

Advances in targeting vasculogenic mimicry in malignant tumors using monomeric compounds from Traditional Chinese Medicine (Review)

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Abstract. Vasculogenic mimicry (VM), a pivotal mechanism underlying tumor resistance to anti-angiogenic therapies, presents key challenges in oncology treatment. Chinese herbal monomers exhibit notable therapeutic potential in cancer treatment, particularly regarding their capacity to inhibit tumor VM formation. However, to the best of our knowledge, no comprehensive literature review has systematically explored the specific molecular mechanisms through which Chinese herbal monomers exert their anti-VM effects in tumor cells, to date. Therefore, the present systematic review evaluates the therapeutic potential of 46 natural monomers derived from Traditional Chinese Medicine (TCM) across 16 cancer

types, through a comprehensive analysis of 64 preclinical studies. TCM monomers inhibit VM formation by modulating key signaling pathways (PI3K/AKT, MAPK and Notch) and downregulating key molecular markers (vascular endothelial-cadherin, MMPs and hypoxia inducible factor-1 α). The identified compounds exhibit multi-target regulatory capabilities through epithelial-mesenchymal transition suppression, matrix metalloproteinase inhibition and angiogenesis-related signaling pathway modulation. These findings elucidate the mechanistic basis for the anti-VM effects of TCM and propose a novel therapeutic avenue to potentially overcome resistance in malignant tumors, highlighting the translational value of phytochemical-based combination therapies in precision oncology.

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Abbreviations: AMF, amentoflavone; ART, artesunate; AST, astilbin; ATR, atractylonin; AU, aucubin; BBB, blood-brain barrier; BC, bladder cancer; CaMKII, calmodulin-dependent kinase II; CCL2/CCR2, C-C motif chemokine ligand 2/receptor 2; CM, choroidal melanoma; c-Met, cellular-mesenchymal epithelial transition; CSLCs, cancer stem cell-like cells; DHA, dihydroartemisinin; ECM, extracellular matrix; EGCG, epigallocatechin gallate; EMT, epithelial-mesenchymal transition; EVO, evodiamine; FMN, formononetin; GBM, glioblastoma; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; MAT, Matrine; NSCLC, non-small cell lung cancer; PAAD, pancreatic adenocarcinoma; PPEE, *Paris polyphylla* ethanol extract; Pris, pristimerin; RES, resveratrol; RGWE, *Ruta graveolens* water extract; RPS, rhizoma *Paridis saponins*; Sal-A, salvianolic acid A; SAV1, Salvador homolog-1; SHH, Sonic hedgehog; TCM, Traditional Chinese Medicine; VM, vasculogenic mimicry

Key words: vasculogenic mimicry, Chinese medicine monomers, cancer types, malignant tumor, epithelial-mesenchymal transition

Contents

1. Introduction
2. Search and selection criteria
3. Inhibition of multiple cancer VM processes by herbal monomers
4. Discussion
5. Conclusion

1. Introduction

Vasculogenic mimicry (VM), first described in 1999, refers to the ability of highly aggressive melanoma cells to generate fluid-conducting channels independent of the vascular network of the tumor. In this distinctive phenomenon, tumor cells imitate endothelial cells in a way that promotes tumor growth, invasion and metastasis.

VM exhibits certain key characteristics: i) Staining patterns. VM channels stain negative for vascular endothelial markers such as CD34/CD31 but positive for periodic acid-Schiff, which is specific to the extracellular matrix (ECM); ii) absence of endothelial cells. Unlike conventional blood vessels, these VM-derived channels lack vascular

endothelial cells; iii) ECM remodeling. These channels are essentially microcirculation pathways reshaped by the ECM; and iv) interconnection with tumor micro-vessels. VM channels connect with the micro-vessels of the tumor, allowing for blood flow. Furthermore, the relatively thin walls of these VM channels provide a conducive environment for tumor cell infiltration and extravasation, bolstering the migratory and metastatic potential of tumor cells. The presence of VM often predicts a highly aggressive tumor and a worse prognosis (1). Since VM does not depend on traditional angiogenic pathways, anti-angiogenic drugs, such as sorafenib and bevacizumab, have a limited effect on VM-forming tumors, potentially affecting tumor response to therapy (2).

Despite the pivotal role of anti-angiogenic therapies in cancer management, their clinical efficacy remains markedly limited by VM-mediated resistance. Current anti-VEGF strategies frequently fail to target these VM channels due to their distinct molecular regulation, creating an urgent need for innovative therapeutic approaches. Emerging evidence positions Traditional Chinese Medicine (TCM) monomers as multifaceted agents capable of concurrently addressing angiogenesis and VM (3). The present systematic analysis of preclinical studies revealed that TCM monomers demonstrate cross-cancer efficacy in VM suppression. This multi-target capacity circumvents resistance mechanisms and may synergize with existing anti-angiogenic regimens.

2. Search and selection criteria

Web of Science (<https://www.webofscience.com/>), PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) and China National Knowledge Infrastructure (CNKI; <https://www.cnki.net/>) databases, employed as mining tools, were searched for the following terms: ['vasculogenic mimicry' in the database (title/abstract) and (extracted compounds)] and ['neoplasms' or all its synonyms (cancer) in the database (title/abstract)]. Publications up to April 1, 2025, were imported into Zotero (version 6.0; Hongzhou Intelligent Technology Co., Ltd.). After removing duplicates, 2,358 initial records were screened, yielding 64 eligible studies based on the following criteria: i) *In vitro/in vivo* experiments; ii) VM quantification; and iii) TCM monomer intervention. Case reports and reviews were excluded.

3. Inhibition of multiple cancer VM processes by herbal monomers

The mechanisms by which various TCM monomers inhibit VM formation in malignant tumors were summarized (Fig. 1).

These monomers potentially inhibit the aggressiveness and metastasis of liver and breast cancer, as well as other solid tumors, by disrupting the VM-associated tumor microenvironment. Their multi-target mechanism of action enhances chemotherapy sensitivity and reduces drug resistance. Due to their natural origin, these compounds offer advantages such as low toxicity and high efficacy, providing a novel strategy for the treatment of tumors. Fig. 2 displays the role of herbal compounds in the formation of VM. Table I summarizes the anti-VM mechanisms of Chinese herbal components across different cancer types.

Liver cancer. Hepatocellular carcinoma (HCC) had a global incidence of 865,269 cases in 2022 and is the third most common cause of mortality worldwide (4). Metabolism-related diseases, such as alcoholic liver disease, diabetes and non-alcoholic fatty liver disease, are emerging as a cause of HCC (5). Anti-angiogenic drugs, such as sorafenib and bevacizumab, have exhibited limited long-term efficacy in HCC, with VM being associated with the malignant phenotype and prognosis of HCC, as well as resistance to such treatments (6). TCM monomers inhibit VM formation through multi-target mechanisms.

Melittin. Melittin, a 26-residue cationic peptide from bee venom, exhibits notable anticancer properties (7). Melittin can reverse epithelial-mesenchymal transition (EMT) in HCC induced by CoCl₂. Notably, it reduced hypoxia inducible factor (HIF)-1 α , p-AKT, VEGF, MMP-2 and MMP-9 expression. *Ex vivo and in vivo* investigations underscored its robust biological efficacy in inhibiting VM formation. This inhibitory effect was primarily mediated through the suppression of the HIF-1 α /AKT signaling pathway (8).

Myricetin (MYR). MYR is a flavonoid commonly found in bayberry and other plants (9). MYR, a highly potent antagonist of production of anthocyanin pigment 1 (PAP1), inhibits VM formation in HCC cells. Molecular docking studies revealed that MYR binds specifically to Leu258 and Thr261 residues within the PAP1 protein (10,11). The regulatory effects of MYR on EMT are mediated by upregulating E-cadherin protein levels and downregulating intracellular expression of VEGFR1 and VEGFR2.

Others. Daurisoline (DAS) is a bisbenzylisoquinoline alkaloid isolated from *Menispermum dauricum* and rhizoma Menispermi. DAS inactivates Ras homolog family member A (RhoA)/Rho-associated coiled-coil containing protein kinase 2 (ROCK2), inhibits AKT and ERK-p38 MAPK signaling, induces HCC cell apoptosis and inhibits VM formation. The combined use of DAS with sorafenib can potentially improve the sensitivity of sorafenib (12).

The ethanolic extract of *Elephantopus scaber* (ESEE), a traditional medicinal plant, contains a diverse array of bioactive compounds, including epifriedelinol, lupeol, flavonoids and glucosides (13). ESEE exhibits potent antitumorigenic effects in HepG2 HCC cells by inhibiting the expression of MMP-2, VEGFA and MMP-9. Furthermore, it reduces the number and area of cell-formed luminal structures *in vitro*, thereby suppressing HCC cell proliferation, metastasis and VM formation (14).

Celastrus orbiculatus (oriental bitter-sweet), a member of the Celastraceae family, is a medicinal plant whose vines and stems possess notable antitumor and anti-inflammatory activities. *Celastrus orbiculatus* is also called Dragon Grass or Yellow Vine (15). The main target of *Celastrus orbiculatus* extract in liver cancer is ephrin type-A receptor 2 (EphA2), a gene associated with VM in liver cancer cells. Knockdown or overexpression of EphA2 markedly affects VM in liver cancer, with the expression levels of VE-cadherin (VE-CAD) changing with EphA2 changes (16).

Although the aforementioned natural products demonstrate inhibitory effects on EMT and VM in combating HCC, their mechanisms of action exhibit distinct pharmacological profiles: Melittin and ESEE converge on the HIF-1 α /AKT signaling axis; MYR functions exclusively as a PAP1 antagonist; DAS predominantly targets the RhoA/ROCK2-MAPK

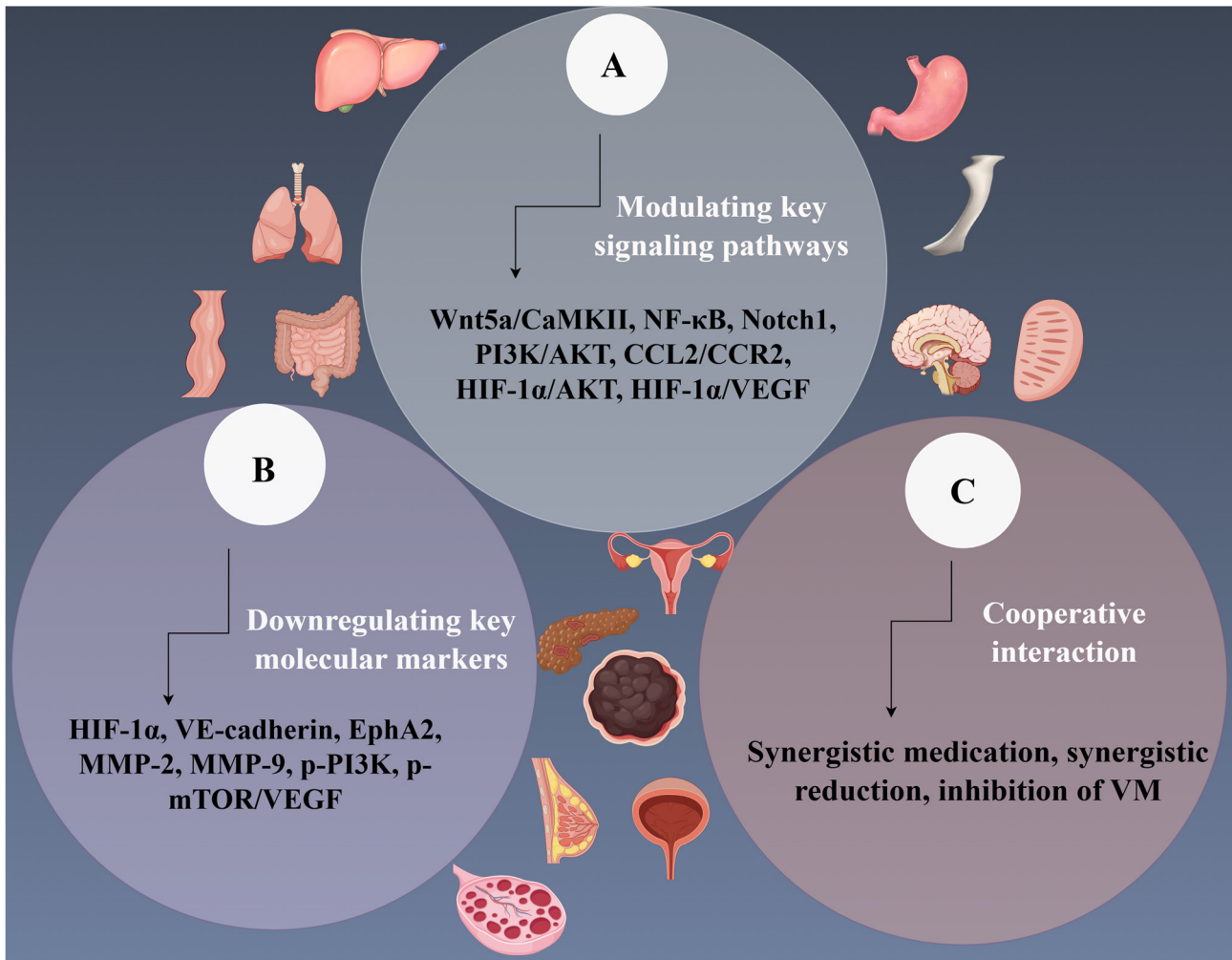


Figure 1. Mechanisms associated with the inhibition of VM formation in malignant tumors by various TCM monomers. The mechanisms of VM inhibition by herbal monomers include the following three main aspects: A) Modulating key signaling pathways; B) downregulating key molecular markers; and C) cooperative interaction. VM, vasculogenic mimicry; TCM, Traditional Chinese Medicine; HIF-1α, hypoxia inducible factor-1α; CaMKII, calmodulin-dependent kinase II; CCL2/CCR2, C-C motif chemokine ligand 2/receptor 2; EphA2, ephrin type-A receptor 2.

pathway; while *Celastrus orbiculatus* exerts its effects through EphA2 gene modulation. However, notable limitations persist in current research paradigms. First, mechanistic investigations remain insufficiently characterized, with a lack of direct target validation studies. Second, pharmacokinetic profiles and *in vivo* efficacy data remain limited, which creates key obstacles for clinical translation. Challenges including suboptimal bioavailability, tumor microenvironment heterogeneity and lack of standardized extraction protocols collectively present substantial barriers to clinical application. Therefore, the path from bench to bedside for these compounds remains fraught with complexities requiring systematic resolution.

Lung cancer. Lung cancer caused 1,817,172 cases of mortality worldwide in 2022 (4). Accounting for ~85% of cases, non-small cell lung cancer (NSCLC) is the predominant form of lung cancer, with high mortality and low survival rates, necessitating novel therapeutic options (17). VM is widespread in lung cancer and associated with poor prognosis (18).

Baicalein. Derived from the medicinal plant *Scutellaria baicalensis* (TCM), baicalein is a therapeutically active flavonoid and has been extensively studied for its potent anticancer

effects across various malignancies, such as lung cancer, liver cancer and colorectal cancer, acting at the molecular and cellular levels (19). In A549 lung cancer cells, baicalein dose-dependently suppressed the mRNA expression of VM-associated genes, including VE-CAD, EphA2, MMP14, MMP2, MMP9, PI3K and laminin subunit γ -2 (LAMC2). *In vitro* and *in vivo* investigations have demonstrated that baicalein suppresses VM formation in NSCLC by targeting the RhoA/ROCK signaling cascade (20).

Lycorine. Derived from the Amaryllidaceae family, the natural alkaloid lycorine exhibits diverse pharmacological properties encompassing anti-inflammatory, antifungal, antiviral, antimalarial and antitumor activities (21). Lycorine inhibits Salvador homolog-1 (SAV1) degradation and activates mammalian Sterile 20-like kinase 1 (MST1), thereby reversing SAV1 deficiency in lung cancer cells. MST1 activation suppresses oncogene-driven transcription and attenuates AKT and NF- κ B signaling pathways, markedly inhibiting lung cancer cell proliferation, metastasis and VM formation (22).

Others. Curcumin, a natural polyphenolic phytoalexin, has attracted notable scientific interest due to its pleiotropic biological activities (23). Curcumin-docetaxel micelles

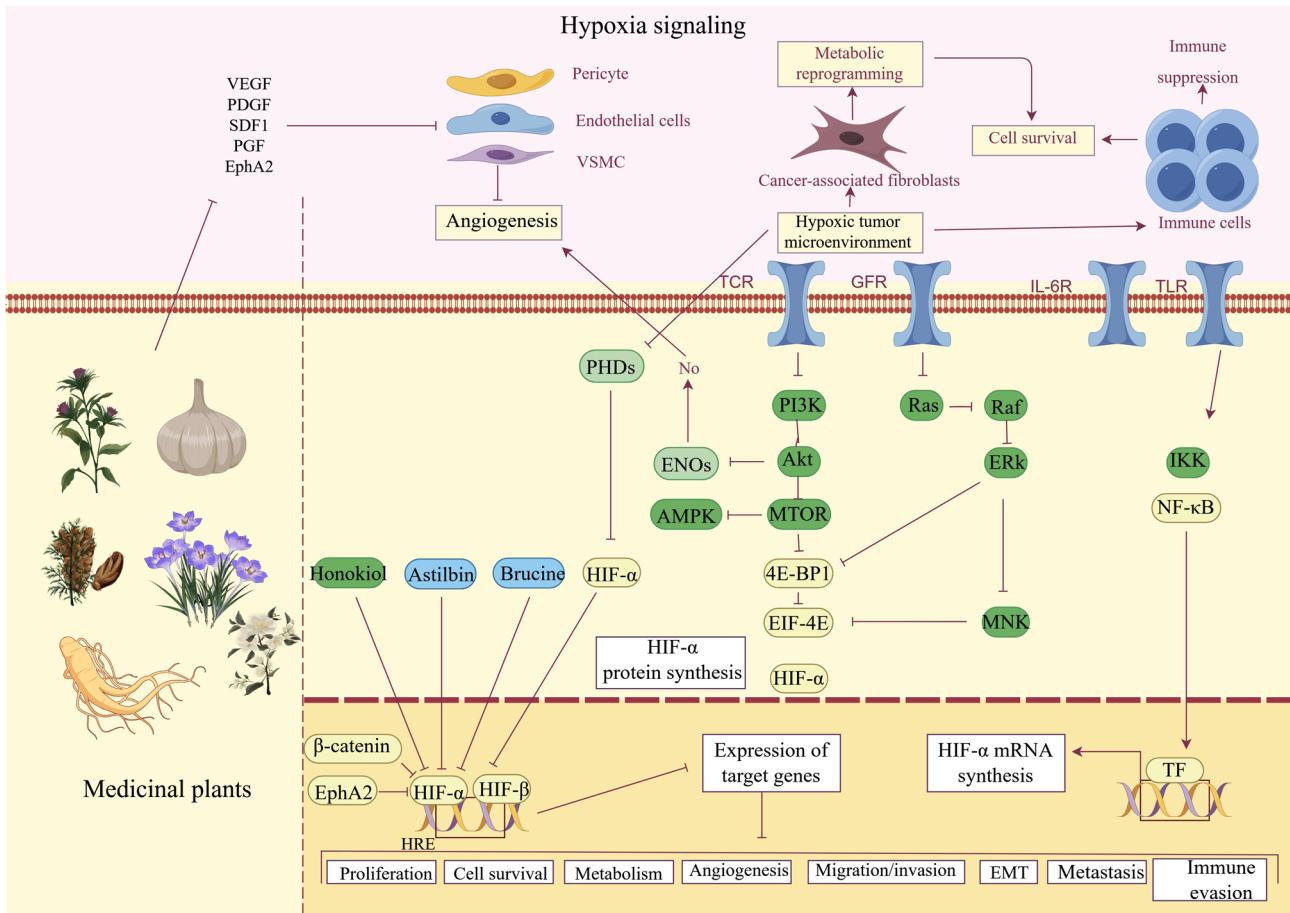


Figure 2. Mechanisms by which herbal compounds inhibit VM by affecting hypoxia signaling pathways and their associated molecules. Under hypoxic conditions, PHDs activity is inhibited, leading to enhanced stability of HIF- α protein and formation of a complex with HIF- β , which activates downstream target genes (e.g., VEGF, PDGF and SDF1), driving angiogenesis, metabolic reprogramming, cell survival and immune suppression. In addition, hypoxic conditions can activate PI3K/AKT/mTOR, Ras/Raf/ERK, AMPK-mTOR and NF- κ B axes to promote HIF- α synthesis (e.g., blocking HIF- α degradation) and activate downstream effector molecules (e.g., VEGF monoclonal antibody or receptor inhibitor), and a variety of compounds isolated from herbs can reverse this process by blocking the relevant signaling pathways and their associated factors. VM, vasculogenic mimicry; PHDs, prolyl hydroxylases; HIF, hypoxia inducible factor; PDGF, platelet-derived growth factor; SDF1, stromal cell-derived factor-1; AMPK, AMP-activated protein kinase; EMT, epithelial-mesenchymal transition; EphA2, ephrin type-A receptor 2; VSMC, vascular smooth muscle; TF, transcription factor; ENOs, endothelial nitric oxide synthase; HRE, hypoxia response element; TCR, T cell receptor; GFR, glomerular filtration rate; TLR, target lesion revascularization; PGF, placental growth factor.

modified with octreotide downregulated MMP-2 and HIF-1 α , exhibited robust cytotoxicity and suppressed VM in A549 lung cancer cells (24). Tetramethylpyrazine (TMP), a bioactive alkaloid compound isolated from TCM herbs, has demonstrated diverse pharmacological properties over the past few decades. The therapeutic efficacy of TMP has been validated across various diseases, such as urinary tract infections, cystitis, pneumonia, diarrhea and otitis media, underscoring its clinical potential (25). TMP reduced the number of lumens and crossovers in A549 lung cancer stem cell-like cells (CSLCs) *in vitro* under hypoxia, mediated through modulation of the hepatocyte growth factor (HGF)/cellular-mesenchymal epithelial transition (c-Met) signaling axis (26).

Dihydroartemisinin (DHA) is an active metabolite of artemisinin and its derivatives artesunate (ARTs) (27). DHA downregulates VE-CAD mRNA and protein expression levels and inhibits VM formation in NSCLC A549 and H3255 cells (28). Salvianolic acid A (Sal-A), an active component of the traditional herbal medicine *Salvia miltiorrhiza*, markedly attenuates the activity and invasiveness of NSCLC cells and

suppresses capillary-like structure formation. These effects are mediated by the downregulation of key VM-associated proteins, including EphA2, VE-CAD and MMP2, as well as the inhibition of phosphorylated PI3K (p-PI3K), p-AKT and p-mTOR within tumor cells (29).

Baicalin, DHA and Sal-A demonstrate inhibitory effects on VM formation in NSCLC through multifaceted mechanisms involving modulation of VM-related core genes (e.g., VE-CAD, EphA2 and MMP2/9) and suppression of the PI3K/AKT/mTOR signaling pathway. Notably, baicalin exhibits specificity for the RhoA/ROCK pathway, while Sal-A further enhances its anti-VM activity by inhibiting mTOR phosphorylation (30). In parallel, lycorine reverses SAV1 deficiency through activation of the MST1 kinase and concurrent suppression of the AKT/NF- κ B axis, whereas curcumin uniquely targets VM formation in CSLCs by regulating the HGF/c-Met signaling cascade (22). Furthermore, nanomedicine-based strategies synergistically augment anti-VM efficacy through dual actions: Downregulation of MMP-2/9 and HIF-1 α , modulation of E-cadherin expression and enhanced

Table I. Specific molecular mechanisms underlying the inhibition of VM in multiple cancer types by TCM monomers.

TCM monomer	Cancer models	Concentrations	Model	Key targets	Effects	(Refs.)
Melittin	SMIMC7721, Huh7 and Hep G2 cells	2 and 4 $\mu\text{g/ml}$; 24 h	<i>In vitro</i>	HIF-1 α ↓, p-AKT↓, VEGF↓, MMP-2↓ and MMP-9↓	Inhibiting VM formation	(10)
Myricetin	Male BALB/c nude mice HCC cells	50 and 100 $\mu\text{g/kg/d}$ 80 $\mu\text{mol/l}$; 48 h	<i>In vivo</i> <i>In vitro</i>	E-cadherin↓, VEGFR1↓ and VEGFR2↓	Inhibiting HCC cells invasion, metastasis, VM formation and angiogenesis	(12,13)
Daurisoline	Female BALB mice HCC cells	15 and 30 mg/kg/d 5, 10 and 20 $\mu\text{mol/l}$; 48 h	<i>In vivo</i> <i>In vitro</i>	AKT↓, ERK-p38↓, RhoA↓ and ROCK2↓	Inducing apoptosis, inhibiting VM and improving drug sensitivity	(14)
Ethanolic extract of <i>Elephantopus scaber</i>	Male BALB/c nude mice HepG2 cells	20 mg/kg/d 75 and 125 $\mu\text{g/ml}$; 48 h	<i>In vivo</i> <i>In vitro</i>	VEGFA↓, MMP-2↓ and MMP-9↓	Inhibiting cell proliferation, migration and VM formation	(16)
Celastroribiculatus extraction	MHCC97-H cells and HepG2 cells Male BALB/c nude mice	80 $\mu\text{g/ml}$; 48 h -	<i>In vitro</i> <i>In vivo</i>	MMP2↓, MMP9↓, Twist1↓ and EphA2↓	Inhibiting VM formation	(18)
Baicalein	A549 cells Male BALB/c nude mice	60 $\mu\text{mol/l}$; 72 h 10 mg/kg/d	<i>In vitro</i> <i>In vivo</i>	VE-CAD↓, EphA2↓, MMP14↓, MMP2↓, MMP9↓ and PI3K↓	Inhibiting VM formation	(22)
Lycorine	SPC-A-1 and A549 cells Female nude mice	60 $\mu\text{mol/l}$; 72 h 10 mg/kg/d	<i>In vitro</i> <i>In vivo</i>	SAV1↑	Inhibiting cell proliferation, migration and VM formation	(24)
Curcumin	A549 cells Male BALB/c nude mice	10 $\mu\text{g/ml}$; 48 h 150 $\mu\text{g/kg/d}$	<i>In vitro</i> <i>In vivo</i>	MMP-2↓ and HIF-1 α ↓	Inhibiting VM formation	(26)
Tetramethylpyrazine	A549 cancer stem-like cells	100 and 400 $\mu\text{mol/l}$; 24 and 48 h	<i>In vitro</i>	HGF↓ and c-Met↓	Inhibiting stem cell-like cell VM formation	(28)

Table I. Continued.

TCM monomer	Cancer models	Concentrations	Model	Key targets	Effects	(Refs.)
Dihydroartemisinin	A549 and H3255 cells	50 $\mu\text{mol/l}$; 24 and 48 h	<i>In vitro</i>	E-cadherin \uparrow , N-cadherin \downarrow and VE-CAD \downarrow	Inhibiting cell growth, proliferation, migration and VM formation	(32)
Salvianolic acid A	A549 and H1299 cells	50 $\mu\text{mol/l}$; 24 h	<i>In vitro</i>	EphA2 \downarrow , VE-CAD \downarrow , p-PI3K \downarrow , p-AKT \downarrow , p-mTOR \downarrow and MMP2 \downarrow JNK \downarrow and ERK \downarrow	Inhibiting cell invasion and VM formation	(33)
Matrine	CT26 SW480 and KM12 cells	4 mmol/l; 24 h	<i>In vitro</i>		Inhibiting VM formation	(42)
Amentoflavone	HCT-116 cells	150 $\mu\text{mol/l}$; 24 h	<i>In vitro</i>	HIF-1 α \downarrow , β -catenin \downarrow , VEGF \downarrow , vimentin \downarrow and Snail \downarrow	Inhibiting cell proliferation and VM formation	(44)
Delphinidin	SW620 cells	180 $\mu\text{mol/l}$; 48 h	<i>In vitro</i>	RhoA \downarrow , ROCK \downarrow and VEGF \downarrow	Inhibiting VM and inducing apoptosis	(45)
Evodiamine	HCT-116 cells	0.375, 0.75 and 1.5 $\mu\text{mol/l}$; 24 h	<i>In vitro</i>	HIF-1 α \downarrow , VE-CAD \downarrow , VEGF \downarrow , MMP2 \downarrow and MMP9 \downarrow	Inhibiting tumor growth and VM formation	(47)
Saffronin	Female BALB/c nude mice NCI-N87 and Hs- 746T GC cells	10 mg/kg/d	<i>In vivo</i>			(53)
Dihydroartemisinin	HGC-27 and SGC- 7901 cells BALB/c thymus nude mice	100 $\mu\text{mol/l}$; 24 h 320 $\mu\text{mol/l}$; 24 and 48 h 50 mg/kg/d	<i>In vitro</i> <i>In vivo</i>	HIF-1 α \downarrow , Notch1 \downarrow , SHH \downarrow , PTCH2 \downarrow and Gli1 \downarrow FGF2 \downarrow and FGFR1 \downarrow	Inhibiting VM formation Inhibiting VM formation	(54)
Formononetin	MGC-803 cells	80 $\mu\text{mol/l}$; 24 h	<i>In vitro</i>	HIF-1 α \downarrow and VEGF \downarrow	Inhibiting VM formation and inducing apoptosis	(55)
Ginsenoside Rg3	SGC7901 cells	160 mg/l; 72 h	<i>In vitro</i>	GSK-3 β \downarrow , Wnt2B \downarrow , β -catenin \downarrow , MMP2 \downarrow and MMP9 \downarrow	Inhibiting VM formation	(57)
Aucubin	MGC803 cells	80 $\mu\text{mol/l}$; 24 h	<i>In vitro</i>	RhoA \downarrow , ROCK1 \downarrow , N-cadherin \downarrow , vimentin \downarrow and VE-CAD \downarrow	Inhibiting EMT and VM formation	(59)
Jaceosidin	HGC-27 cells	40 $\mu\text{mol/l}$; 24 h	<i>In vitro</i>	SphK1 \downarrow and SIP \downarrow	Inhibiting VM formation	(60)

Table I. Continued.

TCM monomer	Cancer models	Concentrations	Model	Key targets	Effects	(Refs.)
Artemether	BMVEC/U87 cells	30 μ mol/l; 24 h	<i>In vitro</i>	HIF-1 α ↓, MMP-2↓ and PI3K↓	Inhibiting VM formation and inducing apoptosis	(67)
Isoliquiritigenin	ICR mice SHG44 cells	1 mg/kg/d 160 μ mol/l; 24 h	<i>In vivo</i> <i>In vitro</i>	MMP-2↓, VEGF↓ and EphA2↓	Inhibiting VM formation	(72)
Moroidin	U87 cells and U251 cells	2 μ mol/l; 24 h	<i>In vitro</i>	p-ERK↓, β -catenin↓ and MMP-9↓	Inhibiting EMT and VM formation	(73)
Rhizoma <i>Paridis</i> saponins	143B and MG-63 cells Male BALB/c nude mice	1 μ g/ml; 24 h 100 mg/kg/d	<i>In vitro</i> <i>In vivo</i>	p-PI3K↓, p-mTOR↓, MMP-2↓, MMP-14↓, Ln5 γ 2↓ and Ln5 γ 2x↓	Inhibiting VM formation and metastasis	(81,83)
Curcumin	S180 cells	20 μ mol/l; 72 h	<i>In vitro</i>	MMP-2↓ and MMP-9↓	Inhibiting VM formation	(82)
Artesunate	OCM-1 cells and C918 cells	60 μ mol/l; 24 h	<i>In vitro</i>	HIF-1 α ↓, VEGF↓ and PDGF↓	Inhibiting VM formation	(89-92)
Luteolin	C918 and HUVEC cells	25 μ mol/l; 24 h	<i>In vitro</i>	p-PI3K↓, p-AKT↓ and VEGF↓	Inhibiting VM lumen formation	(93)
Brucine	MDA-MB-231 cells	1 μ mol/l; 24 h	<i>In vitro</i>	MMP-2↓, MMP-9↓ and EphA2↓	Disrupting the cytoskeleton and inhibiting VM formation	(100)
Triptonide	MDA-MB-231, MDA-MB-468 and BT-549 cells	10 nmol/l; 72 h	<i>In vitro</i>	Twist1↓, Notch1↓, VEGFR2↓ and VE-CAD↓	Inhibiting VM formation	(102)
Astilbin	NOD-SCID female mice MCF-7 and MDA- MB-231 cells	3 mg/kg/d 300 μ mol/l; 24 h	<i>In vivo</i> <i>In vitro</i>	HIF-1 α ↓, VEGF↓, VE-CAD↓, N-cadherin↓, MMP-2↓	Inhibiting VM formation	(104)
Ginsenoside Rg3	SW-1990 and PCI- 35 cells	500 and 750 μ mol/l; 48 h	<i>In vitro</i>	miR-204↑ and DVL3↓	Inhibiting VM formation	(111,112)
Cinobufagin	SKOV3 cells Female BALB/c nude mice	7.5 μ g/ml; 24 h 1.5, 3 and 6 mg/kg/d	<i>In vitro</i> <i>In vivo</i>	MMP9↓, MMP14↓ and LAMC2↓	Inhibiting macrophage polarization and inhibiting VM formation	(116)

Table I. Continued.

TCM monomer	Cancer models	Concentrations	Model	Key targets	Effects	(Refs.)
Catechins	SKOV3 and ES-2 cells	100 ng/ml 24 h	<i>In vitro</i>	MMP2 ↓ and TGF-β↑	Inhibiting VM formation	(119)
Sinomenine	A2780 cells	8 mmol/l; 24 and 48 h	<i>In vitro</i>	VEGF↓, EphA2↓, MMP-9↓, MMP-2↓, CXCR4↓ and p-STAT3↓	Inhibiting VM formation	(121)
Pristimerin	HeLa cells	2.5 μmol/l; 48 h	<i>In vitro</i>	SHH↓, Gli1 mRNA↓, VEGF-A↓, VE-CAD↓ and Gli1↓	Inhibiting VM formation	(125)
Honokiol	HeLa cells	100 μg/ml; 24 h	<i>In vitro</i>	p-EGFR↓, MMP-2↓, MMP-9↓, EphA2↓, VEGF↓ and CDH2↓	Inhibiting VM formation	(120)
Ligustilide	EC-109 cells	200 μmol/l; 24 h	<i>In vitro</i>	Cyclin-D1↓, Bcl-2↓, RhoA↓, ROCK↓, p21↑, Bax↑ and caspase-3↑	Inhibiting VM formation	(124)
Atractylonin	T24 cells	160 mg/l; 48 h	<i>In vitro</i>	RhoA↓ and ROCK1↓	Inhibiting VM formation	(127)
Lupeol	B16-F16 cells	100 μmol/l; 24 h	<i>In vitro</i>	CD-133↓	Inhibiting VM formation	(132)
Epigallocatechin gallate	PC-3 cells	80 μmol/l; 24 h	<i>In vitro</i>	VE-CAD↓, Twist↓, N-cadherin↓ and AKT↓	Inhibiting VM formation	(137)
Kaempferol	PC-3 cells	15 μmol/l; 24 h	<i>In vitro</i>	PSA↓, TMPRSS2↓ and TMEPA1↓	Inhibiting VM formation	(139)
Resveratrol	PC-3 cells	40 μmol/l; 24 h	<i>In vitro</i>	MMP-2↓, VE-CAD↓, EphA2↓ and 5γ-2↓	Inhibiting VM formation	(141)

↓, downregulated; p, phosphorylated; HIF-1α, hypoxia inducible factor-1α; CaMKII, calmodulin-dependent kinase II; CCL2/CCR2, C-C motif chemokine ligand 2/receptor 2; c-Met, cellular-mesenchymal epithelial transition; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; HGF, hepatocyte growth factor; MAT, Matrine; SAV1, Salvador homolog-1; SHH, Sonic hedgehog; TCM, Traditional Chinese Medicine; VM, vasculogenic mimicry; HCC, hepatocellular carcinoma; VE-CAD, VE-cadherin; EphA2, ephrin type-A receptor 2; PSA, protein-specific antigen; TMPRSS2, transmembrane serine protease 2; TMEPA1, transmembrane androgen-inducible protein 1; RhoA, Ras homolog family member A; ROCK, Rho-associated coiled-coil containing protein kinase; CDH2, cadherin-2; Gli1, glioma-associated oncogene homolog 1; PTCH2, patched-2; CXCR4, C-X-C motif chemokine receptor 4; LAMC2, laminin subunit γ-2; miR, microRNA; DVL3, dishevelled segment polarity protein 3; PDGF, platelet-derived growth factor; FAK, focal adhesion kinase; SphK1, sphingosine kinase; SphK1, sphingosine kinase 1; S1P, sphingosine-1-phosphate; FGF2, fibroblast growth factor 2; FGFR1, fibroblast growth factor receptor 1; Wnt2B, Wnt family member 2B.

drug delivery efficiency (31). However, current mechanistic investigations into VM inhibition remain predominantly constrained to phenotypic associations, with key gaps in rigorous target validation studies, exemplified by the proposed direct interaction between baicalin and RhoA kinase, and insufficient *in vivo* pharmacodynamic characterization. While nanoformulations demonstrate enhanced tumor-targeting capabilities, their complex compositions introduce potential uncontrollable experimental variables that may compromise mechanistic clarity and therapeutic reproducibility (31).

Colorectal cancer. In 2022, colorectal cancer accounted for 1,926,118 novel cases, exhibiting the second-highest mortality rate amongst all cancers in the world (4). Although the targeted therapeutic agent bevacizumab prolongs progression-free survival (32,33), it is associated with adverse effects such as hypertension, proteinuria, hemorrhage, gastrointestinal perforation (34,35), thrombophilia and neurological disorders (36). VM formation is markedly associated with invasion, metastasis and poor prognosis (37).

Matrine (MAT). MAT, a bioactive alkaloid derived from the traditional Chinese herb *Sophora flavescens* Aiton, has demonstrated notable anticancer properties through extensive research. Studies have consistently reported that MAT exhibits multifaceted antitumor effects, including the inhibition of cancer cell proliferation, cell cycle arrest, induction of apoptosis and suppression of metastatic potential in malignant cells (38,39). MAT exhibited potent inhibitory effects on the proliferation and metastasis of colon cancer CT26 cells. Furthermore, it effectively disrupted actin cytoskeleton organization and suppressed VM formation. These effects were mediated by the inhibition of JNK and ERK phosphorylation within the MAPK signaling pathway, blockade of the EMT process and synergistic interactions with claudin-9 silencing (40).

Amentoflavone (AMF). AMF, a natural biflavonoid compound, has been reported to exhibit multiple biological activities (41), including anticancer effects. AMF suppresses the HIF-1 α /VEGF signaling pathway in a concentration-dependent manner, leading to the downregulation of HIF-1 α , β -catenin, VEGF, vimentin, Snail and VM-associated tubulin-like structures. These effects are reversed by dimethylallylglycine (DMOG), an activator of the HIF-1 α /VEGF pathway (42).

Others. Delphinidin, a natural anthocyanin abundant in blue-violet plants and their fruits, exerts anti-VM effects by suppressing the RhoA/ROCK signaling pathway. Mechanistically, it downregulates the expression of key molecular mediators, including RhoA, ROCK and VEGF, thereby markedly diminishing VM-associated tubulin-based network formation. This dual regulatory mechanism disrupts tumor vascularization and promotes apoptosis in cancer cells through cytoskeletal reorganization (43). Evodiamine (EVO) is a quinazoline alkaloid isolated from the herb Wuzhu [*Tetradium ruticarpum* (A. Jussieu) T. G. Hartley] (44). EVO suppresses colorectal cancer tumor growth and VM formation by downregulating key molecular markers, including HIF-1 α , VE-CAD, VEGF, MMP2 and MMP9 (45).

AMF and EVO demonstrate anti-VM activity in colorectal cancer by targeting HIF-1 α and its downstream effectors, including VEGF, MMP2/9 and VE-CAD. Notably, both

Astragalus and *Atractylodis macrocephalae* mixture and AMF exhibit additional modulation of reactive oxygen species (ROS) homeostasis, with the HIF-1 α /VEGF axis confirmed as a key mediator through DMOG-reversible effects. By contrast, MAT and Delphinidin employ distinct mechanisms: MAT suppresses VM formation via MAPK pathway inhibition and EMT disruption, demonstrating synergistic anti-VM effects when combined with claudin-9 silencing; Delphinidin uniquely targets RhoA/ROCK signaling to downregulate VEGF expression while inducing apoptosis. Although HIF-1 α emerges as a convergent target for multiple compounds, current mechanistic conclusions predominantly rely on correlational analyses rather than rigorous direct target engagement validation. This underscores the need for advanced methodologies such as surface plasmon resonance binding assays, cellular thermal shift assays and CRISPR-based genetic validation to establish causal relationships between compound-target interactions and phenotypic outcomes.

Gastric cancer. There were 968,350 novel cases of gastric cancer in 2022, presenting a notable threat to the global health system (4). It has been reported that >33% of patients receiving preoperative chemotherapy followed by surgery experienced disease recurrence, with a median follow-up period of 27.8 months. Notably, 44% of these relapses occurred within the 1st year post-surgery (46). Radiotherapy faces resistance issues (47,48) and has serious side effects, such as inflammatory skin reactions, fatigue and digestive system symptoms (49). The identification of VM in gastric cancer cells offers a novel therapeutic target for drug development, presenting novel opportunities for treatment strategies in the future (50).

Saffronin. Saffronin is an active ingredient extracted from the stigma of saffron. Saffronin regulates several signaling pathways, including HIF-1 α , Notch1 and Sonic hedgehog (SHH), reduces the expression levels of patched-2, glioma-associated oncogene homolog 1 (Gli1) and other related protein factors, and inhibits VM formation and metastasis of human umbilical vein endothelial cells (HUVEC) tubes and gastric cancer cells (51).

DHA. DHA, derived from the antimalarial drug *Artemisia annua*, has potent pharmacological activity. In gastric cancer, the fibroblast growth factor 2 (FGF2) gene is most closely associated with angiogenesis and VM. DHA exerts similar effects as fibroblast growth factor blockers, inhibiting VM formation and decreasing the expression of VM-associated biologically active factors (52).

Others. Formononetin (FMN), a naturally occurring isoflavone, is widely distributed in numerous medicinal plants, including *Astragalus membranaceus*, red clover, *Trifolium pratense* and *Pueraria lobata*. FMN regulates the HIF-1 α /VEGF signaling pathway in a concentration-dependent manner, destroys the lumen structure already formed by VM in gastric cancer cells and markedly induces apoptosis (53). Ginsenoside Rg3 (Rg3), a bioactive steroidal saponin, belongs to the ginsenoside family derived from *Panax ginseng* C.A. Meyer (54). Rg3 inhibits glycogen synthase kinase (GSK)-3 β , Wnt family member 2B mRNA and β -linker protein expression, as well as cellular VM formation, in SGC7901 gastric cancer cells *in vitro* (55).

Aucubin (AU), a bioactive iridoid glycoside, is a principal active constituent derived from *Eucommia ulmoides* Oliv (56).

In vitro treatment of MGC803 gastric cancer cells with AU markedly downregulated metastasis-associated proteins (RhoA, ROCK1, N-cadherin, vimentin and VE-CAD) while upregulating the epithelial marker E-cadherin. These effects collectively suppressed EMT and VM in gastric cancer cells (57). Jaceosidin dose-dependently inhibits VM in HGC-27 gastric cancer cells through selective modulation of the sphingosine kinase 1/sphingosine-1-phosphate (SphK1/S1P) signaling pathway. Experimental data demonstrated that increasing concentrations of jaceosidin progressively inhibit tumor cell clonogenicity and VM-associated tubular network formation. Notably, the compound induces dose-responsive disassembly of preformed VM channels through cytoskeletal reorganization, while simultaneously blocking *de novo* VM formation by suppressing cancer cell plasticity (58).

FMN and Rg3 demonstrate anti-VM activity in gastric cancer through convergent targeting of the HIF-1 α signaling axis, with saffronin exhibiting additional modulation of Notch1 and SHH pathways. Notably, FMN suppresses HIF-1 α /VEGF signaling, while Rg3 inhibits the GSK-3 β /Wnt/ β -catenin cascade. By contrast, AU and jaceosidin employ distinct mechanisms: AU disrupts VM formation via RhoA/ROCK-mediated EMT inhibition and downregulation of metastasis-related proteins, whereas jaceosidin selectively targets the SphK1/S1P pathway to alter cytoskeletal dynamics and cancer cell plasticity. DHA employs a unique strategy by functioning as an FGF2 antagonist, directly inhibiting FGF-driven angiogenesis and VM processes. While these findings underscore the multi-target potential of natural compounds, notable limitations persist. Current mechanistic insights rely predominantly on *in vitro* models (e.g., SGC7901, MGC803 and HGC-27 cell lines) with inadequate validation in complex *in vivo* tumor microenvironments. The recurrent focus on HIF-1 α as a shared target among multiple compounds (saffronin, FMN and Rg3) suggests its role as a convergent signaling hub but raises concerns about therapeutic redundancy and off-target effects.

Glioma. Complete surgical resection of glioma is often limited by its high degree of infiltration, with residual lesions remaining in 60-70% of patients postoperatively (59). Radiotherapy has the risk of damaging normal brain tissue (60,61) and facing local resistance (62), potentially leading to local recurrence, whereas most chemotherapeutic agents, such as platinum-based drugs, methotrexate and doxorubicin, have difficulty crossing the blood-brain barrier (BBB) (63). VM is present in glioma and represents a potential therapeutic target (64). Therefore, the development of novel anti-VM drugs capable of crossing the BBB is key.

Artemether, a derivative of artemisinin, is rapidly absorbed in lipids and represents a highly permeable compound that disrupts VM by downregulating MMP-2 and HIF- α . Dual-targeted artemether/paclitaxel micelles enhanced BBB penetration and tumor accumulation while suppressing glioma VM through coordinated downregulation of HIF-1 α , MMP-2 and PI3K expression (65).

Isoliquiritigenin (ISL) is a bioactive chalcone compound isolated from licorice (66). The combination of ISL and temozolomide, when administered under hypoxic conditions, markedly reduced the number and length of VM channels

in glioma SHG44 cells. This effect was accompanied by a marked downregulation of MMP-2, VEGF and EphA2 protein levels (67).

Artemether and ISL demonstrate anti-VM activity in glioma through modulation of key pro-angiogenic factors, including MMP-2 and HIF-1 α . While both compounds target these core VM mediators, their pharmacological profiles diverge markedly. Artemether, characterized by high lipophilicity, directly suppresses MMP-2 and HIF-1 α expression, with its therapeutic efficacy markedly enhanced when formulated in dual-targeted polymeric micelles co-loaded with paclitaxel. This nanoformulation strategy not only improves BBB penetration through permeability-glyco-protein inhibition but also synergistically inhibits PI3K signaling to disrupt VM network formation. By contrast, ISL exhibits hypoxia-dependent synergism with temozolomide, demonstrating notable VM suppression in glioma stem-like cells. The dual-targeted artemether/paclitaxel micelle system demonstrates BBB penetration and tumor targeting capacity, has notable engineering value but faces challenges in terms of formulation stability and cost. The ISL-temozolomide combination enhances VM inhibition and reverses temozolomide resistance; however, potential drug interactions and long-term toxicity have not yet been clarified.

Glioblastoma (GBM). GBM, the most common primary malignant brain tumor in adulthood, is highly aggressive and heterogeneous (68). It has been reported that 75-90% of cases recur within 1 year after surgery (68,69). The median survival of patients receiving standard treatment in clinical trials is 14.6-21.1 months (70). Radiotherapy, immunotherapy and targeted therapy do not provide satisfactory results. Targeting VM, a key mechanism of tumor angiogenesis independent of endothelial cells, represents a potential therapeutic breakthrough in refractory types of cancer.

Moroidin, a cyclic peptide compound derived from silver chickweed seeds, is a novel microtubule-targeting agent due to its ability to inhibit microtubule polymerization. Moroidin markedly inhibited EMT in GBM by decreasing the protein kinase p-ERK and inhibiting the activation of β -catenin, inhibiting angiogenesis, smooth muscle actin and MMP-9 levels (71).

Ruta graveolens L (RGWE), commonly called rue, is a perennial herbaceous plant native to the Mediterranean region that has become naturalized worldwide (72). RGWE markedly suppresses VM formation in U87-MG GBM cells while concurrently inducing cytotoxicity in GBM-derived cancer stem cells and disrupting existing VM networks (73).

Moroidin functions as a novel microtubule-destabilizing agent that selectively inhibits microtubule polymerization, leading to suppression of ERK phosphorylation and β -catenin activation. This dual inhibition disrupts EMT, angiogenesis and MMP-9 expression, thereby attenuating VM network formation. By contrast, RGWE exhibits broad-spectrum VM inhibition in U87-MG cells while demonstrating dual cytotoxicity against both bulk tumor cells and glioblastoma stem cells, effectively dismantling pre-established VM architectures. Notably, the stem cell-targeting capability of RGWE suggests synergistic potential with conventional therapies, as GSCs are known contributors to therapeutic resistance. Moroidin

focuses on microtubule polymerization inhibition, featuring a novel mechanism and unique target; however, its direct effect on VM core markers (such as VE-CAD) remains to be elucidated. RGWEs exhibit potent killing effects on cancer stem cells and VM structures; however, their complex composition obscures the core active compounds and mechanisms.

Osteosarcoma. Osteosarcoma originates from mesenchymal tissue; the tumor cells produce bone-like material. Surgery is the primary method of treatment; however, it may lead to amputation, which affects the quality of life in patients (74). The effectiveness of chemotherapy is associated with the location of tumor growth; however, it also faces the problem of drug resistance (75). The local recurrence rate of osteosarcoma is often between 7 and 10% (76), and the relevant genetic features of VM are associated with osteosarcoma prognosis (77). TCM herbal therapies can be a good adjuvant treatment.

Rhizoma *Paridis saponins* (RPS). RPS exhibit potent anti-tumor activity by simultaneously suppressing angiogenesis and inhibiting cancer cell migration and invasion through multiple molecular mechanisms (78). RPS treatment in osteosarcoma cells markedly downregulated migration-inducing gene-7 (MIG-7) expression while concurrently inhibiting the PI3K/MMPs/laminin-5 γ 2 chain (Ln-5 γ 2) signaling pathway. These molecular alterations corresponded with marked decreases in downstream effector protein expression, ultimately leading to substantial inhibition of cellular protrusion formation and VM structural development (79).

Others. Curcumin exhibits a concentration-dependent inhibitory effect on the tubular VM structures in osteosarcoma S180 cells, as well as on the reticular networks formed through their interaction with endothelial cells. This antitumor effect is mechanistically associated with the notable downregulation of MMP-2/9 at transcriptional and translational levels (80).

Paris polyphylla ethanol extract (PPEE) demonstrates dual anti-osteosarcoma efficacy *in vivo* and *in vitro* by modulating cell cycle regulators [upregulating p-cyclin-dependent kinase (CDK)1, p-cell division cycle 25C and p-checkpoint kinase 2 (Chk2)], promoting apoptosis, suppressing metastasis-related proteins [focal adhesion kinase (FAK), MIG-7 and MMP-2/9] and inhibiting VM formation (81).

RPS exert their anti-VM activity primarily through modulation of the PI3K/MMPs/Ln-5 γ 2 signaling axis, accompanied by reduced expression levels of MIG-7, thereby attenuating cellular protrusion formation and VM network assembly. Similarly, PPEE targets FAK and MIG-7 while concurrently regulating cell cycle progression and apoptosis through modulation of p-CDK1 and p-Chk2. By contrast, curcumin exhibits concentration-dependent disruption of both VM tubular structures and endothelial-integrated vascular networks, achieving MMP-2/9 suppression at both transcriptional and translational levels. Notably, these compounds demonstrate complementary mechanisms: RPS focuses on ECM remodeling and cell motility, PPEE integrates anti-metastatic and cell cycle control, while curcumin provides broad-spectrum MMP inhibition. However, current findings remain constrained by reliance on two-dimensional cell culture models (e.g., U2OS and MG-63), with limited validation in three-dimensional VM assays or *in vivo* osteosarcoma microenvironments. The target and specific mechanism of RPS are clear; however, *in vivo*

studies are warranted. Curcumin is an old drug used in anti-cancer drugs and breaking through its inherent bioavailability dilemma remains an urgent issue to be solved. PPEE has been thoroughly studied *in vivo* and *in vitro*; however, defining its core active ingredient is challenging because of its mixed nature.

Choroidal melanoma (CM). CM is the most common primary intraocular malignancy in adults, with a unique biological behavior, susceptibility to hepatic metastases, poor prognosis and retinal risks associated with local radiotherapy and surgery (82,83). VM is highly associated with the first symptoms of CM and mortality rates (84,85).

ART has been the focus of its diverse pharmacological actions, including anti-inflammatory, immunoregulatory and anticancer properties (86). Artemisinin treatment markedly suppressed HIF-1 α and angiogenic factor expression in OCM-1 and C918 melanoma cells, concurrently inhibiting VM formation through blockade of the Wnt family member 5a/calcium/calmodulin-dependent protein kinase II (CaMKII) signaling axis (87-90).

Luteolin (LUT), a naturally occurring flavonoid polyphenol, is abundantly present in various plant sources, including fruits, vegetables and medicinal herbs. This bioactive compound demonstrates remarkable pharmacological potential, particularly in oncology and immunomodulation, through its potent antitumor and anti-inflammatory properties (91). LUT exerts potent anti-angiogenic and anti-VM effects in C918 uveal melanoma cells and HUVECs by targeting the PI3K/AKT pathway, markedly downregulating VEGF, PI3K and AKT expression (92,93). The IC₅₀ value of LUT in human C918 choroidal melanoma cells was as low as 24.41 μ mol/l after 24 h. LUT markedly suppresses VEGF expression and PI3K/AKT phosphorylation (p-PI3K/p-AKT) in C918 uveal melanoma cells and HUVECs, inhibiting VM and mosaic vessel formation in choroidal melanoma models (89,90,94).

ART and LUT demonstrate potent anti-VM activity in uveal melanoma, particularly in aggressive C918 cell models, through modulation of distinct signaling hubs. ART exerts its anti-VM effects via suppression of the Wnt5a/Ca²⁺/calmodulin-dependent protein CaMKII axis, leading to downstream attenuation of HIF-1 α and angiogenic factors essential for VM network formation. By contrast, LUT targets the PI3K/AKT pathway with high potency, markedly reducing VEGF expression and PI3K/AKT phosphorylation. Notably, the dual inhibition of VM by LUT and angiogenesis positions it as a multifaceted therapeutic candidate, while the mechanism of ART highlights the therapeutic potential of Wnt pathway modulation in HIF-1 α -driven malignancies. However, current findings remain constrained by reliance on monolayer cultures and lack validation in three-dimensional VM models or *in vivo* uveal melanoma systems.

Breast cancer. There were 2,308,897 novel cases of breast cancer in 2022 (4), the second-highest incidence in the world among cancers. Standardized treatment of breast cancer comes with adverse effects, such as drug resistance problems, neurotoxicity, hot flashes, mood swings, lymphedema, fatigue and cardiotoxicity, which severely affect the quality of life of

patients (95,96). VM is associated with the malignant phenotype of breast cancer (97).

Brucine. Brucine, an extract of the traditional herb *Strychnos nux-vomica* L, disrupts the cytoskeleton and microtubule structure of MDA-MB-231 cells and reduces the tubule number, intersections and average tubule length in a concentration-dependent manner, downregulates MMP-2, MMP-9 and EphA2 and reduces VM formation. These findings provide a novel therapeutic strategy for triple-negative breast cancer (TNBC) (98).

Others. Triptonide, a bioactive diterpenoid tricyclic oxide derived from *Tripterygium wilfordii* Hook F, exerts potent antitumor effects in TNBC by degrading Twist1 and Notch1 oncoproteins, downregulating VEGFR2/VE-cadherin expression, suppressing NF- κ B signaling and markedly inhibiting VM (99).

Astilbin (AST), a bioactive dihydroflavonol glycoside, is widely distributed in medicinal plants and dietary sources, exhibiting diverse pharmacological properties that have garnered notable research interest (100,101). AST demonstrates concentration-dependent anti-angiogenic and apoptosis-inducing activities in breast cancer cell lines (MCF-7 and MDA-MB-231) through dual inhibition of HIF-1 α expression and subsequent VEGF signaling pathway activation. This inhibition concomitantly downregulates angiogenesis-associated markers (VE-CAD, N-cadherin and MMP-2) and reduces VM lumen formation, while inducing tumor cell apoptosis through HIF-1 α /VEGF pathway modulation (102).

Brucine functions as a microtubule-destabilizing agent that disrupts cytoskeletal dynamics by binding β -tubulin, leading to concentration-dependent downregulation of MMP-2, MMP-9 and EphA2, which are key mediators of ECM remodeling and VM network formation. By contrast, triptonide exhibits unique oncoprotein degradation activity, promoting ubiquitination-mediated proteolysis of Twist1 and Notch1 transcription factors. This results in suppression of VEGFR2/VE-CAD signaling and attenuation of NF- κ B-driven pro-inflammatory responses, thereby inhibiting VM channel assembly. Notably, AST employs a dual mechanism targeting both HIF-1 α stabilization and VEGF secretion, reducing angiogenesis-related markers (VE-CAD, N-cadherin and MMP-2) while inducing caspase-dependent apoptosis. These findings highlight the therapeutic potential of combining microtubule disruption (Brucine), oncoprotein degradation (triptonide) and hypoxia/angiogenesis axis inhibition (AST) for VM suppression in TNBC. Triptonide has certain clinical application potential due to its cancer protein degradation mechanism; however, toxicity issues need to be addressed first. AST has potential synergistic advantages due to its simultaneous regulation of VM and EMT. The cytoskeletal targeting of brucine warrants further thorough research.

Pancreatic cancer. In 2022, pancreatic cancer already ranked second in the world with 467,005 cases of mortality, associated with smoking, obesity and diabetes (103). The majority (80-85%) of cases are diagnosed at advanced stages (locally advanced/metastatic), associated with dismal long-term outcomes (5-year survival rate, <10%) (104,105). The risk of complications after surgical treatment, the efficiency of chemotherapeutic agents and drug resistance markedly affect

the prognosis and mortality rate of pancreatic cancer (106). The presence of VM in pancreatic cancer may be associated with prognosis (107).

Rg3 exerts multi-target antitumor effects in pancreatic adenocarcinoma (PAAD) through epigenetic regulation. Rg3 upregulates microRNA-204 to suppress dishevelled segment polarity protein 3-mediated signaling, thereby downregulating VE-CAD expression in SW1990 cells (108). This intervention coordinately inhibits PI3K pathway activation, evidenced by reduced phosphorylation of PI3K and decreased N-cadherin/VE-CAD levels (109). The dual suppression disrupts cancer stemness maintenance and inhibits VM through impaired 3D tube/sphere formation and matrix-remodeling capacity (109,110).

Ginsenoside Rg3 has notable therapeutic potential and is expected to be used in clinical applications; however, its ability to penetrate the pancreatic cancer interstitial barrier *in vivo* has not been verified. Furthermore, its lack of regulation of hypoxic microenvironments (such as HIF-1 α) may weaken its clinical efficacy.

Ovarian cancer (OC). The global incidence of OC has reached 32,439,815 cases (4). Emerging data reveal rising incidence and mortality rates across diverse populations, with notable regional disparities (4). VM networks serve a pivotal role in disease progression by forming functional connections with host blood vessels; this hybrid vascular system promotes hematogenous dissemination of tumor cells, driving metastatic spread and conferring treatment resistance (111-113). VM represents a promising therapeutic target for OC treatment, which offers the potential to disrupt tumor perfusion and metastatic dissemination simultaneously (113).

Cinobufagin. Cinobufagin, a cardiotonic steroid derived from *Bufo* species, demonstrates anti-metastatic mechanisms in OC through ECM remodeling and immune microenvironment modulation. This compound transcriptionally suppresses forkhead box S1 (FOXS1) to inhibit MMP9/MMP14 and LAMC2, blocking VM formation in SKOV3 cells by impairing tumor-driven matrix reorganization (114). The intervention concurrently disrupts the C-C motif chemokine ligand 2/receptor 2 (CCL2/CCR2) chemokine axis, inhibiting protumoral (M2-like) macrophage polarization and reprogramming the immunosuppressive tumor microenvironment (115). Notably, cinobufagin intercepts TGF- β -induced EMT, a key mediator of OC metastasis, through these coordinated multi-target actions (114,115).

Others. Catechins are more commonly referred to as tea polyphenols derived from tea, one of the oldest and most consumed beverages in the world (116). Catechins with specific acyl portions, such as catechin gallate (CG), epi-CG (ECG), gallo-CG (GCG) and epigallocatechin gallate (EGCG), have pharmacological effects that inhibit TGF- β -induced cell migration, MMP-9 and Snail secretion and OC cell VM (117). Sinomenine (SIN), a bioactive alkaloid isolated from the medicinal vine *Sinomenium acutum*, exhibits well-documented anti-inflammatory and antitumor properties with established pharmacological applications (118). SIN demonstrates dose-dependent anti-VM activity in OC A2780 cells through multi-target transcriptional regulation. This compound coordinately suppresses VM-associated markers (VEGF, EphA2 and

MMP-2/9) and disrupts the C-X-C motif chemokine receptor 4 (CXCR4)/STAT3 signaling axis, evidenced by reduced p-STAT3 levels. The dual inhibition mechanism blocks ECM remodeling required for VM channel formation, establishing SIN as a potent VM suppressor in OC (119).

Cinobufagin disrupts matrix remodeling and immune microenvironment dynamics by targeting FOXS1, while concurrently modulating the CCL2/CCR2 axis to attenuate tumor-associated macrophage recruitment. EGCG suppresses TGF- β -induced EMT and MMP-9 secretion, thereby reducing ECM degradation and VM channel formation. By contrast, SIN employs dual pathway inhibition: It directly downregulates VM-related markers (VEGF, EphA2 and MMP-2/9) while intercepting CXCR4/STAT3 signaling, a key axis for cancer stem cell maintenance and metastatic dissemination. Notably, these compounds converge on matrix remodeling but diverge in upstream regulation, cinobufagin integrates immunomodulatory and transcriptional repression, catechins focus on TGF- β blockade and SIN targets chemokine/STAT signaling. However, these findings are mainly based on single cell line models (such as SKOV3 and A2780) and isolated signaling pathway analyses, lacking *in vivo* validation of complex microenvironment interactions and clinical relevance evidence.

Cervical cancer. Cervical cancer ranks among the most prevalent malignancies in women globally and represents the primary cause of cancer-related mortality in 37 countries (4), particularly in low- and middle-income regions (4). Patients with VM-positive cervical cancer exhibited markedly reduced overall survival (OS), with strong correlations to lymph node metastasis, advanced International Federation of Gynecology and Obstetrics stage (III/IV) [hazard ratio (HR)=2.3; 95% CI, 1.8-3.0], tumor size >4 cm and hypofractionation regimens (120), which markedly affects VEGF treatment and induces recurrence (121).

Pristimerin (Pris), a quinone methide triterpenoid derived from *Celastrus* and *Maytenus* species (Celastraceae family), exhibits broad bioactive properties, including anti-inflammatory, antimicrobial and antitumor effects, with emerging potential in oncology (122). Pris inhibited the structure and number of VM lumens in cervical cancer HeLa cells and downregulated the expression levels of SHH, Gli1 mRNA, VEGF-A, VE-CAD and Gli1 proteins, which were associated with the inhibition of the SHH/Gli1 signaling pathway. By contrast, overexpression of SHH impaired the physiological effects of Pris to a certain extent (123).

Honokiol, a bioactive biphenyl neolignan primarily derived from *Magnolia officinalis* bark, has been pharmacologically characterized as the principal active constituent of this TCM herb (124). Honokiol dose-dependently suppresses VM formation in cervical cancer HeLa cells by inhibiting the EGFR signaling pathway, evidenced by reduced p-EGFR and downregulation of downstream effectors (MMP-2/9, EphA2, VEGF and cadherin-2) (125).

Notably, while both compounds disrupt VM formation, their mechanisms diverge fundamentally: Pris targets developmental signaling cascades, whereas honokiol focuses on receptor tyrosine kinase-mediated oncogenic signaling. These findings highlighted the therapeutic potential of combining HH

pathway inhibitors with EGFR antagonists for VM suppression in cervical cancer. To the best of our knowledge, current research on Pris and honokiol lacks *in vivo* experimental data and safety analysis.

Esophageal cancer. Esophageal cancer has the seventh-highest mortality rate in the world (445,129 mortalities and a mortality rate of 4.6%) (4), with anti-angiogenic therapy only achieving limited improvement in OS with increased side effects (126). VM can be an independent prognostic factor for esophageal cancer and is markedly associated with cancer stage, lymph node metastasis and hypo-differentiation (127).

Ligustilide (LIG), a predominant phthalide derivative, serves as a key bioactive constituent in several TCM herbs, notably *Angelica sinensis* and *Ligusticum chuanxiong* (128). LIG dose-dependently suppressed proliferative (cyclin-D1 \downarrow), anti-apoptotic (Bcl-2 \downarrow) and metastatic (RhoA/ROCK \downarrow) proteins in EC-109 esophageal cancer cells while upregulating cell cycle arrest (p21 \uparrow) and pro-apoptotic markers (Bax/Caspase-3 \uparrow). Notably, RhoA activators partially reversed these effects, confirming pathway specificity (129).

The reversal effect of RhoA activators suggests that their action is limited by target dependence and lacks verification of upstream regulatory mechanisms (such as RhoA activating factors) and the effects of the *in vivo* microenvironment.

Bladder cancer (BC). BC is approximately four times more common in men compared to women and has the ninth highest incidence worldwide, with smoking being a major risk factor (4). VM-positive patients with BC have more aggressive tumors and are more prone to poor cancer outcomes (130).

Atractylodin (ATR) is one of the main active ingredients of *Rhizoma Atractylodis*. ATR has various pharmacological features, such as antitumor properties (131). ATR modulates the RhoA/ROCK signaling pathway, concentration-dependently reducing lumen formation in BC T24 cells while enhancing F-actin fluorescence intensity, disrupting cytoskeletal dynamics, downregulating RhoA/ROCK1 expression and ultimately inhibiting VM formation, a process key for cytoskeletal motility and cell adhesion (132).

The effects of ATR are based solely on a single cell line model and isolated signaling pathway analysis, lacking validation in complex *in vivo* microenvironments and evidence of clinical relevance.

Melanoma. Recently, the mortality rate of melanoma has indicated a downward trend, with the number of novel cases having reached 331,647 (4). Factors such as ultraviolet radiation, genetic susceptibility and phenotypic features combine to constitute the major risk factors for melanoma (133). VM was first identified in melanomas, with invasive cell lines being more likely to form VM, which is positively associated with tumor thickness and risk of metastasis. VM represents a key risk factor for melanoma progression, linked with aggressive metastasis and poor patient outcomes (134). VM can counteract antitumorigenic therapy and be used as a prognostic marker for melanoma.

Lupeol, a pentacyclic triterpenoid, is ubiquitously distributed in edible plants (e.g., mango and olive) and medicinal species (e.g., *Ficus religiosa* and *Taraxacum officinale*),

exhibiting notable pharmacological potential (135). Lupeol demonstrates multimodal antineoplastic efficacy in B16-F10 melanoma models, exhibiting direct cytotoxicity alongside dual anti-angiogenic and VM-suppressive effects. Mechanistically, this triterpenoid disrupts tumor-stromal crosstalk by targeting cancer stem cell populations and inhibiting endothelial progenitor cell (EPC) recruitment, thereby attenuating VM channel formation and angiogenesis. Notably, lupeol reverses dacarbazine resistance through epigenetic modulation of EPC differentiation programs, potentially via suppression of EPC-specific growth signaling pathways (136).

Lupeol has exhibited potential in inhibiting VM formation and overcoming drug resistance in melanoma mouse models and cell experiments. However, the causal chain between drug resistance and VM, as well as safety assessments at clinically feasible concentrations, has not been directly verified.

Prostate cancer. Prostate cancer accounted for 1.5 million incident cases and 397,000 cases of mortality globally, ranking as the most frequently diagnosed malignancy across 118 countries/territories (4). The available standardized treatment options, surgery and radiotherapy, as well as androgen deprivation therapy, are associated with large adverse effects (such as frequent urination, urgency, dysuria, diarrhea and sexual dysfunction) and recurrence rates (overall recurrence rate approaches 50%) (137-139). VM is frequently observed in prostate cancer specimens and demonstrates notable associations with aggressive clinicopathological features, including Gleason score ≥ 7 , lymph node involvement (odds ratio, 3.2; 95% CI, 2.1-4.9) and distant metastasis (HR=2.8) (140).

EGCG. EGCG exerts anti-prostate cancer effects by suppressing VM through selective downregulation of the Twist/VE-CAD/AKT axis (Twist \downarrow , VE-CAD \downarrow and p-AKT \downarrow) while maintaining EphA2 expression, revealing pathway-specific modulation (141).

Others. Kaempferol (KMP), a dietary flavonol found in fruits and vegetables, exhibits potent anticancer activity by scavenging ROS and modulating redox-sensitive signaling pathways (e.g., Nrf2/KEAP1 and NF- κ B) (142). KMP, a dietary flavonoid, exerts multimodal anti-prostate cancer effects by simultaneously suppressing androgen receptor (AR) signaling, via dihydrotestosterone antagonism and downregulation of AR-target genes (protein-specific antigen/transmembrane serine protease 2-ETS-related gene) and inhibiting VM in PC-3 cells. Concurrently, KMP disrupts VM formation by inhibiting matrix-remodeling metalloproteinases and EMT-related pathways (such as Nrf2/KEAP1 and NF- κ B pathways). The coordinated suppression of the AR axis and VM plasticity mechanistically contributes to its therapeutic potential against castration-resistant prostate cancer progression (143).

Resveratrol (3,4,5-trihydroxy-trans-stilbene; RES) is a promising candidate for cancer therapy (144). RES inhibits the levels of factors such as MMP-2, VE-CAD, EphA2 and laminin subunit 5 γ -2 in human prostate cancer PC-3 cells. Furthermore, it can inhibit serum-induced and Twist nuclear localization and exerts antitumor vascular effects through inhibition of EphA2/Twist-VE-CAD/AKT signaling VM effects (145).

Notably, while all three compounds converge on VE-CAD and AKT pathway modulation, EGCG and RES share a

marked focus on Twist1-mediated transcriptional regulation, whereas KMP uniquely integrates anti-androgen activity into its anti-VM repertoire. These findings highlight the therapeutic potential of combining AR antagonists with EMT/VM inhibitors in prostate cancer. These conclusions are highly dependent on simplified mechanistic studies using a single cell line model (PC-3) and lack *in vivo* microenvironment validation, clinical relevance evidence and systematic analysis of pathway interactions. Whether the anti-VM effect can be reproduced in androgen-sensitive models or patients remains to be elucidated.

4. Discussion

VM in malignant tumors represents a multifaceted biological process orchestrated by intricate molecular networks and intersecting signaling pathways. The widespread occurrence of VM across diverse malignancies highlights its potential as a novel therapeutic target for cancer treatment. Although VM universally involves tumor cells mimicking endothelial vessel formation to sustain perfusion and evade immunity, its underlying molecular mechanisms and signaling pathways exhibit notable heterogeneity across cancer types.

VM in aggressive tumors, including melanoma, lung cancer, small cell lung cancer, GBM and HCC, is regulated by diverse signaling pathways, such as VEGF, FGF, Notch and RhoA/ROCK cascades (146). In prostate cancer, VM may be associated with signaling pathways such as PI3K-AKT, VEGFR1 and VEGFR2 (147). In gastric cancer, VM formation is closely associated with elevated expression of HIF-1 α and subsequent upregulation of hypoxia-responsive proteins (carbonic anhydrase IX, glucose transporter type 1 and VEGF) (148). The identification of VM as a therapeutic target enables tumor vascular disruption and nutrient deprivation, thereby suppressing tumor growth and metastasis (146,149).

TCM monomers, active ingredients or active substances extracted from Chinese herbal medicines and further isolated and purified, may have specific pharmacological effects. The research and application of CMMs have demonstrated their potential in various fields, including anti-inflammatory, anti-tumor, anti-viral (150), modulation of autophagy (151) and improvement of neurological function (152-154).

Using TCM monomers to target VM for cancer therapy offers various advantages: i) Direct inhibition of the expression of VM-related molecules presents a clear mechanism of action explaining their therapeutic effect; ii) VM is markedly associated with poor prognosis in patients with cancer and TCM monomers can suppress tumor aggressiveness and metastasis by inhibiting VM formation; iii) targeting VM, a key contributor to anti-angiogenic therapy resistance, using TCM monomers enhances antitumor efficacy by overcoming this adaptive escape mechanism; iv) TCM monomers have multi-targeting effects and can simultaneously affect multiple molecules and signaling pathways associated with VM; v) research on the role of TCM monomers in inhibiting VM provides key clues for the development of novel antitumor drugs; and vi) TCM monomers often originate from natural plants, with the cost of their extraction and preparation being relatively low compared with that of traditional antitumor drugs, such as chemotherapeutic drugs and targeted drugs,

which are costly and expensive to develop, produce and evaluate in clinical trials. Monomers are more readily available in several countries and regions, and particularly for patients with a poorer financial situation, TCM monomers may be a more economical option.

VM formation involves the synergistic or independent regulation of multiple signaling pathways, with different pathways serving context-specific roles across different cancer types. Although HIF-1 α /VEGF is central in traditional angiogenesis, it exerts the opposite effect in VM. Hypoxia induces VM formation via HIF-1 α ; nevertheless, VEGF-targeted therapy may fail or even promote VM. Melittin, curcumin, AMF, EVO, saffronin, FMN, artemether, ART and AST inhibit VM formation in tumor cells by suppressing the HIF-1 α /VEGF signaling pathway. Notch1 mediates tumor cell endothelial-like transformation through Δ -like canonical Notch ligand 4, promoting the formation of luminal structures. Saffronin and triptonide inhibit luminal structures in tumor cells by inhibiting Notch1. The SHH/Gli1 and SHH pathways enhance VM capacity by activating EMT and maintaining tumor stem cell characteristics. For instance, Priz and saffronin inhibit the action of SHH, whereas Wnt5a/CaMKII promotes endothelial-like differentiation through β -catenin and EMT regulation, akin to AMF, ginsenoside Rg3 and moroidin. RhoA/ROCK is a core effector pathway for VM. DAS, delphinidin, AU, LIG and atracylonin can directly regulate cytoskeletal reorganization and matrix degradation, whereas PI3K/AKT/mTOR serves as a hub, integrating hypoxia signals (HIF-1 α) and matrix remodeling (MMPs) to promote VM. Melittin, Sal-A, artemether, RPS, LUT and EGCG inhibit this process. Furthermore, NF- κ B indirectly supports VM through the inflammatory microenvironment, whereas CCL2/CCR2 mediates VM formation via macrophage-dependent matrix modification. The cross-activation of these pathways renders VM a mechanism of resistance to anti-angiogenic therapy, necessitating targeted interventions that combine hypoxia regulation (HIF-1 α), EMT inhibition (SHH/Wnt) and cytoskeletal blockade (ROCK) through a multi-pronged strategy.

The clinical translation of CMMs deserves attention. For instance, natural melittin can non-specifically destroy cell membranes, causing hemolysis and posing a risk of hepatotoxicity (155). However, using nanocarriers can optimize its half-life, improving its stability in the blood (155). The novel peptide melittin-K1 has demonstrated a favorable safety profile in normal tissues in a nude mouse model (156). Baicalin concentrations in tumor tissue are markedly higher compared with those in normal lung tissue, with rapid but limited drug absorption (157,158). Furthermore, its derivatives (such as BAL) overcome the low bioavailability of the parent compound through structural modification (water solubility increased by 4-fold, tumor inhibition rate improved to 65.27%) (158). A pharmacokinetic study indicated that this compound exhibits lung tissue-targeted accumulation (lung/plasma concentration ratio of 3-5 times) and demonstrates dose-dependent antitumor effects within the effective dose range (50-100 mg/kg) with controllable toxicity (IC₅₀ >200 μ mol/l for normal cells) (159). Despite the pharmacokinetic limitations of brucine, including poor water solubility, short half-life and low oral bioavailability, encapsulation in bioconjugate-loaded solid lipid nanoparticles

or polylactic acid-based nanoparticles enhances its sustained release and prolongs therapeutic effects, markedly improving bioavailability (160,161).

Although TCM monomers demonstrate multi-target VM inhibition potential across cancer types, clinical translation remains challenged by mechanistic complexity, tumor microenvironment modulation gaps and unvalidated efficacy/safety profiles. This necessitates future advances in multi-omics-guided target discovery, precision combination regimens (e.g., mTOR/VEGF inhibitors) and VM-specific biomarker development to bridge preclinical findings to therapeutic applications.

5. Conclusion

Anti-angiogenic therapy is key in the modern prevention and treatment of malignant tumors; however, clinical practice over recent years has revealed limitations in its efficacy (162). VM emergence underscores the need for novel therapeutic strategies. In this context, the development and application of herbal medicines have introduced promising avenues for VM-targeted therapy. The present review demonstrates that multiple herbal monomers, including curcumin, ART, LUT, TMP and ginsenoside Rg3, suppress VM in cancer cells. This effect is mediated by targeting VM-associated protein expression (e.g., VE-CAD and MMPs), disrupting key signaling pathways (e.g., PI3K/AKT and EphA2), inhibiting CSLC differentiation and reprogramming macrophage polarization. Ginsenoside Rg3 demonstrates broad-spectrum anti-VM activity across multiple cancer types, including gastric adenocarcinoma (SGC7901 cells) and pancreatic ductal adenocarcinoma (SW1990 and PAAD cells), where it markedly reduces luminal-like reticular structures and VM network density. Mechanistic studies revealed that Rg3 employs a dual inhibitory strategy: In gastric cancer, it suppresses HIF-1 α /VEGF signaling and the GSK-3 β /Wnt/ β -catenin pathway to disrupt ECM remodeling (55), while in pancreatic cancer, it additionally targets EMT regulators such as Twist1 and Snail (108). This multi-cancer efficacy positions Rg3 as a versatile therapeutic candidate, although current findings remain constrained by reliance on monolayer cell models and lack of comparative studies across different tumor microenvironments. Future studies can synergize multi-disciplinary expertise and innovative approaches to advance the understanding of VM inhibition. These findings need to be confirmed by more thorough studies, including clinical and preclinical trials. Future research should focus on optimizing drug formulations, expanding the therapeutic window and developing combination therapy strategies. With more thorough research, herbal monomers hold notable promise as agents in the development of novel anti-VM drugs. The present systematic review carries inherent limitations due to publication bias. While rigorous inclusion criteria were employed to mitigate this limitation, the absence of negative/null findings in published databases leaves residual uncertainty. Readers are therefore advised to interpret the conclusions with appropriate caution, recognizing that the true therapeutic potential of these agents may differ from currently reported estimates.

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Availability of data and materials

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Authors' contributions

FYL and YQF prepared the original draft. YS reviewed and edited the manuscript. JL, DND, SXL and YSZ retrieved the data and participated in the conceptualization and design of the article as well as the data analysis. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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