chemotherapy resistance is exacerbated, as mutant p53 impairs doxorubicin-induced apoptosis and promotes stem-like phenotypes via Nanog/Sox2. Prognostically, TP53 mutations portend reduced disease-free survival, particularly in node-positive cases, underscoring p53's prognostic utility and the therapeutic promise of reactivators like APR-246.[32]

VEGF and Angiogenesis

Angiogenesis, the formation of novel vascular networks from pre-existing capillaries, is indispensable for breast tumor progression beyond the diffusion limit (~2 mm^3), enabling nutrient/oxygen delivery and metastatic escape. VEGF-A, the prototypic member of the VEGF family (VEGFs A–D, PlGF), is the principal driver, secreted by hypoxic tumor/stromal cells in response to hypoxia-inducible factor-1α (HIF-1α) stabilization under low O_2 tension. Binding VEGFR-2 on endothelial cells activates PLCγ-PKC-ERK signaling, culminating in endothelial proliferation, migration (via RhoA/ROCK), and tube formation, while MMP-2/9 remodel the extracellular matrix. In breast cancer, VEGF overexpression—evident in 40–60% of cases, amplified by HER2/PI3K mutations—augments microvessel density (MVD), correlating with lymphovascular invasion and distant metastasis to bone/lung.[33] Subtype variations include heightened VEGF in HER2-enriched tumors via heregulin loops, and in TNBC through IL-8/STAT3 axes, fostering an immunosuppressive niche by recruiting myeloid-derived suppressor cells. Beyond vasculature, VEGF exerts autocrine effects on tumor cells, promoting survival via VEGFR-1/Neuropilin-1 and EMT via Twist1. Anti-VEGF therapies like bevacizumab yield modest PFS benefits in metastatic settings but face resistance via alternative angiogens (e.g., FGF2) and hypertension, necessitating combinatorial strategies.[34]

Interconnections

The pathogenicity of breast cancer is amplified by intricate crosstalk among ROS, p53, and VEGF, forming a vicious triad that perpetuates tumor evolution. ROS acts as an upstream orchestrator: excessive H_2O_2 oxidizes p53 at cysteine-277, enhancing DNA-binding but paradoxically stabilizing mutant forms via MDM2 dissociation, thus impairing apoptosis while transactivating VEGF under hypoxia. Mutant p53, in turn, reciprocates by repressing TIGAR (TP53-induced glycolysis regulator), elevating ROS to activate HIF-1α-VEGF transcription, as seen in MDA-MB-231 xenografts where p53 knockdown boosts angiogenesis 2-fold. This ROS-p53-VEGF loop sustains metastasis; for instance, ROS-induced EMT upregulates VEGF via NF-κB, while VEGF feedback amplifies NOX-derived ROS in endothelial-tumor pericytes. In TNBC, this network correlates with chemoresistance, where ROS-mediated p53 mutation fuels VEGF-driven vasculogenic mimicry. Figure 1 schematically depicts this crosstalk: ROS → p53 mutation → HIF-1α stabilization → VEGF ↑, with feedback arrows illustrating bidirectional reinforcement.[35]

Mechanisms of Moringa oleifera in Targeting Breast Cancer Pathways

The multifaceted anticancer potential of *Moringa oleifera* (MO) in breast cancer arises from its ability to modulate key dysregulated pathways—reactive oxygen species (ROS), p53, and vascular endothelial growth factor (VEGF)—through a symphony of phytochemicals acting in synergy. Unlike single-target synthetic drugs, MO's bioactive constituents, including isothiocyanates, flavonoids, and phenolic acids, exert pleiotropic effects that disrupt tumor homeostasis at multiple levels. Preclinical evidence, primarily from in vitro cell lines (e.g., MCF-7, MDA-MB-231) and in vivo xenograft models, demonstrates dose-dependent inhibition of proliferation, induction of apoptosis, and suppression of angiogenesis. These mechanisms not only restore redox balance and tumor suppressor function but also curtail vascular support, collectively impeding tumor progression. This section elucidates the targeted actions, underscoring phytochemical synergies that amplify efficacy while minimizing resistance.[36]

Modulation of ROS Levels

ROS dysregulation in breast cancer fosters genomic instability, proliferation, and metastasis, yet paradoxically, controlled ROS elevation can trigger apoptosis in malignant cells. MO phytochemicals, particularly isothiocyanates like moringin (derived from glucomoringin hydrolysis) and flavonoids such as quercetin, exhibit dual redox-modulating properties: antioxidant at physiological doses to mitigate chronic oxidative stress, and pro-oxidant at therapeutic levels to overwhelm cancer cell defenses. Moringin, for instance, induces ROS generation in MCF-7 and MDA-MB-231 cells, disrupting mitochondrial integrity and elevating intracellular H_2O_2 levels by 2–3-fold, as measured by DCFH-DA assays. This selective cytotoxicity spares non-malignant cells like MCF-10A, achieving a selectivity index of 9.5. Flavonoids in MO leaves, including kaempferol and rutin, scavenge mitochondrial ROS via Nrf2 activation, upregulating antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPx) by 40–60% in treated MCF-7 cells.[37]

In vitro studies corroborate these effects. Aqueous and methanolic MO leaf extracts (50–200 μg/mL) reduce ROS-induced proliferation in MCF-7 cells by 50–70%, correlating with decreased malondialdehyde (MDA) levels and restored mitochondrial membrane potential ($\Delta\Psi m$). Dichloromethane fractions of MO leaves further amplify this by elevating ROS to cytotoxic thresholds, triggering caspase-3 activation and DNA fragmentation. In vivo, high-dose

MO seed residue extracts (750 mg/kg) in MDA-MB-231 xenograft mice lower serum ROS markers by 30–40%, attenuating oxidative stress-mediated tumor growth without hepatotoxicity.[38]

Synergistic interactions enhance these outcomes. Quercetin and moringin co-administration boosts Nrf2 nuclear translocation by 2.5-fold, synergistically quenching ROS while potentiating apoptosis via Bax upregulation. Phenolic acids like chlorogenic acid further amplify this by inhibiting NOX enzymes, reducing superoxide production by 25% in combination with isothiocyanates. Table 1 summarizes key studies, highlighting dose-response and synergistic metrics.

Study Type	Model/System	MO Fraction/Compound	ROS Effect	Key Outcome	Synergy Noted	Ref.
In vitro	MCF-7 cells	Moringin (10–50 μM)	↑ ROS (2–3x), ΔΨm ↓	Apoptosis ↑ (caspase-3 ↑ 3x)	With PHB/DRP1 interaction	39
In vitro	MDA-MB-231	Leaf extract (100 μg/mL)	↓ ROS (40%), Nrf2 ↑	Proliferation ↓ 60%	Quercetin + moringin (Nrf2 ↑2.5x)	40
In vivo	Xenograft mice	Seed residue (750 mg/kg)	↓ Serum ROS 35%	Tumor volume ↓ 64%	Flavonoids + isothiocyanates	41
In vitro	MCF-10A/MCF-7	Dichloromethane fraction (5 μg/mL)	↑ Selective ROS	Selectivity index 9.5	N/A	42

Activation of p53 Pathway

p53 dysfunction in over 50% of breast cancers enables survival under genotoxic stress, but MO compounds restore its transcriptional activity, tipping the balance toward apoptosis. Flavonoids like quercetin and kaempferol, abundant in MO leaves, stabilize wild-type p53 by inhibiting MDM2-mediated ubiquitination, elevating p53 levels by 2–4-fold in MCF-7 cells. This restores p53-Bax transactivation, increasing Bax/Bcl-2 ratios and cytochrome c release. Isothiocyanates such as benzyl isothiocyanate (BITC) further enhance p53 phosphorylation at Ser-15, amplifying DNA damage responses.Preclinical data underscore these mechanisms. Dichloromethane fractions of MO leaf extracts (5–20 μg/mL) selectively upregulate p53 and Bax in MCF-7 cells, inducing G1/S arrest and 40–60% apoptosis, as confirmed by Western blots and flow cytometry. In MDA-MB-231 xenografts, oral MO leaf extracts (200 mg/kg) regress tumors by 50%, correlating with p53 reactivation and reduced Ki-67 staining. Seed extracts, though less potent, synergize with leaf fractions to elevate p21^CIP1, enforcing cell cycle checkpoints.[43]

Synergy is evident in combined phenolics: quercetin-kaempferol mixtures upregulate p21 by 3-fold via p53-dependent promoters, outperforming individual agents in TNBC models. BITC-phenolic blends restore mutant p53 function, as seen in docking studies where they bind p53's DNA-binding domain with -7.5 kcal/mol affinity. Table 2 compiles representative preclinical evidence.

Study Type	Model/System	MO Fraction/Compound	p53 Effect	Key Outcome	Synergy Example	Ref.
In vitro	MCF-7	Leaf dichloromethane (5 μg/mL)	p53 ↑2x, Bax ↑	Apoptosis 50%	N/A	44
In vivo	MDA-MB-231 xenograft	Leaf extract (200 mg/kg)	p53 reactivation	Tumor regression 50%	Phenolics + p21 ↑3x	45
In vitro	MDA-MB-231	Flavonoids (quercetin 20 μM)	p53 stabilization	G1/S arrest 40%	Quercetin + kaempferol	46
In silico	Mutant p53 models	BITC	Binding affinity -7.5 kcal/mol	Function restoration	With phenolics	47

Inhibition of VEGF Pathway

VEGF-driven angiogenesis sustains breast tumour hypoxia and metastasis; MO counters this via HIF-1α suppression and direct VEGFR blockade. Moringin inhibits the HIF-1α-VEGF axis by downregulating HIF-1α transcription, reducing VEGF secretion by 50–70% in hypoxic MCF-7 cells. Flavonoids like isoquercetin bind VEGFR-2 with -8.2 kcal/mol affinity, impeding endothelial signalling. Endothelial cell assays reveal MO pod extracts (100 μg/mL) suppress HUVEC tube formation by 60%, decreasing VEGF-induced migration via MMP-2 inhibition. In tumour vascularization studies, MO leaf extracts in 4T1 mouse models reduce microvessel density (MVD) by 45%, as quantified by CD31 immunohistochemistry. Seed residues (M1S9 ratio) further diminish serum VEGF by 35% in MDA-MB-231 xenografts, halting progression.[49]

Synergistic modulation arises from multi-compound extracts: aurantiamide acetate (AA) and BITC co-target HIF-1α/VEGF/GLUT1, with docking energies of -7.9 and -4.7 kcal/mol, respectively, blocking multiple nodes in 50 ns MD simulations. Flavonoid-isothiocyanate blends outperform singles, reducing angiogenesis by 70% in chorioallantoic membrane assays.

Study Type	Model/System	MO Fraction/Compound	VEGF Effect	Key Outcome	Synergistic Modulation	Ref.
In vitro	HUVEC/MCF-7	Pod extract (100 μg/mL)	VEGF ↓50%, tube formation ↓60%	Migration ↓	N/A	[50]
In vivo	4T1 mice	Leaf extract (300 mg/kg)	MVD ↓45%	Vascularization ↓	Multi-extract nodes block	[51]
In silico	VEGF models	AA/BITC	Binding -7.9/-4.7 kcal/mol	HIF-1α inhibition	AA + BITC (stable 50 ns)	[53]
In vitro	Hypoxic MCF-7	Moringin (20 μM)	HIF-1α-VEGF axis ↓70%	Secretion ↓	Flavonoids + isothiocyanates	[54]

Integrated Synergistic Effects

MO's holistic impact transcends isolated targeting, leveraging phytochemical synergies to disrupt ROS-p53-VEGF crosstalk. Elevated ROS from moringin stabilizes HIF-1α, but co-acting flavonoids quench excess while activating p53 to repress VEGF transcription, forming a feedback loop that collapses tumour vascularity and induces synchronized apoptosis. In network models, this integration yields emergent effects: p53 reactivation amplifies ROS sensitivity, while VEGF inhibition curtails ROS-fueled metastasis.Comparative analyses with doxorubicin (DOX) highlight MO's adjuvant value. In 4T1 breast cancer mice, 2% MO extracts mitigate DOX-induced hepatotoxicity by restoring SOD/GPx (↑40%) and downregulating BAX/NF-κB, enhancing tumor suppression by 30% without worsening progression—unlike seed extracts in obese models. Polyherbal MO formulations synergize with DOX, upregulating p53-Bax while reducing VEGF by 50%, outperforming DOX alone in MCF-7 viability assays (IC50 shift from 1 μM to 0.5 μM).[55]

Preclinical and Clinical Evidence

The preclinical foundation for *Moringa oleifera* (MO) as a breast cancer therapeutic is robust, with extensive in vitro and in vivo data demonstrating its efficacy in modulating ROS, p53, and VEGF pathways. These studies highlight MO's pleiotropic effects, including antiproliferative, apoptotic, and anti-angiogenic actions, primarily through leaf, seed, and pod extracts. However, clinical translation lags, with human data limited to preliminary observations rather than dedicated trials. This section synthesizes the evidence, underscoring mechanistic insights while addressing safety considerations essential for therapeutic advancement.[56]

In Vitro Studies

In vitro investigations predominantly utilize estrogen receptor-positive (MCF-7) and triple-negative (MDA-MB-231) breast cancer cell lines, reflecting the heterogeneity of clinical disease. These models have elucidated MO's capacity to target ROS-mediated oxidative stress, restore p53 function, and inhibit VEGF-driven vascularization, often at concentrations of 50–200 μg/mL for crude extracts or 10–50 μM for isolated compounds.

Methanolic and aqueous leaf extracts of MO exhibit dose- and time-dependent antiproliferative effects in MCF-7 cells, reducing viability by 50–70% via G1/S cell cycle arrest and caspase-3 activation, hallmarks of p53-Bax-mediated apoptosis. Dichloromethane fractions from leaves selectively inhibit MCF-7 proliferation (IC50 ~5 μg/mL) while sparing normal mammary epithelial cells (PMECs), achieving a selectivity index of 9.5 through ROS induction and mitochondrial depolarization. In MDA-MB-231 cells, which harbor mutant p53 and elevated ROS, MO seed extracts (e.g., M1S9 fraction) suppress viability by 60–90%, downregulating VEGF and SLC39A6 (a zinc transporter linked to invasion) while elevating antioxidant enzymes like SOD. Bioassay-guided fractionation of MO leaves identifies niazimicin and β-sitosterol as key actives against MDA-MB-231, inhibiting migration by 40% via HIF-1α-VEGF axis suppression.[57]

Comparative analyses further delineate extract potency. Sugar-rich fractions from MO seeds outperform crude extracts in both MCF-7 and MDA-MB-231, inducing 70% apoptosis through synergistic flavonoid-glucosinolate interactions that amplify Nrf2 activation and ROS quenching. Hexane fractions from seeds trigger p53-independent apoptosis in MCF-7 via extrinsic pathways (FasL upregulation) and intrinsic ROS overload, arresting cells at G2/M. Pod extracts inhibit tube formation in co-cultured HUVECs/MDA-MB-231 by 60%, underscoring anti-angiogenic synergy. Autophagy modulation emerges as a novel mechanism; MO leaf dichloromethane fractions decrease MDA-MB-231 viability by 90% by inhibiting autophagic flux, linking to p53 restoration and VEGF downregulation.These findings collectively affirm MO's multi-target profile: ROS modulation (e.g., 2–3-fold H_2O_2 elevation selectively in cancer cells), p53 reactivation (Bax ↑2–4x), and VEGF inhibition (secretion ↓50–70%). Limitations include variability in extract standardization and subtype bias toward MCF-7/MDA-MB-231, warranting broader panels like HER2-enriched SK-BR-3.[58]

In Vivo Models

Animal models, particularly orthotopic xenografts in immunocompromised mice, validate in vitro efficacy and reveal systemic benefits, such as reduced metastasis and immunomodulation. BALB/c nude mice bearing MDA-MB-231 xenografts represent a standard for TNBC evaluation, while 4T1 models in syngeneic BALB/c mice assess immunogenicity.Oral administration of MO leaf extracts (200–300 mg/kg) in MDA-MB-231 xenografts regresses tumor volume by 50–64%, correlating with decreased Ki-67 proliferation and CD31+ microvessel density (↓45%), indicative of VEGF pathway blockade. Seed residue extracts (750 mg/kg) further attenuate serum ROS markers by 35%, enhancing p53 expression and apoptosis in tumor tissues. Polyherbal infusions combining MO leaves with green tea or saffron amplify these effects, reducing tumor burden by 70% in 4T1 BALB/c models via NF-κB inhibition and Th1 cytokine upregulation (IFN-γ ↑2-fold), suggesting immunomodulatory synergy against metastasis.[59]

In obesity-complicated TNBC, MO seed extracts (500 mg/kg) supplemented with chemotherapy (doxorubicin) paradoxically worsen progression in diet-induced obese mice, increasing tumor vascularity by 30% due to adipose-derived factors overriding anti-angiogenic benefits. However, in lean models, MO alone or with tamoxifen reduces angiogenesis (VEGF ↓35%) and enhances metabolic health, lowering insulin resistance that fuels ROS-driven progression. Silver nanoparticle-conjugated MO leaf extracts in HeLa xenografts (cervical analog) inhibit growth by 60%, but breast-specific data in BALB/c mice confirm similar p53-mediated tumor stasis.These studies highlight dose-dependent efficacy (effective at 200–750 mg/kg) and pathway-specific outcomes: ROS normalization prevents oxidative metastasis, p53 activation curbs recurrence, and VEGF suppression limits vascularization. Challenges include inter-study variability in extraction methods and the need for immunocompetent models to fully capture synergy with host immunity.[60]

Emerging Clinical Data

Despite compelling preclinical evidence, clinical data on MO in breast cancer remain sparse as of October 2025, confined to observational studies and adjunctive pilots rather than randomized controlled trials (RCTs). No dedicated Phase II/III trials for MO monotherapy or combination in breast cancer are registered on ClinicalTrials.gov, reflecting barriers like standardization and regulatory hurdles for botanicals.Observational cohorts in India and Africa, where MO is dietary staple, report inverse associations: women with high MO leaf intake (>50 g/week) exhibit 20–30% lower breast cancer incidence, potentially via ROS-scavenging phenolics. A small pilot (n=25) in Ethiopian TNBC patients supplemented with 1 g/day MO powder alongside chemotherapy noted improved fatigue scores and lipid profiles (LDL ↓15%), but no tumor response data. Another adjunctive study (n=40, HER2+ breast cancer) in Malaysia combined MO seed oil (500 mg/day) with trastuzumab, observing stabilized disease in 60% versus 40% controls, attributed to VEGF modulation, yet lacked biomarker confirmation.[61]

Limitations are pronounced: small sample sizes (n<50), short durations (4–12 weeks), and confounding by polypharmacy in traditional settings. Heterogeneity in MO sourcing (e.g., leaf vs. seed) precludes dose-response analyses, and endpoint biases favor surrogate markers over progression-free survival. Emerging 2025 data from a Phase I safety trial (n=30, advanced cancers including breast) in Thailand report no disease progression acceleration with 2 g/day MO extract, but efficacy endpoints are pending. These nascent findings suggest adjuvant potential, particularly in resource-limited settings, but underscore the imperative for RCTs to validate pathway targeting in humans.[62]

Safety and Toxicity Profile

MO's safety profile supports its therapeutic candidacy, with low acute toxicity (LD50 >2 g/kg in rodents) and no genotoxicity in Ames assays. Human studies up to 3 g/day for 3 months report mild gastrointestinal effects (nausea in 5–10%), resolving spontaneously.ADME profiling reveals favorable pharmacokinetics: flavonoids like quercetin exhibit 40–60% oral bioavailability, with rapid absorption (Tmax 1–2 h) via gut transporters and hepatic metabolism by CYP3A4/UGT1A1, yielding active conjugates excreted renally (half-life 3–11 h). Isothiocyanates (moringin) achieve 60% absorption but short half-life (<2 h), mitigated by nano-formulations extending exposure 2-fold. Distribution favors tissues with high oxidative stress (e.g., breast tumors), with low plasma protein binding (20–40%) enabling tumor penetration.[63]

In breast cancer contexts, MO extracts show no cytotoxicity to normal cells at IC50 doses for MDA-MB-231 (5–20 μg/mL). In silico ADMET predicts optimal drug-likeness for key compounds (logP 1.3–3.0, high GI absorption >90%), with no hepatotoxicity or cardiotoxicity flags. Chronic rodent studies (500 mg/kg, 90 days) confirm no histopathological changes, though high-tannin seeds may impair iron absorption in anemic patients. Interactions with chemotherapeutics are bidirectional: MO attenuates doxorubicin cardiotoxicity (ROS ↓40%) but may alter CYP metabolism, necessitating monitoring.Overall, MO's safety margins (therapeutic index >10) and clean toxicity profile position it as a viable adjuvant, though long-term human data in cancer cohorts are needed.[64]

Challenges and Translational Perspectives

Despite the promising preclinical evidence supporting *Moringa oleifera* (MO) as a modulator of ROS, p53, and VEGF pathways in breast cancer, several hurdles impede its seamless integration into clinical practice. Translational challenges encompass technical, pharmacological, and regulatory dimensions, yet innovative strategies in formulation and combinatorial regimens offer pathways forward. This section explores these barriers, optimization approaches, and adjuvant potentials, emphasizing the need for rigorous standardization and human trials to harness MO's phytochemical synergy for equitable, effective therapies.[65]

Barriers to Clinical Use

Foremost among translational obstacles is the standardization of MO extracts, a prerequisite for reproducible efficacy and regulatory approval. MO's phytochemical profile varies markedly by plant part (e.g., leaves vs. seeds), geographic origin, harvest season, and processing method, leading to inconsistent concentrations of key actives like quercetin (0.5–2 mg/g) and moringin (up to 60 mg/g in seeds). This heterogeneity complicates dose-response modeling and quality control, as evidenced by inter-laboratory variations in antiproliferative IC50 values against MCF-7 cells ranging from 50–200 μg/mL. Regulatory bodies like the FDA demand Good Manufacturing Practices (GMP)-certified extracts with quantified markers (e.g., ≥1% total flavonoids), yet few commercial products meet these criteria, perpetuating skepticism in oncology settings.[66]

Bioavailability issues further exacerbate this gap. MO's polar phytochemicals, such as isothiocyanates and phenolics, suffer from low aqueous solubility and rapid first-pass metabolism, yielding plasma levels <10% of ingested doses in rodent models. Gut efflux via P-glycoprotein and enzymatic degradation by CYP3A4 limit systemic exposure, particularly for anti-angiogenic moringin, which has a half-life of <2 hours. In breast cancer contexts, this attenuates ROS-modulating effects, as suboptimal quercetin bioavailability (20–40%) fails to sustain Nrf2 activation in hypoxic tumours. Patient compliance is also compromised by the plant's bitter taste and bulky dosing (1–3 g/day), deterring long-term adherence in diverse populations.[67]

Drug interactions pose additional risks, potentially altering the pharmacokinetics of standard chemotherapeutics. MO inhibits CYP3A4 and CYP2D6 with IC50 values of 5–15 μM, mimicking grapefruit juice effects and elevating plasma levels of doxorubicin or tamoxifen by 20–50%, heightening cardiotoxicity or endocrine disruption risks. Conversely,

induction of phase II enzymes (e.g., GST) by isothiocyanates may accelerate clearance of cyclophosphamide, reducing efficacy. In polypharmacy-heavy breast cancer regimens, these herb-drug interactions (HDIs) underscore the need for pharmacovigilance, as highlighted in Thai herbal-oncology cohorts where MO co-administration correlated with 15% adverse event increases. Addressing these requires pharmacokinetic interaction databases tailored to MO, alongside Phase I trials stratifying by CYP polymorphisms [68]

Synergy Optimization

Leveraging MO's inherent phytochemical synergy demands advanced delivery systems to amplify bioavailability and target tumour microenvironments. Nano-formulations represent a cornerstone, encapsulating bioactives in carriers like liposomes, micelles, or phytosomes to shield against degradation and enhance tumour accumulation via the enhanced permeability and retention (EPR) effect. For instance, nano-micelles of MO seed oil (particle size 50–100 nm) boost mitochondrial apoptosis in MCF-7 and HCT-116 cells by 2–3-fold, delivering oleic acid and phenolics with 80% encapsulation efficiency and sustained release over 72 hours. Phytosomes—lipid-polyphenol complexes—encapsulate MO leaf polyphenols (MOPP) at 15:1 ratios, yielding 3-fold higher bioavailability in 4T1 breast tumor-bearing mice, where they suppress VEGF by 60% via improved HIF-1α inhibition.[69]

Chitosan nanoparticles (CS-NPs) loaded with MO extracts exemplify biocompatibility and pH-responsive delivery, releasing quercetin in acidic endosomes to activate p53 selectively in MDA-MB-231 cells (IC50 10 μg/mL vs. 50 μg/mL free extract). Green-synthesized silver or gold nanoparticles using MO leaf extracts further potentiate synergy, with MO-AgNPs inducing 70% apoptosis in AGS gastric cells through ROS overload, adaptable to breast models via surface functionalization for HER2 targeting. These strategies not only mitigate bioavailability barriers but also enable co-delivery of synergistic pairs (e.g., moringin-quercetin), as in PLGA-CS-MO nanocomposites that restore wild-type p53 function in mutant-expressing xenografts. Challenges persist in scalability and long-term stability, but FDA-approved nano-herbals like silymarin phytosomes offer precedents for clinical progression.[70]

Integration with Conventional Therapies

MO's multi-target profile positions it as an ideal adjuvant, potentially mitigating ROS-mediated resistance—a key driver of relapse in 30–50% of breast cancers. By quenching chronic ROS and reinstating p53 surveillance, MO extracts sensitize resistant cells to doxorubicin, reducing IC50 by 40% in MCF-7 sublines via Nrf2-mediated GST downregulation. Polyherbal combinations, such as MO with green tea catechins, enhance immunomodulation (IFN-γ ↑2-fold) and apoptosis in 4T1 models, curtailing metastasis without additive toxicity. However, context matters: in obese TNBC mice, high-dose MO seeds exacerbate doxorubicin progression by 30%, likely via adipose-VEGF crosstalk, highlighting subtype- and comorbidity-specific dosing.In adjuvant paradigms, MO attenuates chemotherapy side effects; leaf extracts co-administered with tamoxifen lower lipid peroxidation by 35%, preserving ovarian reserve in rat models. Emerging data suggest ROS-p53 axis targeting reverses endocrine resistance, with MO flavonoids upregulating ERα via epigenetic modulation in long-term estrogen-deprived cells. Translational trials should prioritize neoadjuvant settings, combining nano-MO with anti-VEGF agents like bevacizumab to synergize vascular normalization.[71]

Future Directions

The burgeoning preclinical evidence for *Moringa oleifera* (MO) in breast cancer underscores its potential as a synergistic modulator of ROS, p53, and VEGF pathways, yet significant research gaps persist, impeding clinical adoption. Foremost is the paucity of subtype-specific investigations, as most studies focus on ER-positive (MCF-7) or triple-negative (MDA-MB-231) models, neglecting HER2-enriched or luminal B subtypes where pathway dysregulation varies. For instance, while MO flavonoids inhibit CDK-2 in ER+ cells, their efficacy in HER2-driven angiogenesis remains uncharted, potentially overlooking opportunities for targeted interventions. Long-term studies are equally deficient; chronic rodent models spanning 6–12 months are scarce, leaving uncertainties about sustained ROS modulation or cumulative toxicity in adjuvant settings. Human longitudinal cohorts, tracking MO supplementation (1–3 g/day) over 2–5 years, are absent, particularly in high-risk populations like postmenopausal women in LMICs, where MO's accessibility could address disparities.[72]

Emerging areas offer transformative avenues to bridge these voids. Omics approaches—genomics, transcriptomics, proteomics, and metabolomics—hold promise for mapping phytochemical synergies at molecular resolution. High-throughput RNA-seq and CpG methyl-seq could dissect how MO isothiocyanates and quercetin co-regulate p53-VEGF crosstalk, identifying biomarkers for responders versus non-responders. Recent precedents, such as

epigenomic profiling of MO in epidermal models, suggest applicability to breast tumor organoids, enabling network pharmacology models to predict emergent effects from multi-compound matrices. Personalized medicine further amplifies this: pharmacogenomic stratification by TP53 polymorphisms or CYP3A4 variants could tailor MO dosing, mitigating herb-drug interactions with tamoxifen. AI-driven platforms might integrate multi-omics data with patient genotypes, forecasting subtype-specific responses and optimizing nano-formulated MO for precision delivery.To advance, multidisciplinary consortia should prioritize Phase II RCTs in diverse cohorts, incorporating omics endpoints and real-world evidence from LMIC registries. Funding for GMP-standardized extracts and long-term safety surveillance is crucial. By addressing these gaps, MO could evolve from a folk remedy to a cornerstone of integrative oncology, democratizing breast cancer care by 2030.[73]

Conclusion

Breast cancer's formidable challenge—marked by its heterogeneity, metastatic propensity, and therapeutic resistance—demands innovative, multi-target interventions that address core dysregulations in reactive oxygen species (ROS), p53 tumor suppression, and vascular endothelial growth factor (VEGF)-mediated angiogenesis. *Moringa oleifera* (MO), a phytochemical-rich medicinal tree, emerges as a compelling candidate, with its bioactives orchestrating synergistic assaults on these pathways to curtail tumor progression. This review synthesizes compelling preclinical evidence demonstrating MO's mechanistic prowess: isothiocyanates like moringin and flavonoids such as quercetin modulate ROS levels, shifting from pro-oncogenic oxidative stress to selective apoptotic overload in breast cancer cells (e.g., MCF-7 and MDA-MB-231), as evidenced by reduced malondialdehyde and elevated Nrf2 activation. Simultaneously, these compounds restore p53 functionality by inhibiting MDM2 ubiquitination and upregulating Bax/p21, inducing G1/S arrest and caspase-dependent apoptosis, particularly in p53-mutant subtypes. Anti-angiogenic effects manifest through HIF-1α-VEGF axis suppression, diminishing microvessel density and endothelial tube formation, thereby starving hypoxic tumors of sustenance.

In vitro studies across luminal and basal-like models reveal 50–90% viability reductions with MO extracts (50–200 µg/mL), while in vivo xenografts in BALB/c mice demonstrate 50–70% tumor regression at 200–750 mg/kg, without overt toxicity to normal tissues. These outcomes stem not from isolated compounds but from phytochemical synergy: flavonoids potentiate isothiocyanate bioavailability, amplifying Nrf2-p53 crosstalk and multi-node VEGF blockade, yielding emergent efficacy superior to monotherapies. Such polypharmacology mirrors physiological homeostasis, mitigating resistance mechanisms like ROS adaptation and p53 gain-of-function, while offering a safer profile than conventional cytotoxics.

The translational horizon for MO's phytochemical synergy is bright, promising an adjuvant paradigm that enhances chemotherapy sensitization (e.g., doxorubicin) and reduces ROS-mediated side effects, particularly in resource-constrained settings where MO thrives abundantly. Yet, this potential remains unrealized without bridging the preclinical-clinical chasm. Rigorous, multicenter randomized controlled trials (Phase II/III) are imperative—stratified by subtype, incorporating omics biomarkers for pathway modulation, and evaluating long-term outcomes in diverse cohorts. Standardized GMP extracts, nano-formulations for bioavailability, and pharmacovigilance for herb-drug interactions must underpin these efforts. By investing in such trials, the global oncology community can validate MO as a democratizing force, transforming a humble "miracle tree" into a cornerstone of precision breast cancer care, ultimately alleviating the disease's disproportionate burden on women worldwide.

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