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 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 understood 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).²,³ 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...
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 angiogenesis 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 (PIGF), 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, PIGF, 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 (FGFRI) 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. As described above, VEGFR2 has a dominant proangiogenic activity irrespective of whether mildly increased soVEGFR2 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 progression of tumor metastasis, lymphangiogenesis, and angiogenesis. The transcription of VEGFR3 is mediated by Sp1 and Sp3, known as zinc finger proteins, under epigenetic control. Under physiological conditions, VEGFR3 is expressed restrictively in certain fenestrated vascular endothelial cell proliferation and lymphangions, while massively emerging 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. Deprivation of VEGFR3 expression led to cardiovascular failure and sparse vascular density, indicating the biological activity of VEGFR3 in the formation of blood vessels.

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. In particular, VEGFR3 restrained the activity of VEGFR2, along with the VEGF/VEGFR2 signaling pathway, and prevented excessive vascular permeability in endothelial cells. 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. 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. 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, 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 CoCl2-mimicked hypoxic microenvironment as well. 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. 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. 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. Neovalaconol, 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. Oridonin is the main terpene isolated from *Rabdosia rubescens*, and proved to be equipped with antiangiogenesis, antimetastasis, and antitumor growth properties by the diminution of claudin-1, -4, -7, VEGF-A, VEGFR2, and VEGFR3 expressions.

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 miltiorrhiza**

*Salvia miltiorrhiza* (SM), an eminent Chinese herbal medicine composed of approximately 900 constituents, comprises a massive range of bioactivities with regard to
| 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        |
| Eriocalyxsin B      | *Isodon eriocalyx*             | Breast cancer; MCF-7 cells; MDA-MB-231 cells | LC3B-I↓, p62, ROS↓                                                                     | 2017             | 118       |
| Astragloside IV;    | *Astragalus membranaceus*      | Hepatocellular carcinoma             | FGF2, MMP-2, VEGF, HGF, TF, FVII, miR-221↓, miR-122↑                                 | 2017             | 119       |
| Astragolside IV;    | *Curcuma longa*                |                                      |                                                                                        |                  |           |
| Ginsenoside Rd      | *Panax ginseng*                | Breast cancer; MDA-MB-231 cells      | VEGF↓                                                                               | 2017             | 120       |
| Luteolin            | Aromatic flowering plant       | Gastric cancer; Hs-746T cells; HUVEC | Akt/mTOR/p70S6K pathway↓                                                               | 2017             | 121       |
| Neoalbaconol        | *Albatrellus confusus*         | 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↑; PI3K/Akt, VEGF/KDR↑, Angiopoietins (ANG)/Tie2↓ | 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       | VEGF, bFGF, TGF-β1, Mn1/2, Opa1↓, HIF-1α/j-l-catenin/TCF3/LEF1 signaling pathway↓, Drp1↑ | 2017             | 60, 63    |
| Imperatorin         | *Angelica dahurica*            | Colo rectal cancer; Cervical cancer; Hepatocellular carcinoma; HCT 116 cells; HeLa cells; Hep3B cells | HIF-1α↓↓, mTOR/p70S6K/4E-BPI 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-PGFα↓                                                           | 2017             | 126       |
| Celastrus orbiculatus extract | *Celastrus orbiculatus* | Hepatocellular carcinoma; HCC cells | TGF-β1, Notch1, Hes1↓                                                                  | 2017             | 127       |
| Marsdenia tenacissima extract | *Marsdenia tenacissima* | Lymphoma                             | MMP-2, MMP-9↓                                                                        | 2017             | 128       |
| Gubenyiliu II (Formula) | *Celastrus orbiculatus* | 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)
| 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; PC92D cells                 | Bcl-2↓; Caspase-3, Bax↑; p21 (Waf1,Cip1)↑ | 2016            | 132       |
| Actein                    | Cimicifuga foetida              | Breast cancer; HMEC cells                        | VEGFR1↓, pJNK, pERK, CXC4R4↓             | 2016            | 41        |
| Sinomenine                | Sinomenium acutum               | Osteosarcoma; U2OS cells; HUVEC                 | CXC4R4, STAT3, MMP-2, MMP-9, RANKL, VEGF↓ | 2016            | 133       |
| Isosteroidal alkaloid     | 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, VEGF↓                               | 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; H4-460 cells         | VEGF, FGR-2↓; RB-1↑                     | 2016            | 108       |
| Hedyotis diffusa Wild 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(/)-catenin-VEGF signaling pathways↓ | 2016            | 5         |
| Forsythia fructus aqueous extract | Forsythia 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, BGF, EGF, IGF-1, VEGF-D, IL-8, LEP, RANTES, TIMP-1, TIMP-2, VEGF↓ | 2016            | 141       |
| Xiaoan Sanjie decoction (Formula) | HUVECs                      | Gastric cancer; HUVECs                           | LGR5, ATP-binding cassette subfamily B member 1 (ABCB1), β-catenin, c-Myc↓ | 2016            | 142       |
| Yang Zheng Xiao Ji (Formula) | Lung cancer; A549 cells; SK-MES-1 cells | VEGF↓                                     | VEGF↓                                   | 2016            | 143       |
| Buyang Huanwu decoction (Formula) | Hepatocellular carcinoma     | VEGF, RG55, HIF-1α↓                            | VEGF, VEGFR2↓                           | 2016            | 144       |
| Danugui-Sayuk-Ga-Osuyu-Saenggung-Tang (Formula) | Pancreatic tumor               | VEGF, VEGFR2↓                                 | VEGF, VEGF↓                            | 2016            | 145       |
| Paris saponin II          | Rhizoma paridis                | Ovarian cancer; SKOV3 cells                     | NF-κB, VEGF, Bcl-2, Bcl-xL↓              | 2015            | 146       |
| Scutellaria barbata D.    | Scutellaria barbata            | Lung cancer; Calu-3 cells                       | HER2, Akt, Erk↓                         | 2015            | 147       |
| Don polysaccharides       |                                  |                                               |                                         |                 |           |
| Hydroxysafflor yellow A   | Carthamus tinctorius           | Hepatocellular carcinoma                       | CydinD1, C-myc, c-Fos↓                  | 2015            | 148       |

(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; HCC1937 cells; 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 *Abizia julibrissin* | *Abizia julibrissin* | Hepatocellular carcinoma; EA.hy926 cells; H22 cells | ERK and AKT pathways↓ | 2015            | 156       |
| Alkaloids from Rubus dcefolius Poir | *Rubus alcefolius* | Hepatocellular carcinoma | VEGFA↓ | 2015            | 157       |
| Alkaloids from Rubus dcefolius Poir | *Rubus alcefolius* | Hepatocellular carcinoma; HCC cells | VEGFA, VEGFR2, Notch1, Delta-like Ligand 4 (Dll4), Jagged 1↓ | 2015            | 158       |
| Patrinia scabiosaefila extract | *Patrinia scabiosaefila* | Colorectal cancer; HT-29 cells | CyclinD1, CDK4↓ | 2015            | 159       |
| Feijining decoction (Formula) | | Lewis lung carcinoma; LLC cells | VEGF↓; CD4+, CD8+ cells↑ | 2015            | 160       |
| Astragulus 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; HCT 116 cells | p65, IκBα, 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)
| 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-kB, ERK↓ | 2014 | 167 |
| Celastrol        | Tripterygium wilfordii | Myeloma; LP-1 cells; NCI-H929 cells; HUVEC | TLR4, VEGF, NF-kB p65, IKKα, IκB-α↓ | 2014 | 168 |
| PRP-S1 PRP-S2    | Phellinus ribis | Hepatocellular carcinoma; Ovary cancer; VEGF↓ | | 2014 | 169 |
| Astragalus saponins | Astragalus membranaceus | Colon cancer; LoVo cells | VEGF, bFGF, MMP-2, MMP-9↓ | 2014 | 170 |
| Vinca alkaloid    | Catharanthus roseus | HCC cells | VEGF, bFGF, IL-8, PCNA↓ | 2014 | 171 |
| Sulphated         | Brown algae | Hepatocellular carcinoma; HCC cells | VEGF, bFGF, IL-8, PCNA↓ | 2014 | 172 |
| Scutellaria barbata D. Don extract | Scutellaria barbata | Colon cancer; SW620 cells; HT-29 cells; HCT-8 cells | Bax/Bcl-2↑; Cyclin D1; CDK4↓ | 2014 | 173 |
| PRP-S1 PRP-S2    | Phellinus ribis | Hepatocellular carcinoma; Ovary cancer; VEGF↓ | | 2014 | 174 |
| Cardyceps militaris extract | Cardyceps militaris | Malignant melanoma; HTB-65 cells | VEGF, AKT, GSK-3β↓; p38α↑ | 2014 | 175 |
| Livistana chinensis | Livistana chinensis seeds | Hepatocellular carcinoma; HepG2 cells | VEGFA, VEGFR2, Notch, Dll4, Jagged↓ | 2014 | 176 |
| Anisi stellati fructus extract | Anisi stellati fructus | Lung cancer; B16F0 cells; HUVEC | MMP-9, NF-kB, p38 and JNK | 2014 | 177 |
| Xiaotan Sanjie decoction (Formula) | Scutellaria barbata | Lung cancer; CL-1-5 cells; HEL299 cells; 293T cells; LL2 cells | HIF-1α, AKT↓ | 2014 | 178 |
| Pien Tze Huang (Formula) | Scutellaria barbata | Lung cancer; CL-1-5 cells; HEL299 cells; 293T cells; LL2 cells | HIF-1α, AKT↓ | 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-kB, 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)
| Natural Compound               | Sources of TCMs               | Tumor/Cell Line          | Pharmacological Actions                  | Publication Date | Reference |
|--------------------------------|-------------------------------|--------------------------|------------------------------------------|------------------|-----------|
| Timosaponin A-III             | Rhizoma Anemarrhenae         | Pancreatic cancer;       | VEGF↓; Caspase-3↑                        | 2013             | 185       |
|                               |                               | PANC-1 cells             |                                          |                  |           |
| Rosmarinic acid               | Spica prunelloe               | Colorectal cancer;       | STAT3, Cyclin D1, CDK4, VEGFA, VEGFR2↓    | 2013             | 186       |
|                               |                               | HT-29 cells              |                                          |                  |           |
| Ursolic acid                  | Mirabilis jalapa              | Colorectal cancer;       | VEGFA, bFGF, SHH, STAT3, p70S6K↓         | 2013             | 187       |
|                               |                               | HT-29 cells; HUVEC       |                                          |                  |           |
| Wogonin                       | Scutellaria baicalensis       | Osteosarcoma; LM8 cells; THP-1 cells | VEGFC, VEGFR3, COX-2, IL-1↓             | 2013             | 188       |
| Oxymatrine                    | Sophora japonica              | Pancreatic cancer;       | NF-κB, VEGF↓                            | 2013             | 189       |
|                               |                               | PANC-1 cells             |                                          |                  |           |
| Hedysis diffusa Wild extract  | Hedyatis diffusa              | Colorectal cancer;       | VEGFA, VEGFR2, SHH, PTCH↑, Gli-1↓        | 2013             | 190       |
|                               |                               | HT-29 cells              |                                          |                  |           |
| Marsdenia tenacissima extract  | Marsdenia tenacissima         | Hepatocellular carcinoma; | VEGFA, VEGFR2↓                          | 2013             | 191       |
|                               |                               | HepG2 cells; HUVEC       |                                          |                  |           |
| Patrinia scabiosaefolia extract | Patrinia scabiosaefolia       | Colorectal cancer;       | VEGFA↓                                   | 2013             | 192       |
|                               |                               | HT-29 cells; HUVEC       |                                          |                  |           |
| Pien Tze Huang (Formula)      |                               | Colorectal cancer;       | STAT3, AKT, MAPKs, iNOS, eNOS, VEGFA, VEGFR2, bFGF, bFGFR↓ | 2013             | 193       |
|                               |                               | HT-29 cells              |                                          |                  |           |
| Teng-Long-Bu-Zhong-Tang (Formula) |                               | Colorectal cancer;       | VEGF, XIAP, Survivin↓; Caspase-3, -8, -9, PARP↑ | 2013             | 194       |
|                               |                               | CT26 cells               |                                          |                  |           |
| Jiedu Xiaozheng Yin (Formula) |                               | Hepatocellular carcinoma; HepG2 cells; HUVEC | VEGFA, VEGFR2↓                          | 2013             | 195       |
anti-cholinesterase, antitumor, anti-inflammatory, and anti-angiopathy properties in clinical application. 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.

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. 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. 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. 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. 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. 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.

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. 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. 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. In addition, tanshinone IIA induced the impairment of HIF-1α and VEGF expression and

Figure 1. Proposed schematic of therapeutic mechanisms of traditional Chinese medicines in the treatment of tumor-induced angiogenesis.
Zhang et al. 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 \textit{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**

\textit{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 \textit{C. longa} in the treatment of multiple cancers, including pancreatic cancers, myelomas, as well as colorectal cancers.

Curcumin, as a principal compound in \textit{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{87,88} Ginseng contains various active compounds involving ginsenosides, polysaccharides, mineral oils, fatty acids, as well as polysaccharides.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{93,94} The chemoinvasion and tubulogenesis of endothelial cells could be reversed on ginsenoside Rb1 treatment.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{99} Moreover, in human lung squamous cancer SK-MES-1 cells, the expression of VEGF and its mRNA were reduced via Rg3 treatment.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. baikalenis* 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. baikalenis*, is widely used for its anti-inflammation, anti-tumor, 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 caspase-3 and blockage of tube formation and cell migration of endothelial cells and human prostate tumor growth in vivo and in vitro.109

Wogonoside, a major flavonoid isolated from *S. baikalenis*, 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 DNA-binding activity of β-catenin/TCF/LEF1 complex.112 Oral administration of baicalein exerted beneficial effect on repressing the aggregation of endothelial cells and human prostate tumor growth in vivo and in vitro.110

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

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