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Targeting VEGF/VEGFRs Pathway in the Antiangiogenic Treatment of Human Cancers by Traditional Chinese Medicine

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Abstract

Bearing in mind the doctrine of tumor angiogenesis hypothesized by Folkman several decades ago, the fundamental strategy for alleviating numerous cancer indications may be the strengthening application of notable antiangiogenic therapies to inhibit metastasis-related tumor growth. Under physiological conditions, vascular sprouting is a relatively infrequent event unless when specifically stimulated by pathogenic factors that contribute to the accumulation of angiogenic activators such as the vascular endothelial growth factor (VEGF) family and basic fibroblast growth factor (bFGF). Since VEGFs have been identified as the principal cytokine to initiate angiogenesis in tumor growth, synthetic VEGF-targeting medicines containing bevacizumab and sorafenib have been extensively used, but prominent side effects have concomitantly emerged. Traditional Chinese medicines (TCM)–derived agents with distinctive safety profiles have shown their multitarget curative potential by impairing angiogenic stimulatory signaling pathways directly or eliciting synergistically therapeutic effects with anti-angiogenic drugs mainly targeting VEGF-dependent pathways. This review aims to summarize (*a*) the up-to-date understanding of the role of VEGF/VEGFR in correlation with proangiogenic mechanisms in various tissues and cells; (*b*) the elaboration of antitumor angiogenesis mechanisms of 4 representative TCMs, including *Salvia miltiorrhiza, Curcuma longa*, ginsenosides, and *Scutellaria baicalensis*; and (*c*) circumstantial clarification of TCM-driven therapeutic actions of suppressing tumor angiogenesis by targeting VEGF/VEGFRs pathway in recent years, based on network pharmacology.

Keywords

tumor angiogenesis, traditional Chinese medicine, VEGF

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Introduction

The establishment of a circulatory system for the provision of oxygen and nutrient substances to all body tissues systematically exists in vertebrates. The system is founded in the early phase of embryogenesis via vasculogenesis and angiogenesis, which embrace the formation of capillary plexuses and blood vessels generated from progenitor cells (vasculogenesis) and the expansion and remodeling of preexisting vascular structure (angiogenesis).[1] It can be clearly comprehended that both vasculogenesis and angiogenesis proceed efficiently in response to physiological and pathological conditions. Factors of angiogenesis in multicellular organisms are under strict control and regulation. Accumulating attention has been paid to endothelial cells (EC) in relation to the angiogenesis, but vascularization in vivo requires a combination of pathogenesis such as tumorigenesis and release of proangiogenic factors, including vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs), angiopoietin and platelet-derived growth factors (PDGFs).[2-4] Among these, VEGF/VEGFRs are the critical mediators of vasculogenesis and angiogenesis in terms of their capacity to elicit a broad spectrum of signal transduction cascades in the induction of tumor angiogenesis.

Because of the positive pharmacological activities of traditional Chinese medicine (TCM) in combating tumor-induced angiogenesis, natural compounds as well as formulae derived from TCMs have demonstrated beneficial effects on the regulation of immune function, tumor proliferation and

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metastasis, accelerated angiogenesis and the inhibition of chemotherapy-induced adverse effects.[5,6] This review summarizes the updated essential role of VEGF/VEGFRs-associated tumor angiogenesis in combination with the therapeutic functions of antiangiogenesis involved in various TCMs medicines in the past few years.

Interaction of VEGF/VEGFRs in Tumor Angiogenesis

Properties of VEGF Family in Tumor Angiogenesis

Accumulating attention has been paid to the function of receptor tyrosine kinases and growth factors originating from the VEGF family that possess angiogenic effects. Five glycoproteins, including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF), are the subtype members of VEGF family; VEGF-A is commonly known as the biologically active factor VEGF.[7] The binding of the VEGFs with their transmembrane receptors VEGFR-1, VEGFR-2, and VEGFR-3 strengthens the regeneration of endothelial cell and vascular permeability, which leads to the initiation of tumor growth and physio-pathological characteristics of the vascular network.[8] VEGF generation is widely detected in numerous types of tumors and especially overexpressed from benign to malignant lesions.[9]

It is generally believed that VEGF activity plays a critical role in the paracrine mechanism of tumor-induced neovascularization, that is, VEGF could be produced by tumors cells. On the contrary, VEGF receptors are abundant in endothelial cells.[10] Accumulating studies indicated that VEGF/VEGFR-associated signaling pathways were the most relevant modulators of vasculogenesis, angiogenesis and mobilization of endothelial progenitor cells during development.[11] The increase of the tumor secretion-induced VEGF is caused by the activation of hypoxia and multiple etiological factors involving the mediation of epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor–β (TGF-β), estrogen, and hereditary functional mutant oncogenes of Ras and Src.[12] Pharmacological mechanisms and actions of drugs interfering in tumor-bearing angiogenesis have been extensively studied in the past decade. Bevacizumab, a humanized anti-VEGF monoclonal antibody, has been one of the most prevalent antiangiogenesis treatments, acting to normalize the vasculature and benefit the inhibitory effect of chemotherapeutic drugs, especially in malignant gliomas.[13,14]

The Biological Actions of VEGF Receptors

VEGFR1 has high affinity for binding VEGF, PlGF, and VEGF-B and is pivotal for the ignition of angiogenesis.[10] VEGFR1 is also widely distributed on the cell-surface membrane of non-endothelial cells, including macrophage-lineage cells and vascular smooth muscle cells, and transduces a vital signal for the production of cytokines and chemokines.[15] Intriguingly, the axis containing VEGFR1 and macrophage motivates the inflammatory or noninflammatory reactions in numerous tissues and gives rise to various illness such as cancer growth via the stimulation of angiogenesis, tumor metastasis, formation of lymphatic vessels and atherosclerosis. The VEGFR1-macrophage axis plays a significant role in the recovery of physiological functions such as the rehabilitation of spinal marrow and wound healing.[16] It is noteworthy that VEGF-related autophosphorylation of VEGFR1 and activation of signaling pathways in endotheliocytes are relatively weak in comparison with signaling through VEGFR2.[17] Nevertheless, with regard to the pathological alterations of tumorigenesis and angiogenic cascade, VEGFR1 is a critical mediator of both positive and negative functions in a context-dependent manner.[18,19] In addition, VEGF/PIGF heterodimers have the property to promote intramolecular cross talk between VEGFR-1 and VEGFR-2.[20]

Transmembrane glycoprotein VEGFR2 is the principal signaling receptor for VEGF that mediates the VEGF-associated downstream effects of angiogenesis, including endothelial cell survival, invasion, tube formation and sprouting.[21] VEGFR2 proteolytically processes and binds the VEGF-A, VEGF-C, and VEGF-D. Peak VEGFR2 expression occurs in vascular endothelial cells in the onset of embryonic vasculogenesis and angiogenesis.[22] VEGFR2 level can be enhanced in both physiological and pathological neovascularization. For instance, during reproductive periodicity, mRNA expression of VEGFR2 is elevated in the middle and late stage of the luteal phase within the uterus.[23] Depletion of the expression of Endomucin-1 impaired the migration, proliferation, angiogenesis as well as the tube formation of endothelial cell via the modulation of VEGFR2-related signaling, such as the ERK1/2 and p38 MAPK.[24-26] The density of average microvessels fluctuated synchronously with the expression of VEGFR2 and fibroblast growth factor receptor 1 (FGFR1) in non–small cell lung cancer.[27] Inactive embryos resulted from the devitalization of VEGFR2, leading to deficiencies in vasculogenesis and poor development of hematopoiesis.[28]

In contrast to the down-modulation of VEGFR2 against tumor angiogenesis, the spliced form of VEGFR2 suppressed the activation of VEGF-dependent endothelial cell proliferation. Alternative mRNA splicing of VEGFR2 contributed to the production of a soluble form of VEGFR2 (solVEGFR2) that appeared in numerous tissues including endothelial cell and cancer cells.[29] Additionally, both the vessel maturation and the migration of mural cells are regulated by solVEGFR2. Perhaps because of the enormous overproduction of activated VEGF in numerous tissues, insufficient neutralizing expression of solVEGFR2 is

relatively common.[30] As described above, VEGFR2 has a dominant proangiogenic activity irrespective of whether mildly increased solVEGFR2 binds VEGF. Specific negative regulation of VEGFR2 may efficiently attenuate endothelial cell proliferation and tumor survival.

A tyrosine-protein kinase, VEGFR3, preferentially binds VEGF-C and VEGF-D, and was initially cloned from human placental and leukemia cell lines. It is considered to be uniquely expressed in embryonic vascular endothelial cells and lymphatic endothelium. and plays a vital role in progress of tumor metastasis, lymphangiogenesis, and angiogenesis.[17] The transcription of VEGFR3 is mediated by Sp1 and Sp3, known as zinc finger proteins, under epigenetic control.[31] Under physiological conditions, VEGFR3 is expressed restrictively in certain fenestrated vascular endothelium and lymphangions, while massively emerging in pathological vessels as well as in the proliferation of various tumors involving lung and renal cancer.[32-34] Deprivation of VEGFR3 expression led to cardiovascular failure and sparse vascular density, indicating the biological activity of VEGFR3 in the formation of blood vessels.[35]

It was demonstrated that excessive production of VEGFR3 can be identified in the growth of endothelial tip cells during sprouting angiogenesis in both mouse and zebrafish.[36,37] In particular, VEGFR3 restrained the activity of VEGFR2, along with the VEGF/VEGFR2 signaling pathway, and prevented excessive vascular permeability in endothelial cells.[38] Additionally, during the development of angiosarcoma and other neoplastic growths, increases in vascular branches and endothelial sprouts could be reversed via the blockage of the VEGFR3-associated signaling pathway.[39] Furthermore, activated VEGFR3 can promote the metastasis of breast tumors though regional lymph nodes. Neutralization of VEGFR3 signaling, which was involved in the VEGFC/VEGFR3 autocrine signaling pathway, results in the reduction of breast tumors and lung metastases.[40] Thus, targeting VEGFR3 may afford an efficacious therapeutic method in the resistance of tumor-induced angiogenesis.

Regulation of VEGF/VEGFRs-Related Signaling by TCMs

To date, TCM-derived compounds and formulas have represented their potential in attenuating tumor progression by the downregulation of VEGF-associated signaling pathways. Actein, a natural triterpene glycoside isolated from *Cimicifuga foetida*, exerts profound antiangiogenesis activity by inhibiting protein expression of VEGFR1, pJNK, and pERK, which are involved in the JNK/ERK pathways. Meanwhile, reduction of tumor proliferation, migration and endothelial cell motility in association with the restriction of CXCR4 gene expression has been observed in mice with breast tumor.[41] Total saponins isolated from Radix Astragali, a notable Chinese herbal remedy used to the treatment of diabetes, attenuated the level of VEGFR1, VEGFR2, pAkt, p-mTOR, and COX-2 in xenografted mouse model of colon cancer. Moreover, suppression of VEGF, bFGF and HIF-1α can be demonstrated in HCT 116 colon cancer cells in a $CoCl_2$-mimicked hypoxic microenvironment as well.[42] Bufalin is a biologically active small molecule compound with dramatic anticancer characteristics in prostate, endometrial and ovarian cancers. The pathological status of angiogenesis, which is caused by the phosphorylation of VEGFR1/VEGFR2/EGFR, could be abolished on bufalin administration in human non–small cell lung cancer.[43] H2-P is a synthetic derivative of honokiol and decreases glioblastoma growth by exerting potent anti-angiogenesis effects via the downregulation of the c-MYC/VEGFR2 signaling pathway.[44] Catalpol, a major compound isolated from *Rehmannia glutinosa*, possesses multiple pharmacological functions, including anti-angiogenesis, anti-inflammation and antitumor growth properties. Catalpol attenuated the secretions of numerous proangiogenic markers including VEGF, VEGFR2, HIF-1α, bFGF, interleukin (IL)-1β, IL-6, IL-8, COX-2, and inducible nitric oxide synthase (iNOS), suggesting it as a promising ingredient in treating colon cancer.[45] Neoalbaconol, extracted from *Albatrellus confluens*, displayed inhibition of breast cancer activities associated with the induction of cell apoptosis by blocking EGER2/VEGF production and repressing the proliferation, invasion and migration of endothelial cells both in vitro and in vivo.[46] Oridonin is the main terpene isolated from *Rabdosia rubescens*, and proved to be equipped with anti-angiogenesis, antimetastasis, and antitumor growth properties by the diminution of claudin-1, -4, -7, VEGF-A, VEGFR2, and VEFGR3 expressions.[47]

To further summarize the recent advances in studying the antiangiogenic effect of TCMs, the term "Chinese medicine" in combination with "tumor angiogenesis" was used to search PubMed and Google Scholar within the past 5 years (Table 1). Manual searches of in-text references from the selected articles were further performed. Included studies were to be used to create a table or network graph, respectively, if in vivo or in vitro study was aimed to investigate the antitumor angiogenesis effects and mechanisms of TCMs. Studies inconsistent with the above criteria were excluded. Furthermore, a hypothetical schematic with the aforementioned therapeutic mechanisms of TCMs in the attenuation of tumor angiogenesis is outlined in Figure 1. As illustrated in Figure 2, several intensively studied TCMs are elaborated below.

Salvia mitiorrhiza

Salvia miltiorrhiza (SM), an eminent Chinese herbal medicine composed of approximately 900 constituents, comprises a massive range of bioactivities with regard to

Table 1. Summary on Antitumor Angiogenesis Properties of Traditional Chinese Medicines (TCMs) in Recent 5 Years.

Natural Compound	Sources of TCMs	Tumor/Cell Line	Pharmacological Actions	Publication Date	Reference
Catalpol	*Rehmannia glutinosa*	Colon cancer; CT26 cells	VEGF, VEGFR2, HIF-1α, bFGF, IL-1β, IL-6, IL-8, COX-2, iNOS↓	2017	45
Eriocalyxin B	*Isodon eriocalyx*	Breast cancer; MCF-7cells; MDA-MB-231 cells	LC3B-II↑; LC3B-I, p62, ROS↓ Akt/mTOR/p70S6K pathway↓	2017	118
Astragaloside IV; Curcumin	*Astragalus membranaceus;* *Curcuma longa*	Hepatocellular carcinoma	FGF2, MMP-2, VEGF, HGF, TF, FVII, miR-221↓; miR-122↑	2017	119
Ginsenoside Rd	*Panax ginseng*	Breast cancer; MDAMB-231 cells	VEGF↓; Akt/mTOR/p70S6K pathway↓	2017	120
Luteolin	Aromatic flowering plant	Gastric cancer; Hs-746T cells; HUVEC	VEGF; Notch1↓	2017	121
Neoalbaconol	*Albatrellus confluens*	Breast cancer, HUVEC	VEGF; EGFR2↓	2017	47
Ilexgenin A	*Ilex hainanensis*	Hepatocellular carcinoma; HepG2 cells; H22 cells HUVECs	VEGF, TNF-α, IL-6↓; STAT3 and PI3K pathways↓; AST/ALT↓; Caspase-3/7↑;	2017	122
Plumbagin	*Plumbago europaea;* *Plumbago rosea*	Hepatocellular carcinoma; EA. hy926 cells; SMMC-7721 cells; Hep3B cells	PCTGF, ET-1, bFGF↓ PI3K/Akt, VEGF/KDR↓ Angiopoietins (ANG) /Tie2↓	2017	123
Tanshinone IIA	*Salvia miltiorrhiza*	Colorectal cancer; Osteosarcoma CRC cells; 143B cells HUVEC	VEGF, bFGF, TGF-β1, Mfn1/2, Opa1↓; HIF-1α/β-catenin/TCF3/LEF1 signaling pathway↓ Drp1↑	2017	60, 63
Imperatorin	*Angelica dahurica*	Colon cancer; Cervical cancer; Hepatocellular carcinoma HCT116 cells; HeLa cells; Hep3B cells	HIF-1α↓; mTOR/p70S6K/4E-BP1 and MAPK pathways↓	2017	124
Arctigenin	*Arctium lappa*	Breast cancer; MDA-MB-231 cells	MMP-2, MMP-9, Heparanase↓	2017	125
Danshensu	*Salvia miltiorrhiza*	Lewis Lung Carcinoma; LLC cells	HIF-1α, TXB2, 6-keto-PGF1α↓	2017	126
Celastrus orbiculatus extract	*Celastrus orbiculatus*	Hepathocellular carcinoma; HCC cells	TGF-β1, Notch1, Hes1↓	2017	127
Marsdenia tenacissima extract	*Marsdenia tenacissima*	Lymphoma	MMP-2, MMP-9↓	2017	128
Gubenyiliu II (Formula)		Breast cancer	ERK and AKT pathways↓	2017	129
Curcumin	*Curcuma longa*	Glioma; U87 cells	VEGF, Ang-2, TSP-1↓	2016	130
Cryptotanshinone	*Salvia miltiorrhiza*	Melanoma; B16F10 cells; HUVEC	TNF-α, HuR, NF-κB, STAT3↓	2016	72

(continued)

Table 1. (continued)

Natural Compound	Sources of TCMs	Tumor/Cell Line	Pharmacological Actions	Publication Date	Reference
Eriocalyxin B	*Isodon eriocalyx*	Breast cancer; HUVEC	VEGFR2↓	2016	131
Paris saponins	*Paris polyphylla*	Lung adenocarcinoma; PC9ZD cells	Bcl-2↓; Caspase-3, Bax ↑; p21 (Waf1,Cip1) ↑	2016	132
Actein	*Cimicifuga foetida*	Breast cancer; HMEC cells	VEGFR1, pJNK, pERK, CXCR4↓	2016	41
Sinomenine	*Sinomenium acutum*	Osteosarcoma; U2OS cells; HUVEC	CXCR4, STAT3, MMP-2, MMP-9, RANKL, VEGF↓	2016	133
Isosteroidal alkaloid Chuanbeinone	*Fritillaria pallidiflora*	Ovarian cancer; Hepatocellular carcinoma; Lung carcinoma; A2780 cells; HepG2 cells; A549 cells.	Bcl-2↓; Caspase-3, Bax↑	2016	134
Gamabufotalin	Bufonid	Lung cancer; HUVEC	VEGF, VEGFR2↓	2016	135
Oleanolic acid	Olive oil, *Syzygium* spp, garlic, etc.	Colorectal cancer; HUVEC	VEGF, STAT3, FGF2↓	2016	136
Emodin	Rhubarb, buckthorn, etc.	Breast cancer	IRF4, STAT6, MCP1, CSF1, Thy-1↓;C/EBPβ signaling pathway↑	2016	137
20(s)-Ginsenoside Rg3	Ginseng	Lewis lung cancer	VEGF, MMP-9, HIF-1α↓	2016	138
Baicalein	*Scutellaria baicalensis*	Non-small cell lung cancer; H-460 cells	VEGF, FGFR-2↓; RB-1 ↑	2016	108
Hedyotis diffusa Willd extract	*Hedyotis diffusa*	Colorectal cancer; HT-29 cells	LGR5, ATP-binding cassette subfamily B member 1 (ABCB1), β-catenin, c-Myc↓	2016	139
Ginkgo biloba exocarp extracts	*Ginkgo biloba*	Lewis lung cancer; LLC cells	Wnt/β-catenin-VEGF signaling pathway↓	2016	5
Forsythiae fructus aqueous extract	Forsythiae Fructus	Melanoma; B16-F10 cells	ROS, MDA, TNF-α, IL-6↓; Nrf-2, HO-1, p53, p-PTEN↑	2016	140
Salvia triloba methanolic extract	*Salvia triloba*	Prostate cancer; PC-3 cells, DU-145 cells; HUVECs	ANG, ENA-78, bFGF, EGF, IGF-1, VEGF-D, IL-8, LEP, RANTES, TIMP-1, TIMP-2, VEGF↓	2016	141
Xiaotan Sanjie decoction (Formula)		Gastric cancer; HUVECs	LGR5, ATP-binding cassette sub-family B member 1 (ABCB1), β-catenin, c-Myc↓	2016	142
Yang Zheng Xiao Ji (Formula)		Lung cancer; A549 cells; SK-MES-1 cells	VEGF↓	2016	143
Buyang Huanwu decoction (Formula)		Hepatocellular carcinoma	VEGF, RGS5, HIF-1α↓	2016	144
Danugui-Sayuk-Ga-Osuyu-Saenggang-Tang (Formula)		Pancreatic tumor	VEGF, VEGFR2↓	2016	145
Paris saponin II	Rhizoma paridis	Ovarian cancer; SKOV3 cells	NF-κB, VEGF, Bcl-2, Bcl-xL↓	2015	146
Scutellaria barbata D. Don polysaccharides	*Scutellaria barbata*	Lung cancer; Calu-3 cells	HER2, Akt, Erk↓	2015	147
Hydroxysafflor yellow A	*Carthamus tinctorius*	Hepatocellular carcinoma	CyclinD1, C-myc, c-Fos↓	2015	148

(continued)

Table 1. (continued)

Natural Compound	Sources of TCMs	Tumor/Cell Line	Pharmacological Actions	Publication Date	Reference
Formononetin	*Astragalus membranaceus*	Breast cancer; T-47D cells, SK-BR-3 cells, MCF-7 cells MDA-MB-231 cells; HCC1937cells; HUVEC	FGF2, FGFR2, Akt, VEGFR2↓	2015	149
Curcumin	*Curcuma longa*	Fibrosarcoma cancer; Hepatocellular carcinoma; T241-VEGF cells; HepG2 cells; HUVEC	VEGF, VEGFR1, VEGFR2↓	2015	150, 151
Emodin	*Rheum palmatum*	Breast cancer; MDA-MB-231 cells; HUVEC	MMP-2, VEGFR2, Runx2↓	2015	152
Acetyltanshinone IIA	*Salvia miltiorrhiza*	Breast cancer; MDA-MB-453 cells; SK-BR-3 cells; BT-474 cells	RTKs, EGFR, HER2↓ AMPK↑	2015	153
Raddeanin A	*Anemone raddeana*	Colorectal cancer; HCT-15 cells; HUVEC	VEGFR2, PLCγ1, JAK2, FAK, Src, Akt↓	2015	154
Liposomal curcumin	*Curcuma longa*	Hepatocellular carcinoma	HIF-1α, VEGF↓	2015	155
Saponins from *Albizia julibrissin*	*Albizia julibrissin*	Hepatocellular carcinoma; EA.hy926 cells; H22 cells	ERK and AKT pathways↓	2015	156
Alkaloids from *Rubus alceifolius* Poir	*Rubus alceifolius*	Hepatocellular carcinoma	VEGFA↓	2015	157
Alkaloids from *Rubus alceifolius* Poir	*Rubus alceifolius*	Hepatocellular carcinoma; HCC cells	VEGFA, VEGFR2, Notch1, Delta-like Ligand 4 (Dll4), Jagged 1↓	2015	158
Patrinia scabiosaefolia extract	*Patrinia scabiosaefolia*	Colorectal cancer; HT-29 cells	CyclinD1, CDK4↓	2015	159
Feijining decoction (Formula)		Lewis lung carcinoma; LLC cells	VEGF↓; CD4+, CD8+ cells↑	2015	160
Astragalus membranaceus-Curcuma wenyujin formula		Ovarian cancer	MMP-2, VEGF, FGF-2, Cox-2↓	2015	161
Huanglian Jiedu decoction		Hepatocellular carcinoma; HCC cells	eEF2↓; eEF2K↑	2015	162
Tou Nong San (Formula)		Colonic cancer; Colonic LoVo cells	p-PI3K, p-AKT, p-mTOR, p-p70s6k1, VEGF, CD31↓ Cleaved Caspase-3, -9↑	2015	163
BDL301 (Formula)		Colorectal cancer; HCT116 cells	p65, IκBa, STAT3↓	2015	164
Pien Tze Huang (Formula)		Colorectal cancer; HCT-8 cells; HUVEC	HIF-1α, VEGFA, VEGFR2↓	2015	165
Betulinic acid	*Zizyphus mauritiana*	Breast cancer; MDA-MB-231 cells; MDA-MB-468 cells	Specificity protein (Sp) 1, Sp3, Sp4, ErbB2↓	2014	166

(continued)

Table 1. (continued)

Natural Compound	Sources of TCMs	Tumor/Cell Line	Pharmacological Actions	Publication Date	Reference
Genistein	*Genista tinctoria*	Hepatocellular carcinoma; HepG2 cells, Huh-7 cells; HA22T cells	MMP-9, AP-1, NF-κB, ERK↓	2014	167
Celastrol	*Tripterygium wilfordii*	Myeloma; LP-1 cells; NCI-H929 cells; HUVEC	TLR4, VEGF, NF-κB p65, IKKα, IκB-α↓	2014	168
PRP-S1 PRP-S2	*Phellinus ribis*	Hepatocellular carcinoma; Ovary cancer;	VEGF↓	2014	169
Astragalus saponins Vinca alkaloid	*Astragalus membranaceus* *Catharanthus roseus*	Colon cancer; LoVo cells	VEGF, bFGF, MMP-2, MMP-9↓	2014	170
Sulphated polysaccharide	Brown algae	Hepatocellular carcinoma; HCC cells	VEGF, bFGF, IL-8, PCNA↓	2014	171
Scutellaria barbata D. Don extract	*Scutellaria barbata*	Colon cancer; SW620 cells; HT-29 cells; HCT-8 cells	Bax/Bcl-2↑; Cyclin D1; CDK4↓	2014	172
Coptidis rhizome extract	Coptidis rhizome	Hepatocellular carcinoma; MHCC97L cells; HepG2 cells	VEGF↓;eEF2↑	2014	173
Scutellaria barbata extract	*Scutellaria barbata*	Lung cancer; CL1-5 cells; HEL299 cells; 293T cells; LL2 cells	HIF-1α, AKT↓	2014	174
Cordyceps militaris extract	*Cordyceps militaris*	Malignant melanoma; HTB-65 cells	VEGF, AKT, GSK-3β↓; p38α↑	2014	175
Livistona chinensis alcoholic extract	*Livistona chinensis* seeds	Hepatocellular carcinoma; HepG2 cells	VEGFA, VEGFR2, Notch, Dll4, Jagged1↓	2014	176
Anisi stellati fructus extract	Anisi stellati fructus	Lung cancer; B16F0 cells; HUVEC	MMP-9, NF-κB, p38 and JNK	2014	177
Xiaotan Sanjie decoction (Formula)		Gastric cancer; MKN-45 cells	Notch-1, Hes1, VEGF and Ki-67↓	2014	178
Pien Tze Huang (Formula)		Colorectal cancer; HT-29 cells; HCT-8 cells	ATP-binding cassette sub-family G member 2 (ABCG2), ABCB1↓ HIF-1α, E-cadherin, TWIST1↓; N-cadherin↑	2014	179, 180
Norcantharidin	Blister beetles	Colon cancer; LoVo cells; HUVEC	VEGF, VEGFR2, MEK, ERK, p38 MAPK, Akt, Cox-2↓	2013	181
Bigelovin	*Inula helianthus-aquatica*	Leukemia; PBMC cells	Ang2, Tie2, IFN-γ, IL-2, IL-12, ICM-1, VCAM-1, E-selectin↓	2013	182
Saikosaponin D	*Bupleurum falcatum*	Cervical cancer; Hepatocellular carcinoma; Hela cells; HepG2 cells	NF-κB, NF-AT, AP-1, TNF-α↓	2013	183
Isoliquiritigenin	Licorice	Breast cancer; MCF-7 cells, MDA-MB-231 cells; HUVEC	VEGF, VEGFR2, HIF-1α↓	2013	184

(continued)

Table 1. (continued)

Natural Compound	Sources of TCMs	Tumor/Cell Line	Pharmacological Actions	Publication Date	Reference
Timosaponin A-III	Rhizoma Anemarrhenae	Pancreatic cancer; PANC-1 cells	VEGF↓; Caspase-3↑	2013	185
Rosmarinic acid	*Spica prunellae*	Colorectal cancer; HT-29 cells	STAT3, Cyclin D1, CDK4, VEGFA, VEGFR2↓	2013	186
Ursolic acid	*Mirabilis jalapa*	Colorectal cancer; HT-29 cells; HUVEC	VEGFA, bFGF, SHH, STAT3, p70S6K↓	2013	187
Wogonin	*Scutellaria baicalensis*	Osteosarcoma; LM8 cells; THP-1 cells	VEGFC, VEGFR3, COX-2, IL-1↓	2013	188
Oxymatrine	*Sophora japonica*	Pancreatic cancer; PANC-1 cells	NF-κB, VEGF↓	2013	189
Hedyotis diffusa Willd extract	*Hedyotis diffusa*	Colorectal cancer; HT-29 cells	VEGFA, VEGFR2, SHH, PTCH-1, Gli-1↓	2013	190
Marsdenia tenacissima extract	*Marsdenia tenacissima*	Hepatocellular carcinoma; HepG2 cells; HUVEC	VEGFA, VEGFR2↓	2013	191
Patrinia scabiosaefolia extract	*Patrinia scabiosaefolia*	Colorectal cancer; HT-29 cells; HUVEC	VEGFA↓	2013	192
Pien Tze Huang (Formula)		Colorectal cancer; HT-29 cells	STAT3, AKT, MAPKs, iNOS, eNOS, VEGFA, VEGFR2, bFGF, bFGFR↓	2013	193
Teng-Long-Bu-Zhong-Tang (Formula)		Colorectal cancer; CT26 cells	VEGF, XIAP, Survivin↓; Caspase-3, -8, -9, PARP↑	2013	194
Jiedu Xiaozheng Yin (Formula)		Hepatocellular carcinoma; HepG2 cells; HUVEC	VEGFA, VEGFR2↓	2013	195

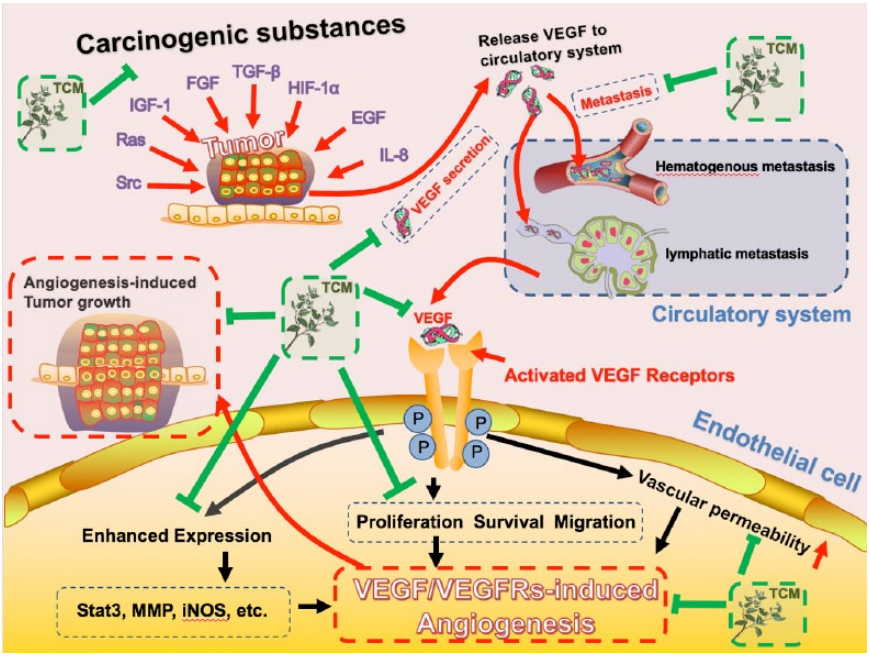


Figure 1. Proposed schematic of therapeutic mechanisms of traditional Chinese medicines in the treatment of tumor-induced angiogenesis.

anti-cholinesterase, antitumor, anti-inflammatory, and anti-angiopathy properties in clinical application.[48,49] Of note, numerous phytochemicals derived from SM attenuate tumor progression involving colorectal cancer, osteosarcoma, Lewis lung carcinoma, melanoma, and prostate cancer through both diminishing the proliferation and migration of vascular endothelial cells and reversing the release of angiogenic cytokines from various types of cancer. Three principal diterpene compounds derived from *S miltiorrhiza*, including tanshinone I, tanshinone IIA and cryptotanshinone, have been extensively applied as natural flavonoids in combating cardiovascular diseases in China. Besides their efficiency in relation with the cardiovascular system, all the 3 compounds are demonstrated to exert distinct antitumor growth properties, including apoptosis induction, cell-cycle arrest and tumor angiogenesis suppression.[50-53]

Tanshinone I, an active ingredient of *S miltiorrhiza*, demonstrated its clinical safety in terms of the high concentration in this herb and therapeutic effect on cardiovascular and inflammatory diseases.[54,55] Tanshinone I efficiently devitalizes drug-resistant tumor cells probably as a result of decreasing the phosphorylated form of signal transducer and activator of transcription 3 (Stat3) at Tyr705 regardless of ambient oxygen conditions and hypoxia-induced HIF-1α accumulation.[52] Additionally, tanshinone I inhibited the transcriptional activity of nuclear factor kappa B (NF-κB) induced by the stimulation of tumor necrosis factor–α (TNF-α) and IL-6.[53,56] However, it is noteworthy that tanshinone I was identified to possess anti-angiogenesis activities in tumor metastasis at either hypoxic or normoxic condition by the direct impact on both endothelial and tumor cells. The proliferation, migration, as well as the differentiation of endothelial cells could be attenuated by tanshinone I, preventing tumor angiogenesis at its initial stage.[57] In a transgenic mouse model of the human vascular endothelial growth factor-A165 (hVEGF-A165) gene-triggered lung cancer, tanshinone I significantly downregulated the over-expression of hVEGF-A165 in vivo, arresting cells at S and G2/M phases favorable for antivasculogenesis therapy.[58] Furthermore, the attenuation of microvessel density in various xenograft tumors and the migration and tube formation capability of HUVEC were inhibited on tanshinone I treatment.[52,59]

Tanshinone IIA, a comprehensively investigated compound in *S miltiorrhiza*, was reported as a potent inhibitor of neovascularization in numerous cancer cell types, including lung cancer and osteosarcoma.[60,61] Tanshinone IIA exerted antiangiogenic effects in various human colorectal cancer cell lines, such as LoVo, SW620, HT-29, HCT-116 as well as HUVEC, by blocking HIF-1α/β-catenin/TCF3/LEF1 signaling pathway in the hypoxic microenvironment.[61,62] Tanshinone IIA inhibited angiogenesis via mediating the protein kinase domains of VEGF/VEGFR2 and triggered cell apoptosis and cell cycle arrest at the S phase in A549 cells.[60] In addition, tanshinone IIA induced the impairment of HIF-1α and VEGF expression and

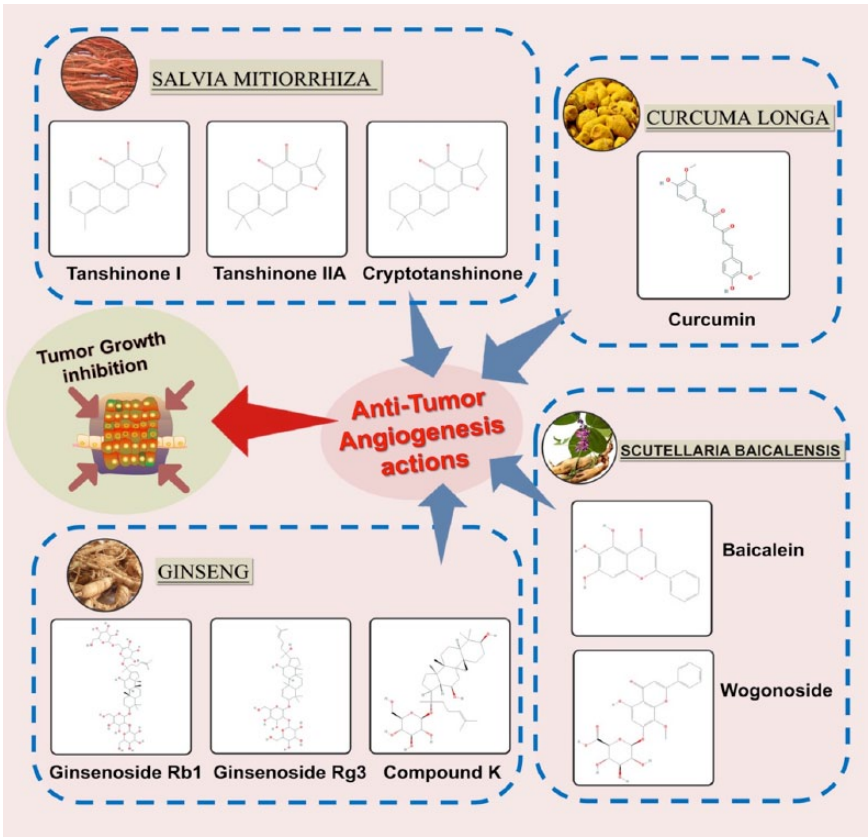


Figure 2. Typical molecular formulas of 9 principal active compounds derived from intensively studied traditional Chinese medicines.

dephosphorylated the levels of mammalian target of rapamycin (mTOR) and its effectors like eukaryotic initiation factor 4E-binding protein-1 (4E-BP1) and ribosomal protein S6 kinase (p70S6K) to suppress the human breast cancer growth.[63,64] Moreover, the secretion of matrix metalloproteinase-2 (MMP-2) is attenuated in combination with the increase of the tissue inhibitor of metalloproteinase-2 (TIMP-2) in vascular endothelial cells.[65]

Cryptotanshinone, a principal lipophilic component extracted from *S miltiorrhiza*, has multiple biological functions involving anti-inflammatory, antineurodegeneration, antioxidative stress, antiplatelet aggregation, antibacterial, and antitumor angiogenesis activities.[66-71] Cryptotanshinone inhibited cell proliferation and VEGF-induced angiogenesis in U2OS osteosarcoma cells.[72] Cryptotanshinone delivered antiangiogenic effects against various cancer cells by destabilizing the mRNA level of TNF-α involving NF-κB and STAT3 pathways and diminishing the cytoplasmic translocation of mRNA stabilization factor HuR.[73,74] In addition, cryptotanshinone repressed cell viability, tubular-like structure formation, migration, and invasion in HUVEC by blocking β-catenin dependent transcription and expression of VEGF and cyclin D1.[70]

Curcuma longa

Curcuma longa, a rhizomatous plant of the ginger family, has revealed profound anti-inflammatory and antioxidative functions for centuries.[75] Clinical trials were organized by the 2005 National Institutes of Health to explore the usage of *C longa* in the treatment of multiple cancers, including pancreatic cancers, myelomas, as well as colorectal cancers.

Curcumin, as a principal compound in *C longa*, is a natural polyphenol with multiple effects on antioxidative, anti-inflammatory, and antiseptic properties in combating tumor growth and inflammation.[76] Accumulating evidence revealed that curcumin possessed potential antiangiogenic property in vitro and in vivo by modulating expression of various genes.[77,78] Curcumin attenuated VEGF-A secretion and mRNA synthesis and HIF-1α production in corticotroph AtT20 mouse, human pituitary adenoma cells, as well as in lactosomatotroph GH3 rat pituitary cancer cells under $CoCl_2$-induced hypoxia conditions.[79] VEGF-associated angiogenesis in human intestinal microvascular endothelial cells (HIMEC) could be blocked through suppressing the expression of COX-2 and MAPK by curcumin treatment.[80] Treatment with curcumin gave rise to the inhibition of

ovarian cancer growth and angiogenesis by regulation of NF-κB-related pathways.[81] Furthermore, in a cervical cancer xenograft mouse model, the proliferation and angiogenic activities could be attenuated through downregulating the expression of COX-2, VEGF, and EGFR.[82] In line with other studies, integrative therapy of curcumin and metformin could not only promote cancer cells into apoptosis by the activation of mitochondrial pathways but also ameliorate the metastasis and invasion of HCC cells as well as the angiogenic capability of HUVEC cells. These effects were correlated with the downregulation of MMP2/9, VEGF, and VEGFR-2 expression and inactivation of the PI3K/Akt/mTOR/NF-κB and EGFR/STAT3 signaling pathways, whereas protein levels of P53 and PTEN were increased on curcumin treatment.[83] Similar results are also observed in a bladder cancer orthotopic mouse model and MB49 cells. Both expressions of Cox-2 and Cyclin D1 are decreased for the modulation of NF-κB-related genes.[84] Tetrahydrocurcumin, a main metabolite of curcumin, has been shown to be more effective than curcumin in the prevention of carcinogenic and angiogenic effects in azoxymethane-induced colon carcinogenesis in vivo through mediating a decrease in the protein expression of Wnt-1 and β-catenin in cancerous colonic tissue.[85,86]

Ginseng

Ginseng is a herbal name mainly linked with 2 botanical species, *Panax ginseng* (Asian ginseng) and *Panax quinquefolius* (American ginseng), and has been regarded as a Chinese medicine for improving diabetes and cardiovascular diseases, as well as suppressing tumor growth and angiogenesis over centuries.[87,88] Ginseng contains various active compounds involving ginsenosides, polysaccharides, mineral oils, fatty acids, as well as polysaccharides.[89] Ginsenosides are extensively considered as the principal bioactive constituent derived from ginseng regardless of different species and are also responsible for the major pharmacological effects of anti-inflammatory and antiangiogenic activities.[90,91] Ginsenosides could be classified and identified in 2 categories, the 20(S)-protopanaxadiol (eg, Rb1, Rb2, Rg3, Rh2) and the 20(S)-protopanaxatriol (eg, Rg1, Re, Rh1). Existing literature has demonstrated that ginsenosides Rb1 and Rg3 exhibit significant antiangiogenic actions in blocking the proliferation of numerous tumors, including pulmonary, gastric, and ovarian cancers.[92]

Ginsenoside Rb1, a major compound of ginseng, has been demonstrated to potently reverse the in vivo and in vitro angiogenic status. Rb1 reduced the formation of tube-like structures by HUVEC cells through modulating the expression of pigment epithelium-derived factor (PEDF) in association with the transfection of estrogen receptor β.[93,94] The chemoinvasion and tubulogenesis of endothelial cells could be reversed on ginsenoside Rb1 treatment.[95]

Ginsenoside Rg3 could impair the proliferation and migration of colorectal cancer (CRC) in vitro by downregulating the levels of B7-H1 and B7-H3 and angiogenesis-related genes, such as ANGPT1, EGF, and TIMP1. Meanwhile, Rg3 enhanced the cytotoxic effect of oxaliplatin and 5-fluorouracil in a colorectal cancer-bearing orthotopic xenograft mouse model, resulting in suppression of angiogenesis and remodeling of the tumor microenvironment.[96] Temozolomide treatment combined with Rg3 enhanced the inhibitory effect on the proliferation of both HUVEC and rat C6 glioma cells by arresting the cell cycle, inducing apoptosis and reducing the expression of Bcl-2 and VEGF-A in HUVEC. Furthermore, similar results were presented in an orthotopic glioma rat model where VEGF expression and microvessel density were attenuated on Rg3 treatment.[97] In addition, after Rg3 administration, an elevated level of miR-520h may profoundly suppress the protein expression of EphB2 and EphB4, cell proliferation, tubulogenesis of HUVEC cells, as well as the formation of the subintestinal vessel in zebra embryos.[98] The tumor progression, microvessel density, loss of body weight, and metastasis rate were inhibited in an orthotopic HCC transplantation mouse model by the attenuation of VEGF and VEGF receptor 2 and phosphor-VEGF receptor 2 levels.[99] Moreover, in human lung squamous cancer SK-MES-1 cells, the expression of VEGF and its mRNA were reduced via Rg3 treatment.[100] In terms of the result from a Matrigel plug assay, Rg3 apparently diminished the basic fibroblast growth factor (bFGF)-induced tumor neovascularization, owing to the decline of MMP-2 and MMP-9 expression, which contributed to the basement membrane degradation in the emergence of tumor angiogenesis.[101]

Compound K is an active metabolite originating from ginsenoside in the gut. Apart from the anti-apoptotic property of compound K in treating a variety of cancers, including human leukemia cell HL-60 by direct or indirect impact on decreasing the activation of caspase-3, compound K exhibited the characteristics of antiplatelet aggregation and antiangiogenesis through the decrease of primary tumor proliferation in a mouse model of spontaneous metastasis.[92,102] Angiosuppressive property of compound K could be related with the decrease of MMP-9 mRNA expression, which was associated with the attenuation of MMP-9 promoter activity.[103] Additionally, migration and tube-like structure formation of HUVEC have been significantly suppressed on compound K treatment, which may result from the reduction of VEGF, p38 MAPK and AKT expressions while upregulation of the expression of pigment epithelium-derived factor (PEDF) in HUVEC cells.[104]

Scutellaria baicalensis

Scutellaria baicalensis has been known as a traditional Chinese medicine to treat numerous medical conditions,

including cardiovascular disease and tumors. Studies on the efficacy of *S baicalensis* have disclosed that various flavonoids isolated from the herb have beneficial antineoplastic, antioxidant, antiplatelets aggregation, and antiangiogenesis properties.[105]

Baicalein, a natural active flavonoid derived from *S baicalensis*, is widely used for its anti-inflammation, antitumor, and neural protective effects.[106] Baicalein treatment induced B16F10 and LLC cell death by the activation of caspase-3 and blockage of tube formation and cell migration of HUVEC cells. Moreover, the reduction of tumor size simultaneously greatly inhibited the rate of tumor growth, metastasis, and neovascularization in the early phase of tumorigenesis.[106] Baicalein could attenuate the production of new vessels in chicken chorioallantoic membrane, as well as in rat aorta, and lessen the motility and invasion of HUVEC cells. Furthermore, baicalein was shown to directly bind with AP-1 and downregulate the expression of c-Jun and c-Fos.[107] Proliferation and angiogenesis in lung cancer could be inhibited both in vitro and in vivo on baicalein treatment by reducing cellular F-actin level, expression of 12-lipoxygenase, FGFR-2, and VEGF, while increasing RB-1 level, nuclear condensation, and potential of mitochondrial mass in H-460 cells and an orthotopic transplantation model.[108] Orally administered baicalein exerted beneficial effect on repressing the aggregation of endothelial cells and human prostate tumor growth in vivo and in vitro.[109]

Wogonoside, a major flavonoid isolated from *S baicalensis*, has been demonstrated to be an inhibitor of VEGF and possesses anticancer and antiangiogenesis activities.[110] Therapeutic effects of wogonoside in breast cancer MCF-7 cells and xenografted mouse illustrated that the secretion of VEGF and intracellular level of Wnt3a were decreased, which in turn boosted the expression of GSK-3β, AXIN and phosphorylated β-catenin for proteasomal degradation. Meanwhile, DNA-binding activity of β-catenin/TCF/LEF1 complex was attenuated by wogonoside treatment as well.[111] Wogonin, the metabolite of wogonoside, enhanced the ubiquitination and nuclear translocation of HIF-1α by reducing its stability and binding with heat-shock protein 90 in MCF-7 cells.[112] In addition, wogonin inhibited hydrogen peroxide and IGF-1-induced migration and proliferation of HUVEC cells through decreasing the binding capacity of NF-κB in combination with exogenous consensus DNA oligonucleotide and suppressing P13K/Akt signaling pathway.[113]

Discussion

Network Construction and elaboration

Compounds from TCMs provide promising prospects for the treatment of complicated diseases, including tumor angiogenesis, in a synergistic manner. Nevertheless, searching a way to screen the effective and synergistic combinations from various TCMs as well as finding prominent pathogenic factors contributing to tumor angiogenesis is still a continuous challenge. As an innovative screening method to prioritize the targets of TCM to the treatment of tumor angiogenesis, TCM-based network pharmacology provides a holistic and in-depth understanding of the association between herbal ingredients and therapeutic targets in a systematic manner.[114] All the pharmacological actions not only can be visualized directly, but the curative mechanisms regarding antitumor angiogenesis therapy on TCM treatment can be comprehensively analyzed as well.

With regard to clarifying the potential pathogenic factors and the regulatory mechanisms of TCMs for the treatment of tumor angiogenesis, a database for network pharmacology was established as previously described.[115] Hands-on literature mining in PubMed and Google Scholar with keywords as "Chinese medicine" integrated with "Tumor angiogenesis" was performed. All the data were searched for the past 5 years (2013-2017), as summarized in Table 1. After a comprehensive screening, approximately 200 entities, including TCMs and biological factors, have been enrolled in the construction of the network. After comprehensive screening, all the filtered data were imported into Cytoscape, a professional software package in bioscience research for the analysis of network pharmacology (available online at http://www.cytoscape.org/).[116,117] The detailed relationships regarding the well-accepted ideology of "multitarget, multidrug" among each factor can be straightforwardly observed in Figure 3. More specifically, the nodes represent the TCMs-related compounds, refined extracts and biological factors (protein or mRNA). Since edges encode the TCM-target interactions, a relationship between 2 targets can be directly observed though edge-combined 2 nodes. The degree of correlation between 2 nodes could be analyzed by Cytoscape. Notably, nodes with high centrality and edges represented as more indispensable in the network.[114] The top 10 influential factors have been identified in Figure 3, such as VEGF, VEGFR2, MMP-2, STAT3, and so on, indicating that targeting VEGF/VEGFRs pathway acts as the dominant role for TCMs in treating tumor angiogenesis.

Ethnopharmacology-Related Challenges and Threats

Up until now, it remains unclear if the complicated and abnormal conditions of tumor vasculature are coupled with the multiple paths for the formation of blood vessels. In accordance with combination of both the theory of TCMs and aforementioned research findings, rigorous challenges and threats have been considered into 6 aspects, which include the following: (*a*) The identification standards of certain TCMs with antitumor angiogenesis property is

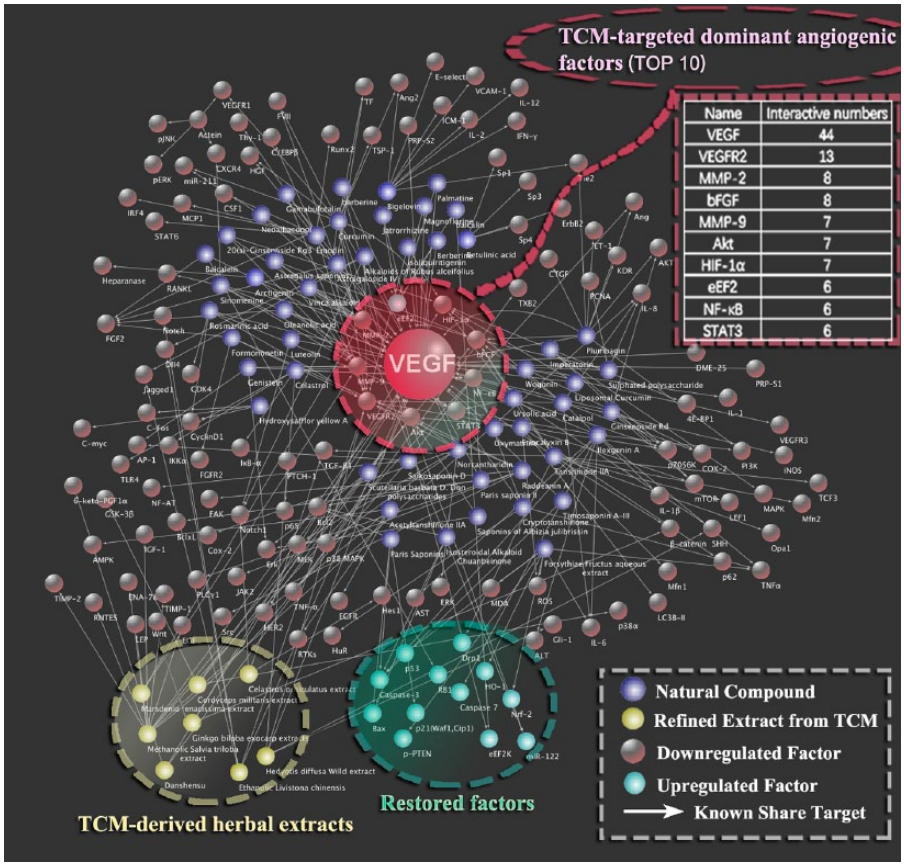


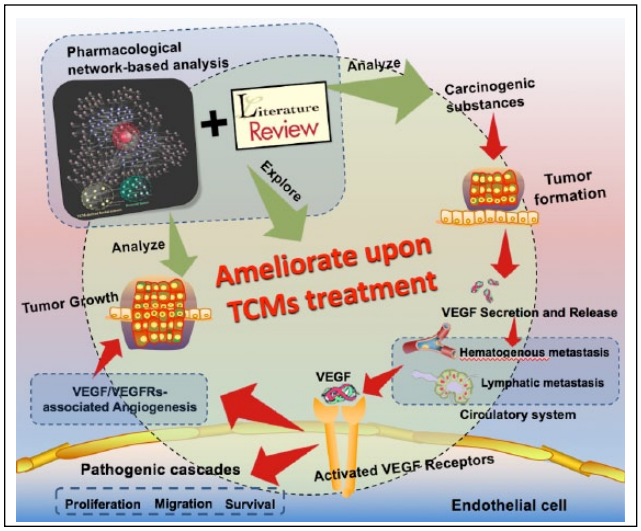
Figure 3. Target identification of traditional Chinese medicines (TCMs)–derived natural compounds and extracts for the alleviation of tumor angiogenesis.

ambiguous. (*b*) Only a minority of TCMs have been screened and validated as potential inhibitors in combating the establishment of tumor vasculature at present. (*c*) The majority of studies focus on TCM-derived herbal compounds rather than the formulae, targeting the occurrence of tumor angiogenesis. Of note, in the theory of TCMs, formulae with multiple combinations of herbs are the dominant form and more frequently used for cancer therapy. Therefore, studies of Chinese formulae against tumor-induced neovascularization should be comparatively enhanced to explore more TCMs with potent therapeutic effects. (*d*) Monotherapy of suppressing angiogenesis can merely inhibit the tumor proliferation and metastasis instead of directly eliminating the existing tumor cells, which is attributable to tumor heterogeneity and the diversity of proangiogenic cytokines released from cancer cells with different species. (*e*) Studies of antiangiogenic mechanisms of TCMs are mostly at the experimental stage, lacking in large-scale samples and multicenter clinical trials. (*f*) An extensive range of mechanisms may be involved together; for instance, baicalein inhibits tumor-triggered angiogenesis mainly through 3 potential mechanisms, the induction of apoptosis, antimigratory and antiendotheliocyte growth. Thus, similar to other TCMs, it is uncertain to confirm which functional mechanism has the dominant and uncontestable impact on the alleviation of tumor angiogenesis.

Conclusion and Perspective

Systematic screening of pathological factors contributing to the activity of tumor-associated angiogenesis has given rise to the progression of TCM-associated therapeutic modalities, which probably function through the amelioration of overexpressed VEGF/VEGFRs (Appendix). Numerous herbal compounds and formulae originating from TCMs afford an affluent source for exploring efficient anti-tumor angiogenesis agents. Because of the multiple genes conducive to the initiation of angiogenesis in burgeoning tumors and the multitarget characteristic of TCMs, the application of TCMs should be superior to agents aiming at a single molecular target, even though the prevention of tumor angiogenesis using TCMs is still in its infant period. Therefore, TCMs may provide permanent and attractive effects on inhibiting tumor angiogenesis as underlying chemopreventive agents in the treatment of diversified cancers.

Appendix



Schematic flowchart on the strategy of elaborating the underlying anti-tumor angiogenesis mechanism treated by traditional Chinese medicine

Declaration of Conflicting Interests

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