Emodin as a multi-target modulator of tumor angiogenesis: Mechanisms, microenvironment and therapeutic potential (Review)

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Abstract. Angiogenesis is central to tumor development and metastasis as it facilitates oxygen and nutrient supplies to cancer cells. The inhibition of angiogenic pathways is a commonly used strategy in the treatment of cancer, usually through inhibitory actions that first lead to the targeted suppression of the key pro-angiogenic factor, vascular endothelial growth factor (VEGF), and its upstream regulator, hypoxia-inducible factor 1α (HIF-1α). Emodin, a common anthraquinone derivative of natural origins, has a variety of actions to inhibit angiogenesis, which include the ability to inhibit the expression of VEGF, as well as the ability to reverse the stabilization of HIF-1α and inhibit tumor microvessel branching. Moreover, emodin is recognized for pathways other than those involving VEGF, such as fibroblast growth factor and platelet-derived growth factor, which affect endothelial cell proliferation and pericyte recruitment. Emodin can facilitate vessel destabilization by acting on several angiopoietins, leading to the disruption of the function of the tumor vasculature. These mechanisms collectively obstruct tumor vascularization, deprive tumor cells of vital nutrients and prevent cancer progression. *In silico* molecular docking analyses suggest that emodin may interact with the ATP-binding pocket of VEGFR-2 and the oxygen-dependent degradation domain of HIF-1α. Although these findings support a plausible multi-target inhibitory profile for emodin, direct biochemical and structural validation of these interactions remains limited. Pre-clinical studies to date have determined it to be a critical anti-angiogenic agent and a synergistic agent in combination with chemotherapy and/or targeted therapies that can be administered to patients. Future studies are required to address bioavailability issues, target the associated resistance mechanisms, and explore mechanisms with which to increase its efficacy as an adjuvant in the treatment of cancer.

Contents

1. Introduction

Angiogenesis is the formation of new blood vessels from the existing network and is critical for tumor progression (1). Solid tumors require a continuous supply of oxygen and nutrients from the vascular system to support rapid growth. Angiogenesis allows the vascular system to create a large surface area (2). It also enables cancer cells to enter the circulation and travel to distant locations, which is crucial for metastasis and disease progression (3). Given its role in cancer pathology, angiogenesis has received considerable attention as a potential target for therapy (4). Molecular pathways that regulate tumor angiogenesis form a complex network involving various proteins, among which vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1α (HIF-1α) are among the

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most significant. VEGF is a clearly defined, major regulator of endothelial cell growth and movement, whilst HIF-1α is instigated under conditions of hypoxia, regulates VEGF and promotes constant angiogenic signaling (5). There are also distinct pathways for additional pro-angiogenic factors, including fibroblast growth factors (FGFs) and platelet-derived growth factors (PDGFs), that contribute to tumor vascular development (6). The inhibition of these pathways has shown promise in suppressing tumor growth and improving patient outcomes (7,8).

Emodin, a naturally occurring anthraquinone derivative found in various medicinal plants, has garnered significant interest for its anti-proliferative, pro-apoptotic and anti-metastatic properties (9). Recent research has demonstrated that emodin interferes with the VEGF and HIF-1α signaling pathways, thereby exhibiting anti-angiogenic activity (10). In addition to regulating these pathways, emerging evidence suggests that emodin may also modulate FGF-associated signaling (11), thereby suppressing endothelial cell proliferation, while the indirect regulation of PDGF-mediated pathways may influence pericyte recruitment (12,13). Given the essential roles of FGF and PDGF signaling in early angiogenesis, vessel maturation and vascular stability, these mechanisms may collectively contribute to impaired neovascularization, although further mechanistic studies are required to establish direct interactions. Molecular docking analyses have predicted the favorable binding of emodin to VEGFR-2 (14) and HIF-1α, suggesting, but not yet structurally confirming, that emodin may function as a multi-target inhibitor of angiogenesis (15). The inhibition of these angiogenesis pathways by emodin could limit tumor vascularization and slow the growth of cancer cells (16).

Despite increasing evidence supporting its therapeutic potential, a comprehensive mechanistic and translational understanding of emodin in tumor angiogenesis remains incomplete. In this context, the present review aimed to elucidate the translational potential of emodin, its pharmacokinetic limitations, emerging drug delivery strategies and prospective applications in combination therapy. Furthermore, it addresses resistance mechanisms associated with anti-angiogenic therapy and discusses how such challenges may be mitigated through multi-targeted agents, such as emodin. Overall, the present review provides a comprehensive perspective on the anti-angiogenic properties of emodin, integrating molecular, cellular and translational insights to support its development as a therapeutic agent in the treatment of cancer.

Literature search strategy. A literature search was carried out on the PubMed, Web of Science, Scopus, and Google Scholar databases to identify relevant studies that have focused on the role of emodin in cancer and tumor angiogenesis. The search involved using combinations of key words and related terms, such as 'emodin', 'cancer; 'tumor angiogenesis', 'anti-angiogenic', 'VEGF', 'VEGFR-2', 'HIF-1α', and related angiogenic signaling pathways/molecules. The first search was primarily on studies published since 2015 until May, 2026 (until the time of manuscript submission). Relevant seminal publications prior to 2015, particularly those from ~2000-2015, were also identified and added when they were instrumental in providing interesting or foundational mechanistic, historical or background information on the topics addressed. Therefore, literature selection included recent data with the inclusion of some earlier studies that provided a mechanism of the action and the evolution of studies concerning emodin and its anti-angiogenic activity in cancer.

2. Mechanisms of tumor angiogenesis

Angiogenesis is closely controlled, which permits the further development of the tumor, as it provides cancer cells with a means of survival, access to oxygen and nutrients, and enables metastasis (17). One of the most critical mediators of this process is VEGF; it promotes the growth, movement and development of new blood vessels by endothelial cells (18). VEGF interacts with endothelial cell receptors (VEGFR-1 and VEGFR-2) to stimulate downstream cell survival, permeability and tube formation (19).

High VEGF expression is commonly observed in tumors that are aggressive, and which exhibit rapid vascular growth and resistance (20). HIF-1α is a regulated transcription factor that increases VEGF expression under hypoxic conditions that is inherent to solid tumors (21). Under these hypoxic conditions, HIF-1α is stabilized and translocates to the nucleus, facilitating the expression of VEGF and other pro-angiogenic genes (22). This type of adaptation allows tumors to circumvent oxygen shortage by inducing the development of new blood vessels (23). In addition to VEGF regulation, HIF-1α also regulates other angiogenic factors, including PDGF and FGFs (Fig. 1) thereby enhancing the angiogenic response (24,25).

Moreover, apart from directly signaling tumor angiogenesis through molecules, such as VEGF, tumor angiogenesis is extended even further through interactions of the cancer cells with endothelial cells (24). Oncogenic cells localize VEGF and other angiogenic proteins, which recruit endothelial cells and pericytes to form a disorganized vasculature (26,27). The tumor microenvironment releases growth factors from endothelial cells to enhance the survival of cancer cells and their invasive potential (28). Collectively, this dualistic exchange of information between malignant cells and the vascular component creates an auto-proliferative pro-angiogenic loop which potentiates cancer progression while promoting resistance to anti-cancer approaches (29). Understanding these mechanisms is essential for the development of effective anti-angiogenesis strategies, including those targeting VEGF and HIF-1α (30).

3. Anti-angiogenic effects of emodin

Targeting angiogenesis is a viable therapeutic approach for the treatment of cancer, where restricting blood vessel development and tumor perfusion means limiting potential tumor growth and increasing metastasis (31). Emodin can inhibit the proliferation and migration of endothelial cells and their ability to form microvessels. These processes are essential for maintaining the vascular network that functions for tumors (32). Understanding the associated molecular mechanisms of action of emodin may provide insight into its potential as an anti-angiogenic agent in cancer therapy (33).

Inhibition of VEGF and HIF-1α pathways. Emodin demonstrates its anti-angiogenic properties by inhibiting key molecular regulators of tumor vascularization, particularly

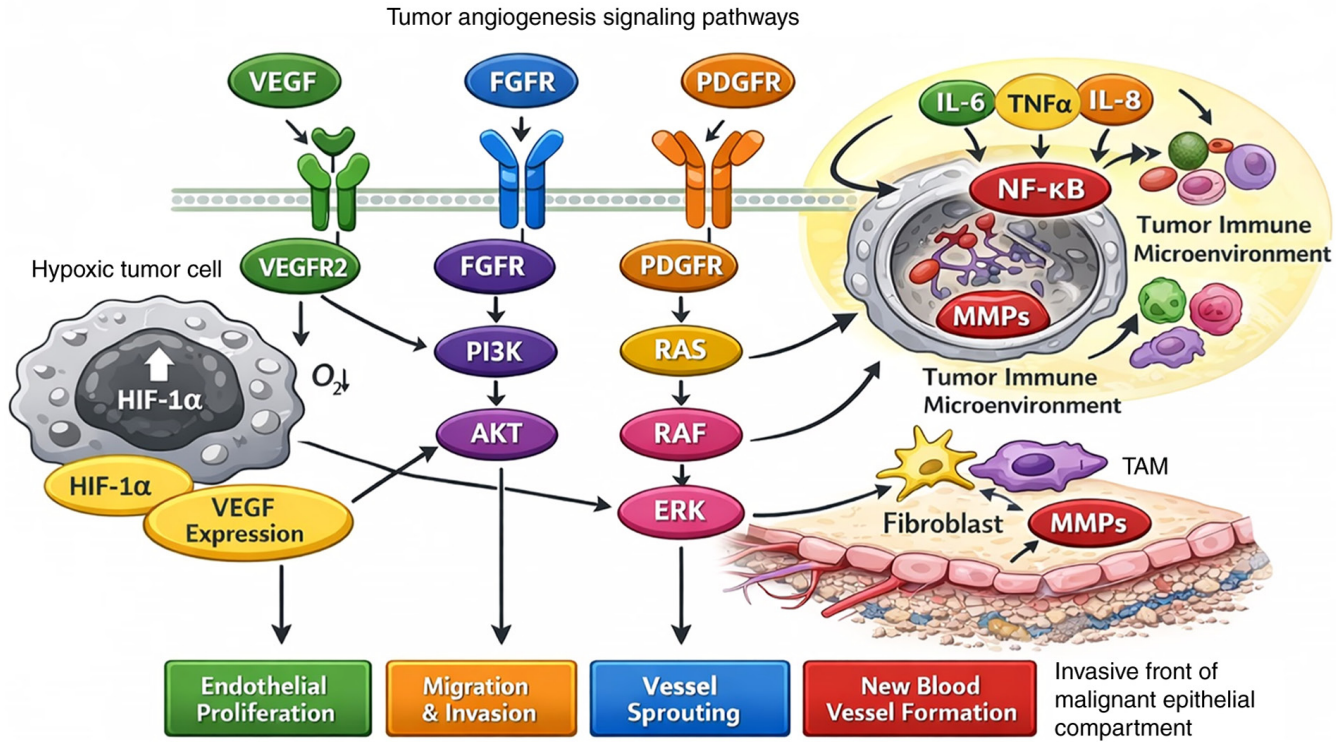

Figure 1. Hypoxia stabilizes HIF-1α, promoting its nuclear translocation and induction of VEGF and other pro-angiogenic factors. VEGF/VEGFR2, together with FGF and PDGF signaling, activate PI3K/AKT and other pathways, driving endothelial proliferation, migration and vessel sprouting. In parallel, NF-κB activation within the nucleus induces secretion of pro-inflammatory cytokines (IL-6, TNF-α and IL-8), modulating the tumor immune microenvironment. MMPs, primarily released by tumor-associated macrophages and fibroblasts, mediate extracellular matrix remodeling at the invasive front, facilitating tumor invasion and neovascularization. HIF-1α, hypoxia-inducible factor 1-α; VEGF, vascular endothelial growth factor; MMP, matrix metalloproteinase; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor.

the HIF-1α and VEGF pathways (34). VEGF is a critical pro-angiogenic factor that induces endothelial cell proliferation, migration and survival through receptor stimulation. Emodin can inhibit VEGF expression at different levels (Fig. 2) (35). At the mechanistic level, emodin downregulates VEGF transcription by targeting key transcription factors involved in VEGF gene activation. These factors are HIF-1α and NF-κB under hypoxic or inflammatory conditions (36).

By acting on these transcriptional and inflammatory processes, emodin reduces VEGF secretion from tumor cells, resulting in less VEGF available for receptor binding and activation of the angiogenic signaling pathway (37). Emodin also prevents autophosphorylation of the VEGFR-2 receptor and interferes with downstream signal transduction, including the PI3K/Akt and MAPK/ERK pathways (Fig. 3), which are essential for endothelial cell survival and migration (37,38). All these processes act in synergy to inhibit the angiogenic capacity of the tumor by inhibiting endothelial cell proliferation, tubule formation and microvessel sprouting (39). While these processes decrease the vascular density, the extent of inhibition may vary with cancer type and tumor microenvironment.

Some tumors may overcome VEGF inhibition by activating alternative pro-angiogenic pathways, including FGF and PDGF, thereby contributing to resistance to VEGF-targeted therapies (40). Consequently, compensatory activation of such pathways could potentially limit the efficacy of emodin as a single-agent anti-angiogenic therapy. The effects of emodin on HIF-1α, a master regulator of angiogenesis when exposed to hypoxia has been previously reported (41). In a hypoxic environment, HIF-1α is stabilized and translocated to the nuclei, where it binds to the hypoxia-responsive element sites located on the VEGF promoter, increasing its production (42). However, available evidence suggests that emodin suppresses HIF-1α primarily by reducing its biosynthesis and associated upstream signaling, rather than by enhancing HIF-1α degradation (43).

In addition, emodin has been reported to downregulate HIF-1α mRNA expression, suggesting that its effects on HIF-1α may involve regulation at the transcriptional level, in addition to its effects on HIF-1α protein expression (44). By suppressing HIF-1α, emodin may consequently attenuate downstream hypoxia-responsive programs involved in metabolic adaptation, tumor invasion, and angiogenesis, including VEGF (41). The multi-target functionality of emodin may provide a complementary approach to inhibiting angiogenesis and potentially overcoming resistance associated with single-pathway targeting; however, key limitations remain (45). Notably, the anti-angiogenic effects of emodin have primarily been investigated in pathological or tumor-associated angiogenic settings, and its effects on physiological vascular processes remain insufficiently characterized (46).

Effects on additional angiogenic pathways. The established effects of emodin on inhibiting VEGF and HIF-1α are only part of its anti-angiogenic effects (47), which also extend to

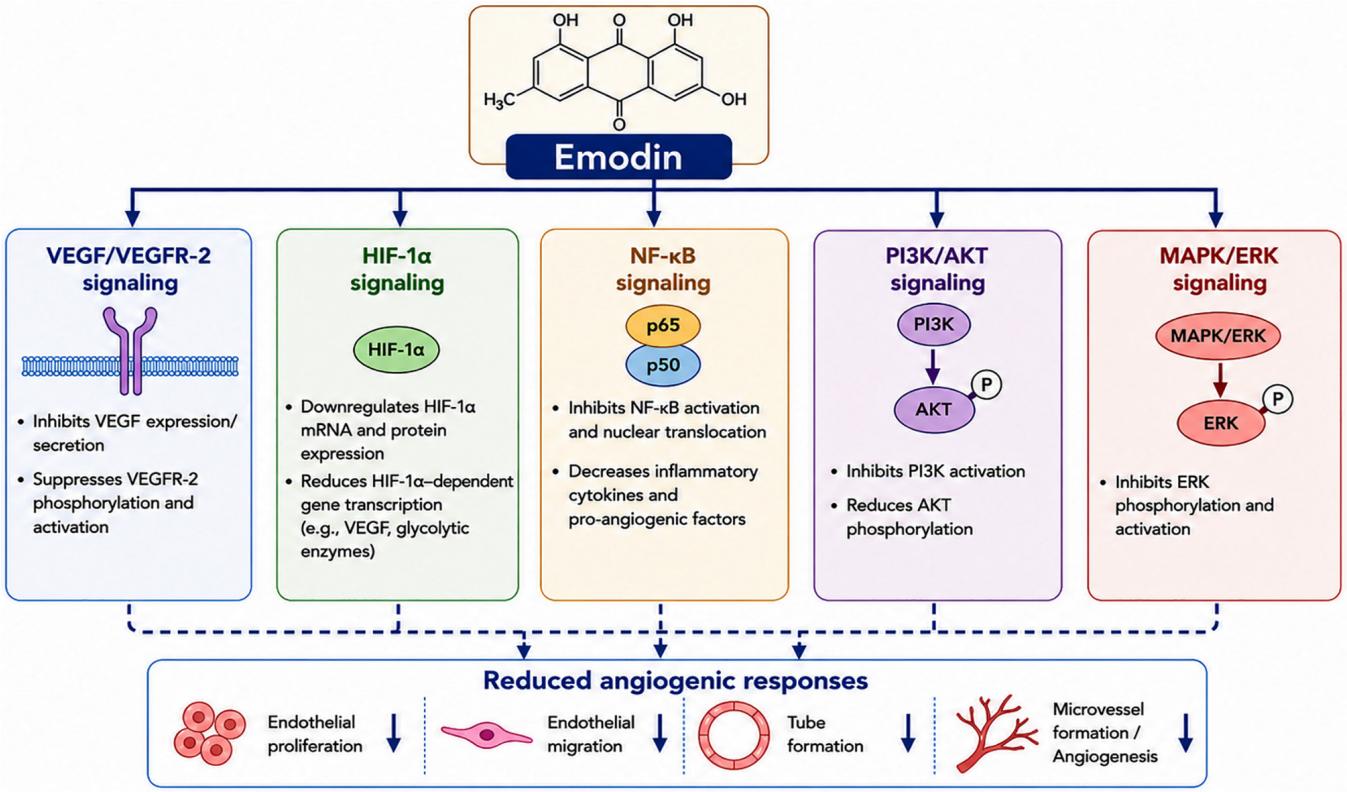

Figure 2. Multi-pathway modulation of tumor angiogenesis by emodin. Emodin has been reported to modulate multiple signaling pathways involved in tumor angiogenesis, including VEGF/VEGFR-2 (32,38,65), HIF-1α (41,43,44,112), NF-κB (36,52), PI3K/AKT and MAPK/ERK signaling (53,55,60). These effects are associated with reduced endothelial cell proliferation, migration, tube formation and microvessel formation. The pathways are presented as partially independent signaling nodes, rather than as a single linear mechanistic cascade, and the figure does not imply direct physical interaction between emodin and each molecular target. Solid arrows indicate experimentally reported effects, whereas dashed arrows indicate proposed or inferred downstream relationships based on available evidence. VEGF, vascular endothelial growth factor; HIF-1α, hypoxia-inducible factor 1-α.

additional pro-angiogenic pathways beyond direct VEGF signaling (48). As PDGF-B/PDGFRβ signaling is essential for pericyte recruitment and tumor-vessel stabilization (49), the modulation of this pathway could potentially contribute to the vascular-disruptive effects of emodin; however, direct evidence that emodin inhibits PDGF-mediated pericyte recruitment remains limited (Fig. 3). Emodin has been shown to inhibit the basic FGF-induced proliferation and migration of endothelial cells (32), indicating that its anti-angiogenic activity extends to the FGF pathway. However, FGF signaling can serve as a compensatory mechanism in tumors subjected to VEGF-targeted inhibition, whereby increased FGF activity may sustain angiogenesis and contribute to resistance to anti-VEGF therapies (50). The extent to which emodin can counteract such compensatory FGF signaling remains insufficiently characterized. It may also exert inhibitory effects on angiopoietin signaling, which regulates endothelial cell activation and vessel destabilization during tumor angiogenesis (51), although direct evidence for this remains limited as well.

Emodin, apart from silencing pro-angiogenic signaling pathways, directly inhibits angiogenesis by inducing endothelial cell apoptosis and reducing vessel formation (52). The overall suppression of tumor vascularization may be achieved by the combined effect of inhibition of angiogenic signaling and the induction of endothelial apoptosis. Emodin also directly inhibits the formation of microvessels. *In vivo* experiments have demonstrated that tumors treated with emodin exhibit decreased microvessel density, a lower expression of CD31 and CD105, and disorganized vascular networks, leading to insufficient oxygen and nutrient supply and increased hypoxia (52). Mechanistically, emodin hinders the migration of endothelial cells by interacting with cytoskeletal organization, including the PI3K-Cdc42/Rac1 pathway and the associated cytoskeletal remodeling (53). In addition to the VEGFR-2 signaling described above, emodin has been shown to inhibit the phosphorylation of VEGFR-1 and VEGFR-3 (54,55). Moreover, emodin suppresses the activities of matrix metalloproteinases (MMPs; MMP-2 and MMP-9), thus inhibiting angiogenesis-driven extracellular matrix remodeling (56). These findings highlight the complexity of tumor angiogenesis, and support the further investigation of additional angiogenic pathways that may influence the response to emodin.

Potential for preventing tumor growth through anti-vascular mechanisms. Emodin can suppress tumor growth by inhibiting angiogenesis, a process essential for tumor development (57). Tumors also depend on neovascularization; this is a process whereby new blood vessels are formed to supply the necessary oxygen and nutrients to support the swift growth of the tumor. Emodin has been shown to effectively deplete tumors by blocking key angiogenesis pathways, resulting in reduced proliferation and increased cell death (58). One of the primary effects of tumor inhibition by emodin is vascular destabilization. Through the inhibition of the VEGF and HIF-1α

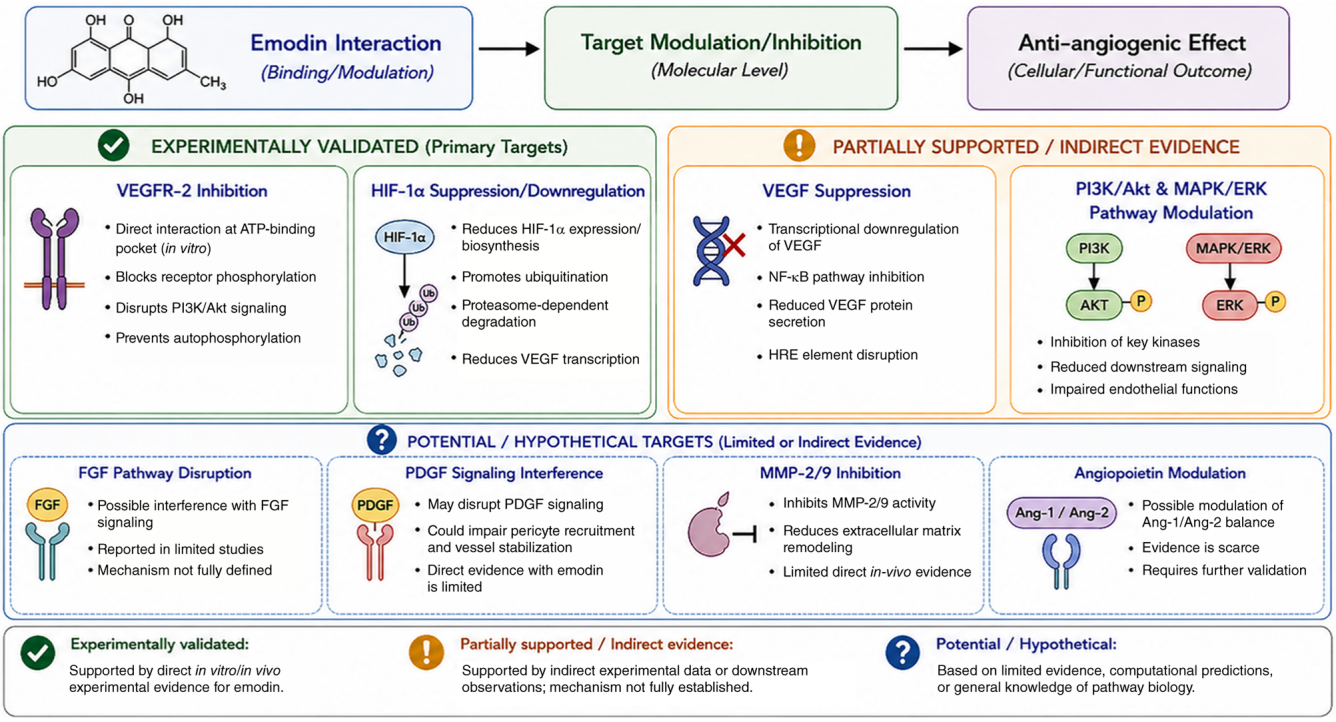

Figure 3. Emodin targets angiogenesis through multiple molecular mechanisms. The figure summarizes the molecular targets and signaling pathways modulated by emodin and categorizes them according to the strength of available evidence. Targets shown in the green boxes are supported by direct experimental evidence, whereas those in the orange boxes are supported primarily by indirect or downstream evidence. Targets in the blue boxes represent potential or hypothetical interactions for which direct experimental evidence remains limited. The diagram does not imply direct physical binding of emodin to all targets unless experimentally demonstrated. The following references correspond to studies supporting the effects of emodin on the indicated targets or signaling pathways: VEGFR-2 inhibition (32,38,65), HIF-1α suppression/downregulation (41,43,44,112), VEGF suppression (47,52,58), PI3K/AKT and MAPK/ERK signaling (53,55,60), FGF pathway disruption (11,25), PDGF signaling interference (12,49), MMP-2/9 inhibition (73) and angiopoietin modulation (73,75).

pathways, emodin not only blocks the development of new blood vessels, but also causes a regression of small vessels that already exist in the tumor. This leads to vascular hypoxia, where the microenvironment of the tumor becomes even more deprived of oxygen, and this process activates several metabolic stresses and induces the apoptosis of the cancer cells (59). The ability of emodin to inhibit endothelial cell survival signaling, particularly through the suppression of the PI3K/Akt pathway, also compromises the structural integrity of the vascular component of the cancer, further diminishing its capabilities to support tumor growth (60).

Critical appraisal of preclinical evidence. The aforementioned preclinical data are mostly positive and are not homogeneous in their composition. Reported effects are derived from a combination of cancer cell lines, xenograft models, and, in some instances, non-mammalian systems (such as zebrafish angiogenesis assays) with varying vascular architecture and drug exposure kinetics. The effective concentrations *in vitro* (usually low micromolar range) and dosages *in vivo* (usually tens of mg/kg, i.p. injection) differ widely across studies (61,62) and are often not justified by prior pharmacokinetic studies, making it challenging to determine a dose-response curve or optimum therapeutic window. Equally important, the available studies have primarily focused on tumor-associated angiogenesis, with limited attention to the effects of emodin on normal vasculature. This distinction is particularly relevant as the VEGF/HIF-1α and PI3K/Akt signaling pathways targeted by emodin are fundamental regulators of vascular biology and participate in both physiological and pathological angiogenesis (62). Therefore, the specificity of emodin for pathological vs. physiological angiogenesis remains unresolved (63). Although emerging evidence indicates that emodin can modulate biological processes involved in normal tissue repair, including skin cell migration relevant to wound healing (64), its potential off-target effects on physiological angiogenesis, such as wound healing and reproductive angiogenesis, have not yet been comprehensively investigated. A reliable estimate of the therapeutic index of emodin requires addressing these gaps, particularly by using uniform dosages in similar tumor models, as well as incorporating normal-tissue vascular endpoints.

4. Molecular docking and structural insights

Molecular docking analyses provide further insight into the anti-angiogenic mechanisms of emodin, particularly its predicted binding interactions with VEGFR-2, a central kinase involved in angiogenic signaling (65). Computational simulations suggest that emodin may occupy the ATP-binding pocket of VEGFR-2, disrupt its dimerization and downstream signaling (65). Binding energies ranging from -7.0 to -9.0 kcal/mol have been reported for anthraquinone-class VEGFR2 inhibitors, indicating moderate to strong predicted binding affinity comparable to that reported for several small-molecule kinase inhibitors (66,67). Lending further

plausibility to this mechanism, a structurally related anthraquinone derivative, PPemd26, has been experimentally shown to inhibit VEGFR2 signaling and suppress VEGF-A-induced endothelial cell proliferation, migration and tube formation, although this finding derives from a synthetic emodin-class derivative rather than emodin itself, and reflects experimental, rather than computational evidence (68). These findings provide plausible mechanistic hypotheses regarding the anti-angiogenic activity of emodin, although they remain computational predictions that require experimental confirmation.

The anthraquinone scaffold of emodin provides several advantages compared to synthetic inhibitors (69). The planar, fused ring structure allows for π-π stacking with aromatic residues of target proteins, which may enhance binding affinity and potentially improve selectivity (69). Unlike many synthetic inhibitors that are designed to engage a single molecular target, emodin's natural scaffold may possess the structural flexibility to interact with multiple proteins, thereby providing a broader inhibitory profile (70). While these structural characteristics support the rationale for emodin as a promising multi-target therapeutic candidate, they should be interpreted alongside the current limitations of computational prediction methods and therefore require rigorous biochemical and structural validation (71).

Accordingly, although molecular docking and network pharmacology studies have provided valuable mechanistic hypotheses regarding the anti-angiogenic activity of emodin, these computational approaches should not be interpreted as definitive evidence of direct target engagement (72). Current biological evidence largely demonstrates that emodin suppresses VEGF expression (58), inhibits VEGFR-2 phosphorylation (32), and reduces HIF-1α accumulation in cellular and animal models (41); however, these downstream effects do not necessarily confirm direct physical binding to either protein. Such observations may also result from the modulation of upstream signaling pathways, transcriptional regulation, altered protein stability, or indirect network-level effects, as broadly characterized for VEGF/VEGFR signaling (27). Therefore, the available evidence supports the notion that emodin is a promising putative multi-target modulator of angiogenesis rather than an experimentally validated direct inhibitor of VEGFR-2 or HIF-1α (73). Future studies integrating computational predictions with biochemical and structural validation are essential for establishing its precise molecular mechanism of action (74).

5. Synergistic effects with chemotherapy and targeted therapies

Emodin has demonstrated notable potential as an adjuvant to conventional cancer therapies due to its ability to modulate angiogenic signaling pathways and tumor vascular structure. Insufficient oxygen delivery is a key feature of solid tumors with abnormal vasculature, contributing to cancer cell resistance to chemotherapy and radiation (75). Given the demonstrated anti-angiogenic and vascular-disruptive effects of emodin, it is plausible that emodin could favorably alter tumor vasculature to improve cytotoxic drug delivery, although this specific mechanism has not yet been directly tested for emodin. Preclinical studies have reported synergistic interactions between emodin and established anticancer drugs, including doxorubicin and cisplatin (76,77). These combinations may improve drug efficacy and, in the case of doxorubicin, have been shown to reverse acquired chemoresistance. As emodin suppresses pro-survival pathways and pathways that induce epithelial-mesenchymal transition (EMT), it may reduce metastatic spread, when combined with traditional chemotherapeutic agents such as doxorubicin (76).

Pharmacokinetic challenges. Although there is sufficient evidence for the effectiveness of the activity of emodin, the anti-angiogenic actions of emodin do not affect all tumors equally. Some cancers may recruit compensatory pathways to bypass the inhibitory effects of emodin (78,79). The extended inhibition of the tumor vasculature can inadvertently select for hypoxia-resistant and more aggressive cancer cells, which will have a greater propensity to be invasive and metastatic (80). A major challenge to the therapeutic development of emodin is its limited bioavailability and unfavorable pharmacokinetic profile. Although effective in preclinical models, its low solubility and limited metabolic stability *in vivo* may limit its therapeutic efficacy (81). While a low aqueous solubility limits gastrointestinal dissolution and absorption, a low intestinal permeability limits systemic availability, leading to low plasma concentrations after oral intake (82). In addition, extensive hepatic first-pass metabolism, primarily involving phase II conjugation reactions, such as glucuronidation and sulfation (83), can rapidly convert emodin into inactive or less active metabolites, thereby contributing to high hepatic clearance and limited systemic exposure of the active compound.

Animal pharmacokinetic profiling has indicated a high hepatic extraction ratio and rapid plasma elimination, with reported half-lives of ~1 to 3 h, consistent with extensive first-pass clearance (84). Consequently, achieving therapeutically relevant concentrations at target tissues may be challenging, while dose escalation may be limited by the potential for toxicity associated with increased systemic exposure. These pharmacokinetic limitations greatly reduce the therapeutic potential of emodin that can be attained *in vivo* and highlight the necessity for formulation approaches or chemical modifications to reach sustained exposure and enhanced tissue distribution (85). Advanced drug delivery systems, including nanoparticle-based formulations, may help improve bioavailability and maintain therapeutically relevant concentrations in tumor tissues (86). Further studies are required to establish optimal dosing regimens and exposure levels that can achieve therapeutically relevant concentrations, while minimizing systemic toxicity (87,88).

Drug delivery and formulation strategies. The pharmacokinetic limitation of emodin is being addressed by exploring several formulation strategies to improve its therapeutic efficacy. Liposomal encapsulation has the capability of enhancing aqueous solubility (89), protecting emodin against early hepatic metabolism (90), and allowing localization into tumor tissues by passive targeting mechanisms. Another promising approach that can enhance the pharmacokinetic profile of emodin is polymeric nanoparticle systems, such as poly (lactic-co-glycolic acid) and PEGylated carriers (91). Biodegradable polymer nanoparticles have controlled release

kinetics enhancing circulation half-life and protecting emodin against enzymatic breakdown, consequently maintaining therapeutic levels and improving anti-angiogenic effects (92). These systems may also take advantage of the enhanced permeability and retention effect (93), whereby preferential accumulation of nanoparticle-encapsulated emodin occurs in tumor tissues with permeable vasculature.

Apart from nanotechnology-based strategies, prodrug design strategies are also being studied to enhance the pharmacological properties of emodin. Tumor specificity and reduced off-target exposure may be further improved by incorporating tumor-homing moieties (e.g., RGD peptide or folate) on the ligand-functionalized nanoparticles (94). Another potential way of increasing treatment efficacy is the use of prodrug, where emodin is chemically altered to enhance its oral absorption and metabolic stability and is selectively activated by the tumor microenvironment (95). Taken together, these approaches reflect preclinical potential; however, nanoparticle toxicity, scalability in manufacturing and regulatory issues continue to pose significant clinical translation challenges.

6. Effects on cancer growth

In addition to its anti-angiogenic effects, emodin has also been found to exert direct inhibitory effects on tumor cell proliferation and survival. A number of *in vitro* and *in vivo* experiments have shown emodin to suppress the growth of various cancer cells such as liver, colon, lung (96-99), colorectal (100), pancreatic (101) and gastrointestinal cancer (88). These anticancer effects are mediated by a variety of molecular mechanisms, such as the induction of apoptosis, cell cycle arrest, and the alteration of several critical signaling pathways that can help tumors to survive. Emodin induces programmed cell death, which is known to be one of the primary mechanisms through which it inhibits tumor growth (102). Emodin has also been reported to lead to the activation of intrinsic apoptotic processes through mitochondrial dysfunction, the enhancement of reactive oxygen species production, as well as to the activation of caspase-dependent signal transduction (103). Through these mechanisms, crucial cellular proteins may be broken down and eventually, tumor cells may undergo apoptosis. Furthermore, to this *in vitro* and *in vivo* evidences, animal research has demonstrated that emodin disrupts the tumor microenvironment function nutrient and oxygen supply (58), further sensitizing cancer cells to apoptosis.

Current clinical evidence and the translational gap. Although preclinical studies provide strong support of the anticancer properties of emodin (104), direct clinical evidence for its anti-angiogenic effects remains absent. Current evidence supporting the anti-angiogenic activity of emodin is derived solely from *in vitro* tests, mouse xenograft models, and, in some experiments, zebrafish angiogenesis models, which thus far have not reached the phase of human testing for this indication (104). This is in contrast to other well-stablished anti-angiogenic drugs, such as bevacizumab, sunitini, and sorafenib that have been tested in multiple phase II/III trials with clearly defined efficacy and safety endpoints (105). However, the lack of clinical evidence for emodin does not detract from the mechanistic rationale presented in the present review, but rather should be viewed as a hypothesis-generating rather than clinically substantiated claim for emodin's therapeutic usefulness (106). Formal pharmacokinetic and toxicology studies in larger animal models, followed by early-phase clinical trials to establish safety and pharmacodynamic biomarker changes (such as circulating VEGF levels, tumor perfusion imaging) will be required to bridge the gap before any efficacy claims can be made in a patient population (56).

Tumor heterogeneity and resistance to anti-angiogenic therapy. The differential activity of emodin in different tumors (Table I) may be attributed to various resistance mechanisms that are commonly observed with anti-angiogenic agents in general. First, compensatory pathway activation can cause tumors to continue angiogenesis without the involvement of VEGF/HIF-1α by upregulating other pro-angiogenic factors, such as FGF, PDGF, or angiopoietin-2, effectively bypassing the pathways emodin primarily targets (107). Second, some tumors, particularly in highly vascularized organs like the liver and lung, can maintain perfusion without relying heavily on new vessel formation, making angiogenesis inhibitors such as emodin intrinsically less effective (108,109). Third, hypoxia can induce metabolic reprogramming of tumor cells to reside in an environment that is more glycolytic and/or enhance the presence of subpopulations of tumor cells tolerant to hypoxia, which diminishes the therapeutic effects of vascular disruption (110). Fourth, chronic hypoxia could also induce EMT and cancer stem cell enrichment as indirect effects of anti-angiogenic pressure, resulting in the production of a more aggressive and resistant tumor cell population.

These mechanisms are not mutually exclusive and likely act in combination, which may explain why the anti-angiogenic efficacy of emodin varies substantially across the tumor models summarized in Table I, and underscores the rationale for combining emodin with agents targeting complementary resistance pathways rather than relying on VEGF/HIF-1α inhibition alone.

7. Conclusion and future perspectives

Angiogenesis is a key contributor to tumor development, as it allows cancer cells to adapt to hypoxic stress and continue uncontrolled growth. Even though ample progress has been made in anti-angiogenic therapies, the clinical response is frequently impaired due to resistance mechanism, toxicity and countermeasures, such as the activation of compensatory signaling pathways. In that regard, the identification of multi-target agents that can control the complex tumor networks is of significant therapeutic value. The present review supports the premise that emodin functions as a multi-target metabolic and angiogenic modulator through several mechanisms. Across preclinical models, emodin has demonstrated anti-angiogenic activity involving VEGF/HIF-1α signaling as well as additional angiogenic pathways, although the magnitude of these effects varies across tumor types and biological contexts (32,33).

Preclinical evidence also suggests that emodin may enhance the activity of conventional and targeted anticancer therapies, supporting its investigation as a combination partner, rather than solely as a single-agent anti-angiogenic

Table I. Reported activity of emodin in various tumor types.

Cancer type	Experimental model	Molecular target(s)	Anti-angiogenic effect	Level of evidence	(Refs.)
Hepatocellular carcinoma	*In vivo* xenograft	VEGF, HIF-1α	Reduced microvessel density; disrupted vascular perfusion	*In vivo* (preclinical)	(38)
Glioblastoma	*In vivo* xenograft	HIF-1α, VEGF	Decreased microvessel density; reduced hypoxia-driven angiogenesis	*In vivo* (preclinical; indirect evidence)	(37,45)
Breast cancer	*In vitro* + *in vivo* xenograft/ TNBC mouse model	VEGF transcription, EMT-associated pathways	Reduced endothelial proliferation and vascular development; suppressed metastasis	*In vitro* + *in vivo* (preclinical)	(35,58)
Colorectal/colitis-associated tumorigenesis	*In vitro/in vivo*	VEGF/VEGFR2	Suppressed colorectal cancer growth and invasion associated with VEGFR2 inhibition	*In vitro* + *in vivo* (preclinical)	(65)
Anaplastic thyroid cancer	*In vitro* + *in vivo*	TRAF6-mediated signaling	Suppressed angiogenesis and metastasis	*In vitro* + *in vivo* (preclinical)	(39)
Osteosarcoma	*In vitro* human osteosarcoma cells + *in vivo* nude-mouse xenograft	SIRT1/HMGB1-associated VEGF signaling	Reduced HMGB1-induced VEGF production and tumor angiogenesis; increased SIRT1 expression and deacetylation activity	*In vitro* + *in vivo* (preclinical)	(48)
VEGFR-2/HIF-1α (target-level, cross-tumor)	Molecular docking (*in silico*)	VEGFR-2 ATP-binding pocket; HIF-1α oxygen-dependent degradation domain	Predicted binding interactions consistent with kinase/transcription-factor inhibition	*In silico* (computational; direct experimental target validation unavailable)	(71-74)

VEGF, vascular endothelial growth factor; HIF-1α, hypoxia-inducible factor 1-α; EMT, epithelial-mesenchymal transition; TNBC, triple-negative breast cancer.

compound (111-115). The poor aqueous solubility, as well as the low systemic availability, high first-pass metabolism and rapid elimination of emodin, however, limit its potential application as a therapeutic agent (81,84-85). These limitations could make it difficult to reach sufficient and long-lasting exposures at target tissues even if activity is demonstrated in preclinical studies.

Thus, formulation and drug delivery strategies are critical approaches to enhance the therapeutic potential of emodin. Liposomal and polymeric nanoparticle-based system can improve solubility, protect emodin from premature metabolism, prolong systemic exposure and may improve tumor accumulation, and prodrug approach may improve absorption and metabolic stability (89-95). Nevertheless, these strategies are largely in the preclinical stages and challenges such as formulation stability, toxicity associated with nanoparticles, manufacturing scalability, regulatory issues, and reproducible tumor targeting need to be studied further. Therefore, it is advisable to perform a systematic pharmacokinetic/pharmacodynamic evaluation to confirm that the optimized formulation would yield a desirable therapeutic effect, which is reflected in increased exposure.

In parallel, tumor heterogeneity and adaptive responses including hypoxia-associated signaling, activation of alternative angiogenic pathways, and vessel co-option, may limit the durability of anti-angiogenic effects and contribute to resistance (107,116). Future studies are thus required to integrate pharmacokinetic optimization with mechanistic evaluation of angiogenic signaling and tumor-microenvironment responses. Biomarkers capable of identifying tumors most likely to respond, potentially including VEGF-dependent or HIF-1α-active phenotypes and relevant tumor-microenvironment characteristics, may also facilitate patient stratification and clinical translation (56). Overall, integrating improved formulation and pharmacokinetic strategies with mechanistic and biomarker-guided approaches will be important for determining whether the promising preclinical activity of emodin can be translated into clinically relevant anticancer therapies.

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Authors' contributions

SK and RN were involved in the study design. SD, AD and KL were involved in the literature search, preparation of the rough draft, and in the subsequent writing of the manuscript. JK, JSA, LK and AGB were involved in the review and editing of the manuscript. AGB and LK supervised the study. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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