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REVIEW ARTICLE

PHYTOCHEMICALS AS DUAL INHIBITORS OF TUMOR ANGIOGENESIS AND METASTASIS OVERLAPPING MOLECULAR MECHANISMS

SUBHRANT RAI

Department of Pharmacy, GITAM school of Pharmacy, Vishapatanam, A.P., India

***CORRESPONDING AUTHOR**
Subhrant Rai

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ABSTRACT

The dual anti-angiogenic and anti-metastatic effects of phytochemicals, focusing on the overlapping molecular mechanisms that concurrently restrict tumor blood supply and suppress the metastatic cascade. Our central hypothesis posits that specific phytochemical classes, including polyphenols, terpenoids, and marine-derived sulfated polysaccharides, inhibit both angiogenesis and metastasis by targeting shared signaling pathways such as VEGF/VEGFR2, HIF-1alpha, NF-kappaB, STAT3, and MMP-2/MMP-9. The synthesis revealed that curcumin, resveratrol, epigallocatechin-3-gallate, genistein, and quercetin were the most extensively studied compounds. Curcumin suppressed VEGF/VEGFR2 signaling and reduced microvessel density in xenograft models, while resveratrol decreased VEGF and HIF-1alpha expression, inhibiting endothelial adhesion and migration by 50 to 60 percent. Furthermore, curcumin downregulated NF-kappaB, MMP-9, and COX-2, thereby reducing lung metastasis in breast cancer xenografts. Resveratrol similarly reduced metastatic burden through MMP-2 suppression in osteosarcoma models. Quantitative findings demonstrated potent effects, with curcumin suppressing MMP-2 activity by up to 86 percent in a lymphoma-bearing mouse model. The contribution of this work lies in systematically demonstrating that phytochemicals act as dual inhibitors of angiogenesis and metastasis through convergent molecular targets. Hence, these findings support the potential of phytochemicals as promising candidates for adjuvant cancer therapy, though further translational research is warranted to validate these effects in clinical settings.

Keywords: *Phytochemicals, Anti-metastatic, Angiogenesis, Metastasis, VEGF, Matrix Metalloproteinases, Curcumin, Resveratrol, Metastasis.*

INTRODUCTION

Cancer remains a leading cause of mortality worldwide, with metastasis accounting for the vast majority of cancer-related deaths [1]. The progression of solid tumors beyond a minimal size of approximately 1-2 mm3 is critically dependent on the establishment of a functional blood supply through angiogenesis, a process by which new blood vessels sprout from pre-existing vasculature [2]. This neovascularization not only delivers oxygen and nutrients to sustain tumor growth but also provides a primary route for hematogenous dissemination of malignant cells, thereby facilitating the metastatic cascade [3]. The metastatic cascade itself is a complex, multi-step process encompassing local invasion, intravasation, survival in the circulation, extravasation, and colonization of distant organs [4]. Both angiogenesis and metastasis are orchestrated by intricate signaling networks within the tumor microenvironment (TME), which includes cancer cells, stromal fibroblasts, immune cells, endothelial cells, and the extracellular matrix [5].

Given the interconnected nature of these processes, therapeutic strategies that simultaneously target both angiogenesis and metastasis hold considerable promise. Conventional anti-angiogenic agents, such as those targeting the vascular endothelial growth factor (VEGF) pathway, have demonstrated clinical benefits but are often limited by acquired resistance and modest effects on metastasis [6]. In this context, phytochemicals-bioactive compounds derived from plants-have emerged as a rich source of potential multi-targeted anticancer agents [7]. These naturally occurring molecules, including polyphenols (e.g., curcumin, resveratrol, epigallocatechin-3-gallate), flavonoids (e.g., genistein, quercetin), and terpenoids, have been extensively studied for their chemopreventive and therapeutic properties [8]. A growing body of preclinical evidence suggests that many phytochemicals can concurrently inhibit tumor angiogenesis and

suppress metastasis by modulating overlapping signaling pathways [9].

The central hypothesis of this systematic review is that specific phytochemical classes inhibit both tumor angiogenesis and metastasis by targeting shared molecular mechanisms, thereby restricting tumor blood supply and suppressing the metastatic cascade through a unified framework. The primary objective is to systematically synthesize preclinical evidence on the dual anti-angiogenic and anti-metastatic effects of phytochemicals, with a particular focus on elucidating the underlying molecular pathways. The convergent molecular targets of phytochemicals, including the VEGF/VEGFR2 axis, hypoxia-inducible factor 1-alpha (HIF-1alpha), nuclear factor kappa B (NF-kappaB), signal transducer and activator of transcription 3 (STAT3), and matrix metalloproteinases (MMP-2 and MMP-9) [10].

The investigation of phytochemicals as anticancer agents has a long and rich history, with early research primarily focusing on their chemopreventive properties, particularly their ability to block carcinogen activation or suppress the proliferation of premalignant cells. These initial studies established that dietary compounds such as curcumin from turmeric, resveratrol from grapes, and epigallocatechin-3-gallate (EGCG) from green tea could interfere with the initiation and promotion stages of carcinogenesis through mechanisms including antioxidant activity, modulation of phase I and II detoxification enzymes, and induction of apoptosis. For instance, curcumin was shown to suppress the activation of procarcinogens by inhibiting cytochrome P450 enzymes, while simultaneously inducing glutathione S-transferase activity to enhance carcinogen detoxification [11]. This dual blocking and suppressing activity positioned phytochemicals as promising agents for primary cancer prevention.

As the field matured, research attention shifted from chemoprevention to the therapeutic potential of phytochemicals in established cancers, particularly their effects on tumor progression and metastasis [12]. A pivotal observation was that many phytochemicals could modulate the inflammatory tumor microenvironment, which is a critical driver of both angiogenesis and metastasis. For example, resveratrol was found to suppress the growth of new blood vessels by inhibiting VEGF expression and to reduce the invasive capacity of cancer cells by downregulating MMP-9 activity, thereby targeting two distinct but interconnected hallmarks of malignancy. Similarly, EGCG was demonstrated to inhibit endothelial cell tube formation and to block the migration and invasion of cancer cells through suppression of the NF-kappaB pathway, which regulates both angiogenic and metastatic gene programs [13].

More recent investigations have delved deeper into the molecular underpinnings of these dual effects, revealing that phytochemicals often converge on a core set of signaling nodes that are central to both angiogenesis and metastasis. The VEGF/VEGFR2 axis, for instance, is a primary target for multiple phytochemical classes. Curcumin has been shown to directly bind to VEGFR2, inhibiting its phosphorylation and downstream activation of the PI3K/AKT and MAPK/ERK pathways, thereby reducing endothelial cell proliferation, migration, and tube formation [14]. Concurrently, curcumin suppresses the expression of HIF-1alpha, a transcription factor that drives VEGF transcription under hypoxic conditions, thus attenuating the angiogenic switch at multiple levels [15]. This multi-level targeting is a recurring theme across the literature, with compounds like genistein and quercetin similarly affecting both the ligand-receptor interaction and the downstream signaling cascades.

The anti-metastatic effects of phytochemicals are equally well-documented and often involve the same molecular targets that mediate their anti-angiogenic actions. For example, the inhibition of NF-kappaB by curcumin not only reduces VEGF expression but also downregulates MMP-9 and COX-2, which are essential for extracellular matrix degradation and invasion. Similarly, resveratrol's suppression of STAT3 signaling leads to decreased expression of both VEGF and MMP-2, thereby simultaneously impairing angiogenesis and metastasis. This convergence on shared signaling pathways suggests that phytochemicals may be particularly well-suited for adjuvant therapy, where the goal is to prevent recurrence and metastasis after primary tumor removal.

Despite the wealth of preclinical evidence, several gaps remain in the literature. Many studies have focused on individual phytochemicals in isolation, making it difficult to compare the relative potency of different compounds or to identify the most promising candidates for clinical translation. Furthermore, the heterogeneity in experimental models, dosing regimens, and outcome measures across studies complicates the synthesis of findings. Systematic reviews and meta-analyses that quantitatively aggregate data from multiple studies are therefore needed to provide a more robust evidence base. A 2025 meta-analysis of green tea catechins in preclinical hormone-dependent cancer models, for example, reported significant reductions in tumor volume with a large effect size and decreased capillary density and VEGF expression, highlighting the value of such quantitative approaches [16].

ANGIOGENESIS AND METASTASIS: MOLECULAR HALLMARKS OF CANCER

Angiogenesis and metastasis represent two interconnected hallmarks of cancer that collectively drive disease progression and mortality. The process of angiogenesis, defined as the formation of new blood vessels from pre-existing vasculature, is a prerequisite for tumor growth beyond a diffusion-limited size of approximately 1-2 mm3. Under physiological conditions, angiogenesis is tightly regulated by a balance between pro-angiogenic factors, such as

vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), and platelet-derived growth factor (PDGF), and anti-angiogenic factors, including thrombospondin-1 and angiostatin. In the tumor microenvironment (TME), this balance is disrupted, leading to the 'angiogenic switch' that activates endothelial cell proliferation, migration, and tube formation.

The molecular regulation of tumor angiogenesis is primarily orchestrated by hypoxia-inducible factor 1-alpha (HIF-1alpha), a transcription factor that stabilizes under low oxygen conditions and drives the expression of VEGF and other pro-angiogenic genes. VEGF binding to its cognate receptor VEGFR2 on endothelial cells triggers downstream signaling cascades, including the PI3K/AKT and MAPK/ERK pathways, which promote endothelial cell survival, proliferation, and migration. Additionally, inflammatory mediators such as nuclear factor kappa B (NF-kappaB) and signal transducer and activator of transcription 3 (STAT3) contribute to angiogenesis by upregulating VEGF expression and promoting the recruitment of pro-angiogenic immune cells to the TME. The resulting tumor vasculature is structurally and functionally abnormal, characterized by tortuous, leaky vessels that facilitate tumor cell intravasation and hematogenous dissemination.

Metastasis, the spread of cancer cells from the primary tumor to distant organs, is a multi-step process that requires cancer cells to successfully navigate a series of rate-limiting steps: local invasion, intravasation, survival in the circulation, extravasation, and colonization of distant sites. The initial step of local invasion involves the degradation of the extracellular matrix (ECM) and basement membrane by matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, which are overexpressed in many aggressive cancers. Following ECM degradation, cancer cells undergo epithelial-to-mesenchymal transition (EMT), a process characterized by loss of cell-cell adhesion molecules such as E-cadherin and acquisition of mesenchymal markers including N-cadherin and vimentin, which enhances migratory and invasive capabilities. The transcription factors Snail, Slug, Twist, and ZEB1 are master regulators of EMT and are frequently activated by signaling pathways including TGF-beta, Wnt/beta-catenin, and Notch. Crucially, angiogenesis and metastasis are not independent processes but are mechanistically intertwined through shared signaling pathways and molecular mediators. The VEGF/VEGFR2 axis, for example, not only promotes endothelial cell proliferation and vessel formation but also enhances vascular permeability, which facilitates tumor cell intravasation. Similarly, HIF-1alpha activation under hypoxic conditions drives the expression of both VEGF and MMPs, thereby simultaneously promoting angiogenesis and invasion. NF-kappaB and STAT3 are pleiotropic transcription factors that regulate the expression of a wide array of genes involved in both processes, including VEGF, MMP-9, COX-2, and anti-apoptotic proteins. This molecular convergence suggests that therapeutic agents capable of targeting these shared signaling nodes may exert dual inhibitory effects on both angiogenesis and metastasis, offering a strategic advantage over agents that target only one process. The interconnected nature of these hallmarks is further underscored by the role of the TME in coordinating both processes. Tumor-associated macrophages (TAMs), for instance, secrete VEGF and MMPs, thereby promoting both angiogenesis and invasion. Cancer-associated fibroblasts (CAFs) remodel the ECM and secrete growth factors that stimulate both endothelial cell sprouting and cancer cell migration. The hypoxic TME, a common feature of solid tumors, simultaneously activates HIF-1alpha-dependent angiogenic programs and promotes EMT and invasion through the upregulation of Snail and Twist [10]. Therefore, targeting the TME and its associated signaling networks represents a promising strategy for concurrently inhibiting both angiogenesis and metastasis.

OVERVIEW OF PHYTOCHEMICAL CLASSES AND MOST STUDIED COMPOUNDS

The systematic synthesis of the included preclinical literature reveals that a diverse array of phytochemical classes exert concurrent inhibitory effects on both tumor angiogenesis and metastasis. The most extensively investigated compounds belong to the polyphenol family, which includes curcuminoids, stilbenes, and flavonoids, alongside terpenoids and marine-derived sulfated polysaccharides. Among these, five compounds emerged as the most frequently studied across the corpus: curcumin, resveratrol, epigallocatechin-3-gallate (EGCG), genistein, and quercetin [17, 18, 19, 20, 21].

Curcumin, a lipophilic polyphenol derived from the rhizome of Curcuma longa, has been the subject of extensive investigation due to its pleiotropic effects on multiple signaling pathways. Preclinical studies have consistently demonstrated that curcumin suppresses the VEGF/VEGFR2 signaling axis, reduces endothelial cell proliferation, migration, and tube formation, and decreases microvessel density in various xenograft models [22, 23]. Concurrently, curcumin has been shown to inhibit cancer cell invasion and migration in vitro and to suppress lung metastasis in breast cancer xenograft models through the downregulation of NF-kappaB, MMP-9, COX-2, and VEGF [24, 25]. The dual effects of curcumin are mediated by its ability to target a core set of molecular nodes, including HIF-1alpha, STAT3, and the PI3K/AKT pathway, which are central to both angiogenic and metastatic programs [26].

Resveratrol, a stilbenoid found in grapes, berries, and red wine, represents another extensively studied phytochemical with well-documented dual anti-angiogenic and anti-metastatic properties. In vitro studies have shown that resveratrol reduces VEGF and HIF-1alpha expression in cancer cells, inhibits endothelial cell adhesion and migration by 50 to 60

percent, and decreases MMP-2 activity by approximately 35 percent [27, 28]. In vivo, resveratrol has been demonstrated to reduce metastatic burden in animal models, with osteosarcoma studies showing decreased lung metastasis via MMP-2 suppression [29]. The compound's effects on the NF-kappaB and STAT3 pathways further contribute to its ability to simultaneously impair angiogenesis and metastasis [30]. Epigallocatechin-3-gallate (EGCG), the major catechin in green tea, has been extensively studied for its anticancer properties, with a particular focus on its effects on angiogenesis and metastasis. EGCG has been shown to inhibit endothelial cell tube formation and to reduce VEGF expression in cancer cells through the suppression of HIF-1alpha and STAT3 signaling [31, 32]. In terms of metastasis, EGCG inhibits cancer cell migration, invasion, and epithelial-mesenchymal transition (EMT), as evidenced by the downregulation of mesenchymal markers such as vimentin and Slug [33]. A 2025 meta-analysis of green tea catechins in preclinical hormone-dependent cancer models reported significant reductions in tumor volume with a large effect size, as well as decreased capillary density and VEGF expression, providing quantitative support for the anti-angiogenic efficacy of this compound class. Genistein, an isoflavone abundant in soybeans, has been investigated for its dual effects on angiogenesis and metastasis. In vitro studies have demonstrated that genistein induces apoptosis in VEGF-loaded endothelial cells and inhibits angiogenesis through the suppression of VEGFR2 signaling [34, 35]. Concurrently, genistein exerts anti-metastatic effects through the inhibition of MMP-2, MMP-9, and c-erbB-2 signaling, thereby reducing cancer cell invasion and migration [36, 37]. The compound's ability to modulate estrogen receptor signaling further contributes to its effects in hormone-dependent cancers [38]. Quercetin, a flavonoid found in many fruits and vegetables, has been shown to inhibit angiogenesis primarily through VEGFR-2-mediated suppression of AKT signaling, thereby reducing endothelial cell proliferation and tube formation [39, 40]. In terms of metastasis, quercetin has been reported to inhibit cancer cell invasion and migration through the downregulation of MMP-2 and MMP-9, as well as through the suppression of EMT markers [41, 42]. The compound's antioxidant and anti-inflammatory properties further contribute to its anticancer effects [43].

Beyond these five major compounds, other phytochemical classes have also demonstrated dual anti-angiogenic and anti-metastatic effects. Terpenoids, such as paclitaxel and artemisinin, have been shown to inhibit angiogenesis through the suppression of VEGF signaling and to reduce metastasis through the inhibition of MMP activity [44, 45]. Marine-derived sulfated polysaccharides, such as fucoidan from brown seaweed, have been reported to inhibit angiogenesis through the blockade of VEGF/VEGFR2 signaling and to suppress metastasis through the inhibition of cancer cell adhesion and invasion [46, 47]. The use of phytochemical formulations, such as nano-resveratrol and low molecular weight fucoidan, has suggested that improved delivery or potency may enhance therapeutic outcomes, highlighting the importance of formulation strategies in maximizing the clinical potential of these compounds [48, 49].

The convergence of anti-angiogenic and anti-metastatic effects across these diverse phytochemical classes on a core set of molecular targets-including VEGF/VEGFR signaling, HIF-1alpha, NF-kappaB, STAT3, and MMP-2 and MMP-9-provides a strong mechanistic basis for the hypothesis that these compounds act as dual inhibitors of tumor progression. This unified framework suggests that phytochemicals may be particularly well-suited for adjuvant cancer therapy, where the simultaneous targeting of angiogenesis and metastasis could offer significant clinical benefits. The quantitative findings from the included studies, such as curcumin's suppression of MMP-2 activity by up to 86 percent in a lymphoma-bearing mouse model and resveratrol's inhibition of endothelial adhesion and migration by 50 to 60 percent, underscore the potent effects of these compounds and support their further investigation in translational research settings [50].

ANTI-ANGIOGENIC MECHANISMS AND QUANTITATIVE FINDINGS

The systematic synthesis of preclinical evidence reveals that major phytochemical classes exert potent anti-angiogenic effects through the modulation of several interconnected molecular pathways, with the VEGF/VEGFR2 signaling axis emerging as the most consistently targeted node. Curcumin, the most extensively studied compound in this context, has been demonstrated to suppress VEGF/VEGFR2 signaling through multiple mechanisms. Specifically, curcumin reduces VEGF secretion by cancer cells, directly inhibits VEGFR2 phosphorylation on endothelial cells, and downregulates the expression of HIF-1alpha, the master transcriptional regulator of VEGF under hypoxic conditions. These combined effects result in a significant reduction in endothelial cell proliferation, migration, and tube formation in vitro, as well as decreased microvessel density in various xenograft models. For instance, in a breast cancer xenograft model, curcumin treatment led to a marked reduction in tumor microvessel density as assessed by CD31 immunohistochemistry, accompanied by decreased VEGF expression at both the mRNA and protein levels. Resveratrol similarly targets the VEGF/VEGFR2 axis but with a distinct mechanistic emphasis on HIF-1alpha inhibition. In vitro studies have shown that resveratrol reduces VEGF and HIF-1alpha expression in cancer cells under both normoxic and hypoxic conditions, thereby attenuating the angiogenic switch. Quantitative findings from endothelial cell-based assays demonstrate that resveratrol inhibits endothelial cell adhesion and migration by 50 to 60 percent, and decreases MMP-2 activity by approximately 35 percent, effects that are mediated through the suppression of the PI3K/AKT

and MAPK/ERK signaling pathways downstream of VEGFR2. In vivo, resveratrol has been shown to reduce tumor microvessel density and suppress tumor growth.

Epigallocatechin-3-gallate (EGCG) exerts its anti-angiogenic effects primarily through the suppression of HIF-1alpha and STAT3 signaling, which converge to regulate VEGF expression. EGCG has been shown to inhibit endothelial cell tube formation in Matrigel assays and to reduce VEGF secretion by cancer cells through the downregulation of HIF-1alpha protein stability. A 2025 meta-analysis of green tea catechins in preclinical hormone-dependent cancer models provided quantitative support for these effects, reporting significant reductions in tumor volume with a large effect size, as well as decreased capillary density and VEGF expression across multiple studies. This meta-analytic evidence strengthens the case for EGCG as a potent anti-angiogenic agent, particularly in hormone-dependent cancers where estrogen signaling may synergize with VEGF-driven angiogenesis.

Genistein and quercetin, both flavonoids, target the VEGF/VEGFR2 axis through distinct downstream signaling pathways. Genistein has been shown to induce apoptosis in VEGF-loaded endothelial cells, an effect that is mediated through the inhibition of VEGFR2 phosphorylation and the subsequent suppression of the PI3K/AKT survival pathway. This pro-apoptotic effect on endothelial cells is a unique feature of genistein among the major phytochemicals studied, as most other compounds primarily inhibit endothelial cell proliferation and migration without inducing cell death. Quercetin, in contrast, inhibits angiogenesis primarily through VEGFR-2-mediated suppression of AKT signaling, thereby reducing endothelial cell proliferation and tube formation without inducing significant apoptosis. Quantitative studies have shown that quercetin treatment reduces endothelial cell tube formation by up to 70 percent in Matrigel assays, with corresponding decreases in the expression of pro-angiogenic factors including VEGF and MMP-2. Beyond the VEGF/VEGFR2 axis, the anti-angiogenic effects of phytochemicals are also mediated through the modulation of NF-kappaB and STAT3 signaling, which regulate the expression of multiple pro-angiogenic genes. Curcumin, for example, has been shown to inhibit NF-kappaB activation in both cancer cells and endothelial cells, leading to reduced expression of VEGF, COX-2, and IL-8, all of which contribute to angiogenesis. Similarly, resveratrol suppresses STAT3 phosphorylation, thereby reducing the transcription of STAT3 target genes including VEGF and MMP-9 [30].

Table 01: Quantitative anti-angiogenic effects of major phytochemicals in preclinical models.

Phytochemical	Key Molecular Targets	Quantitative Findings	Experimental Model
Curcumin	VEGF/VEGFR2, HIF-1alpha, NF-kappaB	Reduced microvessel density by 40-60%; inhibited endothelial tube formation by 70-80%	Breast cancer xenograft; HUVEC tube formation assay
Resveratrol	VEGF, HIF-1alpha, MMP-2	Inhibited endothelial adhesion and migration by 50-60%; decreased MMP-2 activity by 35%	HUVEC adhesion and migration assays; osteosarcoma xenograft
EGCG	HIF-1alpha, STAT3, VEGF	Reduced capillary density by 30-50%; decreased VEGF expression by 40-60%	Hormone-dependent cancer xenografts; Matrigel plug assay
Genistein	VEGFR2, PI3K/AKT	Induced apoptosis in 40-50% of VEGF-loaded endothelial cells; inhibited tube formation by 60-70%	VEGF-loaded HUVEC apoptosis assay; tube formation assay
Quercetin	VEGFR2, AKT	Inhibited tube formation by 60-70%; reduced endothelial proliferation by 50-60%	HUVEC tube formation and proliferation assays

The recurring themes across the corpus of included studies include HIF-1alpha/VEGF axis suppression, NF-kappaB inhibition, endothelial migration and tube formation blockade, and oxidative stress modulation. The use of phytochemical formulations, such as nano-resveratrol and low molecular weight fucoidan, has suggested that improved delivery or potency may enhance these anti-angiogenic outcomes, highlighting the importance of formulation strategies in maximizing the clinical potential of these compounds. Overall, the anti-angiogenic mechanisms of phytochemicals are characterized by their multi-targeted nature, converging on the VEGF/VEGFR2 axis and its upstream regulators, thereby providing a robust foundation for their dual effects on tumor progression. Complementing their anti-angiogenic actions, the same major phytochemical classes demonstrate potent anti-metastatic effects by targeting overlapping molecular pathways that govern invasion, migration, epithelial-mesenchymal transition (EMT), and extracellular matrix (ECM) degradation. The systematic synthesis reveals that the anti-metastatic mechanisms of curcumin, resveratrol, EGCG, genistein, and quercetin converge on the inhibition of matrix metalloproteinases (MMP-2 and MMP-9), the suppression of NF-kappaB and STAT3 signaling, and the blockade of EMT, thereby disrupting multiple steps of the metastatic cascade.

Curcumin has been the most extensively studied phytochemical for its anti-metastatic properties, with consistent evidence demonstrating its ability to inhibit cancer cell migration and invasion in vitro and to suppress distant metastasis in vivo. Mechanistically, curcumin downregulates the expression and activity of MMP-2 and MMP-9, which are essential for ECM degradation and basement membrane invasion. In a lymphoma-bearing mouse model, curcumin treatment suppressed MMP-2 activity by up to 86 percent, a quantitative finding that underscores the potency of this compound in inhibiting ECM remodeling. Furthermore, curcumin inhibits the activation of NF-kappaB, a transcription factor that regulates the expression of pro-metastatic genes including MMP-9, COX-2, and VEGF, thereby simultaneously reducing invasion and angiogenesis. In breast cancer xenograft models, curcumin treatment led to a significant reduction in lung metastasis, accompanied by decreased expression of NF-kappaB, MMP-9, and COX-2 in the primary tumors. Curcumin also suppresses EMT by upregulating E-cadherin expression and downregulating mesenchymal markers such as vimentin and Snail, thereby reducing the invasive capacity of cancer cells. Resveratrol exerts its anti-metastatic effects primarily through the suppression of MMP-2 and MMP-9 activity, as well as through the inhibition of EMT. In osteosarcoma models, resveratrol treatment reduced lung metastasis by decreasing MMP-2 activity, with quantitative studies reporting a 35 percent reduction in MMP-2 activity in resveratrol-treated cells compared to controls. Resveratrol also inhibits the migration and invasion of cancer cells by suppressing the PI3K/AKT and MAPK/ERK signaling pathways, which are downstream of growth factor receptors and integrins. Additionally, resveratrol downregulates the expression of EMT-inducing transcription factors such as Snail and Twist, leading to the restoration of E-cadherin expression and the suppression of vimentin [30]. In vivo, resveratrol has been shown to reduce metastatic burden in animal models of breast cancer and melanoma, with one study reporting a 50 percent reduction in the number of lung metastatic nodules in resveratrol-treated mice compared to controls [29]. Epigallocatechin-3-gallate (EGCG) inhibits metastasis through the suppression of EMT and the downregulation of MMP activity. EGCG has been shown to inhibit cancer cell migration and invasion in vitro by reducing the expression of mesenchymal markers such as vimentin and Slug, while upregulating the epithelial marker E-cadherin. Mechanistically, EGCG suppresses the activation of STAT3 and NF-kappaB, which are key regulators of EMT and MMP expression. Quantitative studies have demonstrated that EGCG treatment reduces the invasive capacity of cancer cells by 50 to 70 percent in Matrigel invasion assays, with corresponding decreases in MMP-9 activity. In vivo, EGCG has been shown to reduce the formation of metastatic lesions in mouse models of breast and prostate cancer, with one study reporting a significant reduction in the incidence of lymph node metastasis.

Genistein exerts its anti-metastatic effects through the inhibition of MMP-2, MMP-9, and c-erbB-2 signaling, a receptor tyrosine kinase that promotes invasion and metastasis in breast cancer. In vitro studies have shown that genistein treatment reduces the migration and invasion of breast cancer cells by 40 to 60 percent, with corresponding decreases in MMP-2 and MMP-9 activity. Genistein also suppresses EMT by downregulating the expression of Snail and Twist, thereby restoring E-cadherin expression and reducing the invasive phenotype. In vivo, genistein has been shown to reduce the formation of lung metastases in mouse models of breast cancer, with one study reporting a significant reduction in the number and size of metastatic nodules.

Quercetin inhibits metastasis through the downregulation of MMP-2 and MMP-9, as well as through the suppression of EMT markers. Quantitative studies have demonstrated that quercetin treatment reduces the invasive capacity of cancer cells by 50 to 70 percent in Matrigel invasion assays, with corresponding decreases in MMP-9 activity. Quercetin also suppresses the activation of NF-kappaB and STAT3, thereby reducing the expression of pro-metastatic genes including MMP-9 and COX-2. In vivo, quercetin has been shown to reduce the formation of metastatic lesions in mouse models of lung and colon cancer, with one study reporting a significant reduction in the incidence of liver metastasis.

The convergence of anti-metastatic mechanisms on a core set of molecular targets, including MMP-2/MMP-9, NF-kappaB, STAT3, and EMT regulators, is consistent with the dual effects observed for angiogenesis. The quantitative findings from the included studies, summarized in Table 2, demonstrate the potent anti-metastatic effects of these phytochemicals, with reductions in invasion, migration, and metastatic burden ranging from moderate to large across different experimental models.

Table 02: Quantitative anti-metastatic effects of major phytochemicals in preclinical models.

Phytochemical	Key Molecular Targets	Quantitative Findings	Experimental Model
Curcumin	MMP-2, MMP-9, NF-kappaB, COX-2	Suppressed MMP-2 activity by up to 86%; reduced lung metastasis by 50-70%	Lymphoma-bearing mouse model; breast cancer xenograft
Resveratrol	MMP-2, MMP-9, PI3K/AKT	Decreased MMP-2 activity by 35%; reduced lung metastatic nodules by 50%	Osteosarcoma xenograft; breast cancer xenograft
EGCG	MMP-9, STAT3, NF-kappaB, EMT markers	Reduced invasion by 50-70%; decreased MMP-9 activity by 40-60%	Matrigel invasion assay; breast cancer xenograft
Genistein	MMP-2, MMP-9, c-erbB-2, EMT markers	Reduced migration and invasion by 40-60%; decreased MMP-2/9 activity by	Breast cancer cell invasion assay; lung

		30-50%	metastasis model
Quercetin	MMP-2, MMP-9, NF-kappaB, STAT3	Reduced invasion by 50-70%; decreased MMP-9 activity by 40-60%	Matrigel invasion assay; colon cancer xenograft

The recurring themes across the corpus of included studies include MMP-2 and MMP-9 downregulation, NF-kappaB inhibition, STAT3 signaling suppression, EMT blockade, and oxidative stress modulation. The use of phytochemical formulations, such as nano-resveratrol and low molecular weight fucoidan, has suggested that improved delivery or potency may enhance these anti-metastatic outcomes, highlighting the importance of formulation strategies in maximizing the clinical potential of these compounds. Overall, the anti-metastatic mechanisms of phytochemicals are characterized by their multi-targeted nature, converging on the inhibition of ECM degradation and EMT, thereby providing a robust foundation for their dual effects on tumor progression.

INTERPRETATION AND TRANSLATIONAL IMPLICATIONS

The convergence of anti-angiogenic and anti-metastatic effects on a shared set of molecular targets, including VEGF/VEGFR2, HIF-1alpha, NF-kappaB, STAT3, and MMP-2/MMP-9, carries significant implications for the design of future cancer therapeutic strategies. From a theoretical standpoint, our findings challenge the conventional paradigm of targeting angiogenesis and metastasis as separate biological processes, instead suggesting that phytochemicals may offer a unified pharmacological approach to simultaneously disrupt two critical hallmarks of malignancy. This dual mechanism is particularly compelling because it addresses the clinical reality that tumors often develop resistance to single-pathway inhibitors, such as anti-VEGF antibodies, by upregulating alternative angiogenic or metastatic pathways [51]. The multi-targeted nature of phytochemicals, which simultaneously modulate multiple nodes within interconnected signaling networks, may therefore reduce the likelihood of acquired resistance, a hypothesis that warrants direct experimental investigation.

Practically, these findings suggest that phytochemicals could be developed as adjuvant therapies to complement conventional chemotherapy, radiation, or immunotherapy. For example, curcumin or resveratrol could be administered alongside standard-of-care regimens to patients with high-risk breast or colorectal cancers, where the risk of both angiogenesis-driven tumor growth and metastasis is substantial. The quantitative potency observed in preclinical models, such as curcumin's 86 percent suppression of MMP-2 activity [50] and resveratrol's 50 to 60 percent inhibition of endothelial adhesion, provides a rationale for dose-finding studies in humans. However, the translation of these preclinical findings to clinical practice faces substantial hurdles, primarily related to the poor bioavailability and rapid metabolism of many phytochemicals. The promising results from studies using nano-formulations, such as nano-resveratrol and low molecular weight fucoidan [49], indicate that advanced drug delivery systems may be essential to achieve therapeutically relevant concentrations at tumor sites. Policymakers and funding agencies should therefore prioritize research into formulation science and pharmacokinetic optimization as a prerequisite for clinical translation.

CONCLUSION

This systematic review of preclinical evidence demonstrates that specific phytochemical classes, particularly polyphenols such as curcumin, resveratrol, epigallocatechin-3-gallate, genistein, and quercetin, function as dual inhibitors of tumor angiogenesis and metastasis through convergent molecular mechanisms. Our synthesis confirms the central hypothesis that these compounds concurrently restrict tumor blood supply and suppress the metastatic cascade by targeting overlapping signaling pathways, including the VEGF/VEGFR2 axis, HIF-1alpha, NF-kappaB, STAT3, and MMP-2/MMP-9. The contribution of this work lies in systematically establishing a unified mechanistic framework that challenges the conventional separation of anti-angiogenic and anti-metastatic strategies, thereby providing a rationale for developing phytochemical-based adjuvant therapies that address two critical hallmarks of malignancy simultaneously.

The translational potential of these findings is tempered by significant methodological limitations, including the preclinical nature of the evidence, potential publication bias, and the well-documented poor bioavailability of many phytochemicals. Future research should prioritize the development of advanced formulation strategies, such as nano-encapsulation, to overcome pharmacokinetic barriers, and should employ more clinically relevant models, including patient-derived xenografts and genetically engineered mouse models, to validate these dual effects in complex tumor microenvironments. Longitudinal clinical studies are ultimately necessary to establish safety, tolerability, and efficacy in human populations, with biomarker-driven patient stratification potentially enhancing therapeutic outcomes. The convergence of anti-angiogenic and anti-metastatic mechanisms on a core set of molecular targets offers a promising foundation for the rational design of phytochemical-based interventions, though rigorous translational research remains essential to bridge the gap between preclinical promise and clinical application.

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