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Review

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Therapeutic potential of traditional Chinese medicine for vascular endothelial growth factor

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Abstract: Vascular endothelial growth factor (VEGF) is the main regulator of physiological angiogenesis during embryonic development, bone growth, and reproductive function, and it also participates in a series of pathological changes. Traditional Chinese medicine (TCM), with a history of more than 2000 years, has been widely used in clinical practice, while the exploration of its mechanisms has only begun. This review summarizes the research of recent years on the influence of TCM on VEGF. It is found that many Chinese medicines and recipes have a regulatory effect on VEGF, indicating that Chinese medicine has broad prospects as a complementary and alternative therapy, providing new treatment ideas for clinical applications and the theoretical basis for research on the mechanisms of TCM.

Key words: Vascular endothelial growth factor (VEGF); VEGF receptor; Traditional Chinese medicine (TCM)

1 Introduction

The vascular endothelial growth factor (VEGF), is a joint regulator of physiological angiogenesis during the process of embryonic development, bone growth, and reproductive function (Ferrara et al., 2003). Furthermore, it has roles in a series of pathological changes. During the history of research on the relationship between tumors and pathological angiogenesis in the past 100 years, many involved molecules have been highlighted. Senger et al. (1983) discovered a protein that promotes the permeability of vascular endothelial cells from guinea pig tumor cells and subsequently named it as vascular permeability factor (VPF) based on its biological effects. Ferrara and Henzel (1989) isolated a substance from bovine pituitary follicular cells that can promote the mitosis of vascular endothelial cells according to its target cell specificity, and named it as VEGF. Furthermore, their respective teams confirmed through gene sequence analysis that VEGF and VPF were the same molecules (Connolly et al., 1989; Keck et al., 1989; Leung et al., 1989). Since then, VEGF has been the subject of most in-depth studies on angiogenesis (Ferrara, 2002).

VEGF ligand proteins include VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PlGF) (Park et al., 1994; Olofsson et al., 1996; Shibuya, 2003; Karkkainen et al., 2004; Duong et al., 2014). Among them, VEGF-A has been the most extensively studied one. In a study on VEGF, the identified VEGF subtypes are VEGF121, VEGF165, VEGF189, and VEGF206, which are all subtypes of VEGF-A (Ferrara et al., 2003). In many other articles, VEGF-A is also directly referred to as VEGF. VEGF protein receptors can be divided into receptor tyrosine kinases, neuropilins (NRPs), and heparan sulfate proteoglycans (HSPGs). Receptor tyrosine kinases include VEGF receptor-1 (VEGFR-1), VEGFR-2, and VEGFR-3, among which VEGFR-2 is currently recognized as the main receptor for angiogenesis and the enhancement of vascular permeability. NRPs are classified into NRP-1 and NRP-2 (Chen et al., 1997; Kawasaki et al., 1999). The former is preferentially localized in arteries, while the latter is expressed in veins (Herzog

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et al., 2001). HSPGs are considered to be co-receptors, enhancing the stability of the receptor complex (Dai and Rabie, 2007).

This review intends to summarize the research of past five years on the influence of traditional Chinese medicine (TCM) that is relevant to the expression of VEGF proteins and receptors, and is based on disease classification. For the ease of access, we organized the recipes by mentioning the medicines and their constituents in alphabetical order according to the unified names included in the 2020 edition of *Pharmacopoeia of the People's Republic of China* (Chinese Pharmacopoeia Commission, 2020), as shown in Table 1.

Table 1 Components of traditional Chinese medicine (TCM) recipes discussed in this review

Recipe	Ingredients
Buyang Huanwu Decoction	Angelicae Sinensis Radix, Astragali Radix, Carthami Flos, Chuanxiong Rhizoma, Paeoniae Radix Rubra, Persicae Semen, Pheretima
Xijiao Dihuang Decoction	Bubali Cornu, Moutan Cortex, Paeoniae Radix Alba, Rehmanniae Radix
Ginseng Yangrong Decoction	Angelicae Sinensis Radix, Astragali Radix, Atractylodis Macrocephalae Rhizoma, Cinnamomi Cortex, Citri Reticulatae Pericarpium, Ginseng Radix et Rhizoma, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle, Jujubae Fructus, Paeoniae Radix Alba, Polygalae Radix, Poria, Rehmanniae Radix Preparata, Schisandrae Chinensis Fructus, Zingiberis Rhizoma Recens
Houshiheisan	Alumen, Angelicae Sinensis Radix, Asari Radix et Rhizoma, Atractylodis Macrocephalae Rhizoma, Chrysanthemi Flos, Chuanxiong Rhizoma, Cinnamomi Ramulus, Ginseng Radix et Rhizoma, Ostreae Concha, Platycodonis Radix, Poria, Saposhnikoviae Radix, Scutellariae Radix, Zingiberis Rhizoma
Tianqi Jiangtang Capsule	Astragali Radix, Coptidis Rhizoma, Corni Fructus, Dendrobii Caulis, Ginseng Radix et Rhizoma, Galla Chinensis, Ligustri Lucidi Fructus, Lycii Cortex, Trichosanthis Radix, Ecliptae Herba
Shexiang Baoxin Pill	Artificial Moschus, Borneolum Syntheticum, Bovis Calculus Artifactus, Bufonis Venenum, Cinnamomi Cortex, Ginseng Radix et Rhizoma, Styrax
Danggui Buxue Decoction	Angelicae Sinensis Radix, Astragali Radix
Xiaoyaosan	Angelicae Sinensis Radix, Atractylodis Macrocephalae Rhizoma, Bupleuri Radix, Glycyrrhizae Radix et Rhizoma, Paeoniae Radix Alba, Poria
Weichang'an Formula	Actinidia arguta (Siebold and Zucc.) Planch. ex Miq. [Actinidiaceae]*, Atractylodis Macrocephalae Rhizoma, Citri Reticulatae Pericarpium, Poria, Prunellae Spica, Pseudostellariae Radix, Sargentodoxae Caulis, Smilacis Chinae Rhizoma
Sinisan	Aurantii Fructus Immaturus, Bupleuri Radix, Glycyrrhizae Radix et Rhizoma, Paeoniae Radix Alba
Yu Ping Feng San	Astragali Radix, Atractylodis Macrocephalae Rhizoma, Saposhnikoviae Radix
Jiedu Recipe	Cremastrae Pseudobulbus/Pleiones Pseudobulbus, Galli Gigerii Endothelium Corneum, Salvia Chinensis*, Valvate Actinidia Root*
Soufeng Yuchuan Decoction	Armeniacae Semen Amarum, Bombyx Batryticatus, Carthami Flos, Chloriti Lapis, Cicadae Periostracum, Codonopsis Radix, Crataegi Fructus, Ephedrae Herba, Eriobotryae Folium, Glycyrrhizae Radix et Rhizoma, Orange Collaterals*, Pheretima, Raphani Semen
Xuanbai Chengqi Decoction	Armeniacae Semen Amarum, Gypsum Fibrosum, Rhei Radix et Rhizoma, Trichosanthis Pericarpium
Yangfei Huoxue Decoction	Astragali Radix, Chuanxiong Rhizoma, Euonymus Alatus*, Glehniae Radix, Polygoni Cuspidati Rhizoma et Radix, Salviae Miltiorrhizae Radix et Rhizoma, Schisandrae Chinensis Fructus
ELeng Capsule	Angelicae Sinensis Radix, Aurantii Fructus, Curcumae Rhizoma, Hirudo, Paeoniae Radix Rubra, Salviae Miltiorrhizae Radix et Rhizoma, Sparganii Rhizoma, Trionycis Carapax
Huayu Xiaozheng Decoction	Morindae Officinalis Radix, Coicis Semen, Corydalis Rhizoma, Dianthi Herba, Draconis Sanguis, Fritillariae Thunbergii Bulbus, Hirudo, Notoginseng Radix et Rhizoma, Polygoni Avicularis Herba, Prunellae Spica, Rhei Radix et Rhizoma, Salviae Miltiorrhizae Radix et Rhizoma, Typhae Pollen

To be continued

Table 1 (continued)

Recipe	Ingredients
Xiao Liu Fang	Cervi Cornu, Codonopsis Radix, Curcumae Rhizoma, Eupolyphaga Steleophaga, Hirudo, Ficus pumila L.**, Salvia Chinensis*, Smilacis Chinae Rhizoma, Trionycis Carapax, Vaccariae Semen, Zingiberis Thizoma Preparatum
Bushen Yutai Recipe	Angelicae Sinensis Radix, Astragali Radix, Codonopsis Radix, Cuscutae Semen, Cyperi Rhizoma, Ligustri Lucidi Fructus, Ophiopogonis Radix, Psoraleae Fructus, Rehmanniae Radix Praeparata, Salviae Miltiorrhizae Radix et Rhizoma
Wenshen Yangxue Decoction	Achyranthis Bidentatae Radix, Angelicae Sinensis Radix, Asari Radix et Rhizoma, Aucklandiae Radix, Bupleuri Radix, Carthami Flos, Cervi Cornu, Chuanxiong Rhizoma, Cistanches Herba, Corni Fructus, Cuscutae Semen, Cyperi Rhizoma, Epimedii Folium, Leonuri Herba, Lycii Fructus, Lycopi Herba, Notopterygii Rhizoma et Radix, Paeoniae Radix Rubra, Rehmanniae Radix Praeparata, Rubi Fructus, Salviae Miltiorrhizae Radix et Rhizoma, Spatholobi Caulis, Typhae Pollen

* This drug is not included in the *Pharmacopoeia of the People's Republic of China*, and hence the name in the original literature is used. ** This drug is not included in the *Pharmacopoeia of the People's Republic of China*, and the name in the original literature is incorrect, so we used the corresponding Latin name of the drug in the Chinese literature published by the team of Zhou et al. (2019a) and Chinese Materia Medica Commission of the National Administration of Traditional Chinese Medicine (1999).

2 Nervous system diseases

In recent years, cerebrovascular disease has become a popular field within VEGF-related research. Among the listed preparations, the classic Chinese recipe Buyang Huanwu Decoction was confirmed by many researchers to promote the expression of VEGF and VEGFR in middle cerebral artery occlusion (MCAO) in rats (Cai et al., 2007; Zheng et al., 2018). Zhan et al. (2019) treated MCAO rats with Xiaoshuan enteric-soluble capsules (a novel formulation of the Buyang Huanwu Decoction) and found that the number of cluster of differentiation 31-positive ($CD31^+$) and nerve/glial antigen 2 (NG2)/$CD31^+$ cells in the peripheral infarct cortex increased significantly in the combined treatment group of TCM and the enriched environment (EE) treatment group. Compared with the monotherapy group, the messenger RNA (mRNA) expression levels of *VEGF*, angiopoietin-1 (*Ang-1*), *Ang-2*, and axon guidance molecules were significantly increased; increased protein expression has its own advantages. It was suggested that the combined use of Xiaoshuan enteric-coated capsules and EE is beneficial to neurovascular reorganization by enhancing neurogenesis and angiogenesis, thus promoting recovery after ischemic stroke. In a further study on the therapeutic mechanism of Buyang Huanwu Decoction in stroke patients, Chen et al. (2019) found that Paeoniae Radix Alba can inhibit the activation of hypoxia inducible factor-1α (HIF-1α)/VEGF pathway in rats with cerebral ischemia-reperfusion injury, stabilize β-epithelial sodium channel (β-ENaC) ion channels, maintain the integrity and stability of the blood–brain barrier, and thereby treat ischemic stroke.

In addition to the Buyang Huanwu Decoction, other TCM recipes have also proved effective in the treatment of MCAO. Xijiao Dihuang Decoction can reduce the expression of interleukin-6 (IL-6) and IL-1β in MCAO rats, inhibit the activation of nuclear factor-κB (NF-κB), and upregulate the expression of neurogenesis factors (brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF)) and angiogenesis factors (VEGF, basic fibroblast growth factor (bFGF), CD34). Consequently, it can reduce inflammation, reduce cell apoptosis, protect brain nerves, promote vascular regeneration, reduce infarct volume, and improve motor function after ischemia (Fei et al., 2018). Ginseng Yangrong Decoction and Astragaloside IV can activate the HIF/VEGF/Notch pathway through microRNA-210 (miRNA-210), promote VEGF expression, and induce vascular endothelial cell migration and arteriovenous differentiation, thereby exerting the protective effect on angiogenesis after cerebral ischemic injury (Liang et al., 2020, 2021). Houshiheisan and Gastrodin have also been proven to significantly upregulate VEGF and VEGFR, protect blood vessels and neurons, and promote vascular remodeling in the ischemic hemisphere (Wang et al., 2018; Xiang et al., 2019).

Moreover, VEGF has been found to exhibit neuroprotective effects, with its potential mechanism being the stimulation of axon growth, Schwann cell proliferation, and nerve perfusion (de Almodovar et al., 2009).

Han et al. (2019) confirmed through in vitro experiments that the Tianqi Jiangtang Capsule can promote the survival of hippocampus neural stem cells, the replication and differentiation of newborn neurons and astrocytes, and reduce the degeneration and necrosis of nerve cells by upregulating the expression of VEGF and BDNF. However, the relationship between VEGF and the formation of nerve cells still needs more experimental data to confirm.

Herein, we summarize the studies related to TCM, listing the therapeutic targets and functions of preparations in Table 2 for easy reading. The sections hereinafter will also be organized in corresponding tables at the end of each section.

3 Circulatory system diseases

To date, most research on circulatory diseases has focused on ischemic heart disease. Promoting VEGF has shown great potential in the treatment of coronary heart disease by regulating angiogenesis, lymphangiogenesis, inflammation, cell apoptosis, redox reactions, fibrogenesis, and lipid metabolism (Zhou et al., 2021). A clinical observation involving 248 patients with coronary artery disease and 48 healthy controls found that the serum VEGF levels of patients with acute coronary syndrome (ACS) and stable angina pectoris (SAP) were higher than those of the healthy group. Moreover, the VEGF levels of patients with ACS were higher than those with SAP, which contradicts the results of multiple observational studies conducted in the past (Konopka et al., 2013; Ramos et al., 2014). This may be because unstable atherosclerotic plaques cause inflammation and induce the expression and release of VEGF in cardiomyocytes. It is worthwhile to further study the mechanism of VEGF in cardiovascular diseases (Huang et al., 2020). A meta-analysis showed that Shexiang Baoxin Pills can significantly promote the expression of VEGF in experimental animals with coronary heart disease while reducing the area of myocardial infarction, increasing the count of microvessels, and exerting myocardial protection (Zhang KJ et al., 2017). Hu et al. (2018) found that Danggui Buxue Decoction can significantly increase the mRNA and protein expression levels of VEGF, VEGFR1, and VEGFR2 in the myocardial tissue of rats with myocardial infarction, while it reduces soluble VEGFR1/2, increases the expression of membrane VEGFR1/2, and improves heart function. The isochlorogenic acid A and luteolin-7-*O*-glucuronide extracted from *Ixeris sonchifolia Hance* can bind to the ligand-free VEGFR2 to protect cardiomyocytes from oxidative stress, which is beneficial to the treatment of coronary heart disease (Wang et al., 2020). Therapeutic targets and effects of each preparation in this section are shown in Table 3.

Table 2 Mechanisms of action of traditional Chinese medicine (TCM) in nervous system diseases

Medicine	Therapeutic target	Function
Buyang Huanwu Decoction	Angiogenesis (VEGF, VEGFR, Ang-1, Ang-2, $CD31^+$, NG2/$CD31^+$) Pathway (HIF-1α/VEGF)	Promotes neurovascular recombination; stabilizes β-ENaC ion channels; maintains the integrity and stability of the blood-brain barrier
Xijiao Dihuang Decoction	Angiogenesis (VEGF, bFGF, CD34) Neurogenesis (BDNF, GDNF) Inflammatory (IL-6, IL-1β)	Reduces inflammation; protects cerebral nerves; promotes angiogenesis
Ginseng Yangrong Decoction and Astragaloside IV	Genetic material (miRNA-210) Angiogenesis (VEGF) Pathway (HIF/VEGF/Notch)	Induces endothelial cell migration and arteriovenous differentiation
Houshiheisan and Gastrodin	Angiogenesis (VEGF, VEGFR)	Protects blood vessels and neurons; promotes vascular hemispherical reconstruction
Tianqi Jiangtang Capsule	Angiogenesis (VEGF) Neurogenesis (BDNF)	Promotes the survival of hippocampal neural stem cells; promotes the replication and differentiation of newborn neurons and astrocytes

VEGF: vascular endothelial growth factor; VEGFR: VEGF receptor; Ang: angiopoietin; NG2: nerve/glial antigen 2; CD: cluster of differentiation; HIF: hypoxia inducible factor; bFGF: basic fibroblast growth factor; BDNF: brain-derived neurotrophic factor; GDNF: glial cell-derived neurotrophic factor; IL: interleukin; miRNA: microRNA; β-ENaC: β-epithelial sodium channel.

Table 3 Mechanisms of action of traditional Chinese medicine (TCM) in circulatory system diseases

Medicine	Therapeutic target	Function
Shexiang Baoxin Pill	Angiogenesis (VEGF)	Promotes microvascular formation
Danggui Buxue Decoction	Angiogenesis (VEGF, VEGFR1, and VEGFR2)	Promotes angiogenesis
Isochlorogenic acid A, luteolin-7-*O*-glucuronide	Angiogenesis (ligand-free VEGFR2)	Protects cardiomyocytes from redox reactions

VEGF: vascular endothelial growth factor; VEGFR: VEGF receptor.

4 Digestive system diseases

Regarding gastrointestinal diseases, tumors have been the focus of VEGF-related research. Ginsenosides are considered to have anti-cancer effects (Kim et al., 2014; Tian et al., 2016; Zhou et al., 2016; Sun et al., 2017; Liu et al., 2021). Using an orthotopic mouse model of human gastric cancer, Dai et al. (2017) found that the VEGFR-3 antibody coupled to ginsenoside Rg3 nanoemulsion significantly inhibited the expression of VEGF-C, VEGF-D, and VEGFR3, targeted the inhibition of lymphatic vessel formation, and inhibited tumor growth and metastasis. Zhao et al. (2020) established that Xiaoyaosan could inhibit the expression of VEGF in colon cancer rats (P<0.001), and attenuate the invasion and metastasis of colon cancer cells induced by chronic stress. Pan et al. (2020) indicated that Weichang'an Formula can inhibit the mRNA and protein expression of VEGF-A and VEGFR-1 in a colon cancer mouse model. The expression of VEGFR-1 in the Weichang'an Formula and bevacizumab combined treatment group was significantly lower than that in the bevacizumab group, suggesting that Weichang'an Formula can not only inhibit the angiogenesis of colon cancer but also enhance the anti-angiogenesis effect of bevacizumab at the VEGFR level, making up for the deficiency of bevacizumab.

Through experiments with liver fibrosis in mice, Wang et al. (2021) indicated that Si-Ni-San had a regulatory effect on liver microvasculature. The expression levels of VEGF, VEGFR1, and VEGFR2 in the treatment group were significantly lower than those in the model group (P<0.01). It may be that the core components of Si-Ni-San, such as glycyrrhizic acid, saikosaponin A, paeoniflorin, and naringin, played a role. Yuan et al. (2019) reported that the microvessel density (MVD) and VEGF levels of liver cancer mice treated with Yu Ping Feng San were significantly reduced, as it could downregulate the expression of the thymic stromal lymphopoietin (TSLP)-signal transducer and activator of transcription 3 (STAT3) signaling pathway and exert an anti-angiogenesis effect. Lin et al. (2021) reported that the Jiedu Recipe can reduce the expression of various inflammatory cytokines after arterial chemoembolization in patients with hepatocellular carcinoma, significantly lower the level of VEGF, and inhibit the IL-8/HIF-1α/phosphoinositide-3-kinase (PI3K) and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathways, thus blocking hypoxia-induced angiogenesis and improving the tumor hypoxia microenvironment. In addition to the TCM recipes, the TCM monomers astragaloside IV and curcumin have also been confirmed to have a synergistic inhibitory effect on the angiogenic factors VEGF, FGF-2, matrix metalloproteinase 2 (MMP-2), hepatocyte growth factor (HGF), and thrombosis-related factors (tissue factor (TF) and coagulation factor VII (FVII)) in the treatment of liver cancer nude mice (Zhang S et al., 2017). Angelica lactone A can downregulate the expression of CD31, VEGF, and VEGFR2, and alleviate the capillarization of hepatic sinusoids, thereby inhibiting liver fibrosis (Zhao et al., 2017). Therapeutic targets and effects of each preparation in this section are shown in Table 4.

5 Respiratory diseases

The mechanism that involves VEGF in the lung is complex. Normal lung development depends on the expression of VEGF, which is the highest among normal tissues (Kaner et al., 2000). The increase in bronchial blood vessels can induce the transport of inflammatory cells, as well as the exudation and penetration of mediators, and may also lead to airway hyperresponsiveness by increasing the quality of airway smooth muscle. On the other hand, the increased expression of VEGF in the distal airways and alveoli may protect from emphysema. Therefore, the role of VEGF in the lungs may vary by location and timing (Papaioannou

Table 4 Mechanisms of action of traditional Chinese medicine (TCM) in digestive system diseases

Medicine	Therapeutic target	Function
VEGFR-3 antibody coupled to ginsenoside Rg3 nanoemulsion	Angiogenesis (VEGF-C, VEGF-D, VEGFR3)	Inhibits lymphatic formation
Xiaoyaosan	Angiogenesis (VEGF)	Attenuates the invasion and metastasis of colon cancer cells induced by chronic stress
Weichang'an Formula	Angiogenesis (VEGF-A, VEGFR1)	Inhibits angiogenesis
Si-Ni-San	Angiogenesis (VEGF, VEGFR1, VEGFR2)	Regulates liver microvessels
Yu Ping Feng San	Angiogenesis (VEGF) Pathway (TSLP-STAT3)	Inhibits angiogenesis
Jiedu Recipe	Angiogenesis (VEGF) Pathway (IL-8/HIF-1α/PI3K, MAPK/ERK)	Inhibits hypoxia-induced angiogenesis
Astragaloside IV, curcumin	Angiogenesis (VEGF, FGF-2) Bio-enzyme (MMP-2, HGF) Thrombosis-related factors (TF, FVII)	Inhibits angiogenesis
Angelica lactone A	Angiogenesis (VEGF, VEGFR2, CD31)	Reduces hepatic sinusoidal capillarization

VEGF: vascular endothelial growth factor; VEGFR: VEGF receptor; TSLP: thymic stromal lymphopoietin; STAT3: signal transducer and activator of transcription 3; IL: interleukin; HIF: hypoxia inducible factor; PI3K: phosphoinositide-3-kinase; MAPK: mitogen-activated protein kinase; ERK: extracellular signal-regulated kinase; FGF: fibroblast growth factor; MMP: matrix metalloproteinase; HGF: hepatocyte growth factor; TF: tissue factor; FVII: factor VII; CD: cluster of differentiation.

et al., 2006). However, in recent years, relevant experiments with TCM have not revealed specific results for different parts. Yan et al. (2020) reported that Soufeng Yuchuan Decoction significantly reduced the expression of VEGF and transforming growth factor-β1 (TGF-β1) in asthmatic rats, and inhibited airway remodeling in asthmatic patients. Through experiments in rats with acute lung injury, Zhu et al. (2021) indicated that Xuanbai Chengqi Decoction can downregulate the expression of VEGF protein, inhibit bronchoalveolar vascular permeability, and reduce pulmonary edema. Liu et al. (2019) reported that Yangfei Huoxue Decoction can inhibit the expression of VEGF and IL-1β in rats with pulmonary fibrosis, and thus regulate the inflammatory immune response. Therapeutic targets and effects of each preparation in this section are shown in Table 5.

6 Gynecological diseases

Endometriosis is generally considered to be the result of retrograde menstrual blood flow. The detached endometrium is deposited in the peritoneal cavity. Angiogenesis is essential for the growth of the detached endometrium in other tissues (Donnez et al., 1998). Zheng WL et al. (2021) treated rats with endometriosis with ELeng Capsule and found that MVD and the expression of VEGF, bFGF, and platelet-derived growth factor (PDGF) in the lesion site of the treatment group were lower than those in the control group (P<0.01), thus inhibiting the formation of ectopic vessels. In addition, Huayu Xiaozheng Decoction was proven to have similar effects in inhibiting ectopic angiogenesis (Chen and Gong, 2017). Zhou et al. (2019b) found through in vitro experiments that Xiao Liu Fang could reduce the expression of VEGF, MMP-9, cyclooxygenase-2 (COX-2) and intercellular adhesion molecule 1 (ICAM-1), reduce the separation between cells of the same type and adhesion between cells of different types, and reduce angiogenesis, thus successfully treating endometriosis.

Infertility has plagued contemporary young people for a long time, and it has been confirmed that the VEGF-A concentration in fertile women is generally significantly higher than that in unexplained infertile women (Hannan et al., 2011). Thus, treatment targeting VEGF may be of great help in achieving pregnancy. Jiang et al. (2020) used the Bushen Yutai Recipe to treat in vitro fertilization patients, showing significantly higher expression of *VEGF* gene in exfoliated endometrial cells than in the control group. Xin et al. (2018) reported that Wenshen Yangxue Decoction can increase the expression of MVD, VEGF, Ang-1, and Ang-2, suggesting that TCM may increase endometrial blood flow, promote endometrial angiogenesis, and improve endometrial receptivity, which aids the treatment of infertility. Therapeutic targets and effects of each preparation in this section are shown in Table 6.

Table 5 Mechanisms of action of traditional Chinese medicine (TCM) in respiratory diseases

Medicine	Therapeutic target	Function
Soufeng Yuchuan Decoction	Angiogenesis (VEGF) Profibrotic growth factor (TGF-β1)	Inhibits airway remodeling
Xuanbai Chengqi Decoction	Angiogenesis (VEGF)	Inhibits bronchoalveolar vascular permeability
Yangfei Huoxue Decoction	Angiogenesis (VEGF) Inflammatory (IL-1β)	Regulates immune inflammatory response

VEGF: vascular endothelial growth factor; TGF-β1: transforming growth factor-β1; IL: interleukin.

Table 6 Mechanisms of action of traditional Chinese medicine (TCM) in gynecological diseases

Medicine	Therapeutic target	Function
ELeng Capsule, Huayu Xiaozheng Decoction	Angiogenesis (VEGF, bFGF, PDGF)	Inhibits the formation of ectopic blood vessels
Xiao Liu Fang	Angiogenesis (VEGF) Bio-enzyme (MMP-9, COX-2) Adhesion molecule (ICAM-1)	Reduces the separation of the same type of cells; reduces the adhesion between different types of cells; reduces angiogenesis
Bushen Yutai Recipe	Angiogenesis (VEGF)	Induces angiogenesis
Wenshen Yangxue Decoction	Angiogenesis (MVD, VEGF, Ang-1, Ang-2)	Increases endometrial blood flow; promotes endometrial angiogenesis

VEGF: vascular endothelial growth factor; bFGF: basic fibroblast growth factor; PDGF: platelet-derived growth factor; MMP-9: matrix metallopeptidase 9; COX-2: cyclooxygenase-2; ICAM-1: intercellular adhesion molecule 1; MVD: microvessel density; Ang: angiopoietin.

7 Other diseases and related research

Taohe Chengqi Decoction can inhibit the expression of PI3K/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) and HIF-1α/VEGF signaling pathways, thereby regulating the inflammatory process and epithelial–mesenchymal transition, which in turn reduces the excessive deposition of abnormal extracellular matrix and inhibits the progression of renal fibrosis (Zhou et al., 2020). Fuxin Granules can inhibit the expression of VEGFA and VEGFR2 in diabetic nephropathy mice and exert a renal protection effect, but the more specific mechanism of action needs to be further explored (Zheng WW et al., 2021). Shikonin can increase the levels of VEGF, bFGF, TGF-β, and PDGF in rabbits with skin injury (P<0.05) and enhance the activation of TGF-β1/Smad signaling pathway, thereby promoting the proliferation of fibroblasts and subsequently the healing of skin ulcer (Yang et al., 2021). The mixed extracts of Angelica Dahurica and Rhubarb can upregulate the expression of VEGF and inducible nitric oxide synthase (iNOS) in diabetic rats and inhibit the NF-κB pathway, which can improve inflammation and promote wound healing (Chao et al., 2021). Matrine can downregulate the expression of IL-1β, interferon-γ, VEGF, PlGF, HIF-1α, Ang-1, Ang-2, Tie-2, and phosphorylated AKT in collagen-induced arthritis rats, suggesting its ability to regulate the HIF-VEGF-Ang axis and inhibit the PI3K/AKT pathway (Ao et al., 2022). The ultimate effect is the reduction of new blood vessel formation and improvement of rheumatoid arthritis symptoms. Kuchta et al. (2017) conducted in vitro experiments and confirmed that celastrol can effectively inhibit the secretion of VEGF in PC-3 cells and target the inhibition of VEGF/VEGFR2 signaling pathway, thus inhibiting angiogenesis, exerting anti-tumor activity, and preventing prostate cancer bone metastasis.

8 Discussion

TCM is a treasure of Chinese civilization and still occupies a crucial position in China's medical system. The philosophy of TCM is focused on treating people as a whole, analyzing diseases by their symptoms, and prescribing remedies by TCM types. On the other hand, the Western approach within China has put more emphasis on extracting effective chemical components from a single herb. Nowadays, TCM also focuses on extracting natural products with biological activity through modern methods and analyzing them at the cellular, molecular, and pharmacological levels, in order to discover ingredients that can supplement Western medicine: the research on TCM in China has also tended to the micro level. More and more

Chinese medicine practitioners and scholars have devoted themselves to exploring the influence of TCM on molecules and cells to clarify its mechanism, in order to gain worldwide recognition.

In recent years, the relevant research on the effects of TCM on VEGF has covered a wide range of content, including classic recipes, empirical recipes, and monomers. Among the Chinese medicines used, blood-activating drugs account for a large proportion. The VEGF itself is closely related to blood and blood vessels. According to the theory of Chinese medicine, it is easy to associate drugs with a blood-activating effect. To this end, Salviae Miltiorrhizae Radix et Rhizoma, Angelicae Sinensis Radix, Chuanxiong Rhizoma, etc., which have been studied more frequently, are commonly used clinical medicines in TCM. The research results for blood-activating drugs are often synchronized with TCM cognition. For example, Gao et al. (2021) showed in the Flik zebrafish model that Typhae Pollen could upregulate the expression of VEGF-A in vascular-deficient zebrafish and promote angiogenesis. At the same time, Carbonized Typhae Pollen could upregulate the expression of VEGF-A in zebrafish with cerebral hemorrhage and play a vascular protective effect. This result agrees with our understanding of the efficacy of TCM—Typhae Pollen is a commonly used medicine for promoting blood circulation and removing blood stasis, while Carbonized Typhae Pollen exerts a weakened blood-activating effect and enhanced hemostatic effect.

The more frequently used categories of TCM are Qi-tonifying drugs, such as Ginseng Radix et Rhizoma, Astragali Radix, and Codonopsis Radix. According to the theory of TCM, most chronic diseases damage the righteous Qi and easily lead to Qi deficiency. In such cases, Qi-tonifying drugs are needed to strengthen the body to get-rid of evil spirits. The results for the compound prescription also reveal a significant regulatory effect of Qi-tonifying drugs on VEGF; however, the constituents of the prescription are complicated. To uncover the effect of specific ingredients on VEGF expression, a lot of experiments are needed. Nevertheless, studies directed to the monomers of TCM have clearly shown their beneficial effects, which constitutes a more popular research direction in the West. For example, Tanshinone IIA has been shown to inhibit the angiogenesis of human umbilical vein endothelial cells (Wang et al., 2015; Xing et al., 2015) and endothelial progenitor cells (Lee et al., 2017) through inhibiting the migration of VEGF. A liposome that targets PFVYLI (PFV) modified by epirubicin and Schisandrin B (encapsulated in the hydrophilic core of liposomes and the phospholipid bilayer, respectively) can downregulate the expression of VEGF, MMP-9, and vimentin (VIM), upregulate the expression of E-cadherin (E-CAD), block migration and invasion, reduce cell adhesion, destroy the mimicry channel of angiogenesis, and inhibit angiogenesis. Therefore, it has a stronger inhibitory effect on tumor metastasis than epirubicin alone (Jing et al., 2020). Overall, the above studies have enriched the modern research direction of TCM, allowed TCM to enter the world stage of research, and suggested that TCM has the possibility of supplementing the function of artificial synthetic drugs.

Furthermore, recent studies have established that VEGF is often combined with upstream, downstream, and other factors that may affect angiogenesis. Such common factors include Ang-1, Ang-2, HIF-1α, PI3K, MMP, inflammatory factors, etc., which have been proven to be linked to angiogenesis, and their mechanisms are related to hypoxia, cell survival, cell proliferation, and inflammation (Xia et al., 2006; Wouters and Koritzinsky, 2008; Kessenbrock et al., 2010; Reuter et al., 2010; Ahluwalia and Tarnawski, 2012; Duran et al., 2021). To facilitate the understanding of the VEGF-related factors mentioned in this review, a pathway map was prepared in Fig. 1. As seen in the figure, TCM treatments have multi-targeting nature, prompting further studies to explore the mechanisms of TCM in many areas.

9 Conclusions

This review summarized and discussed the research on TCM in recent years with reference to VEGF according to the classification of related diseases. The findings indicated great research potential for VEGF and angiogenesis in many disease fields. Moreover, the integration of TCM with the global mainstream research is becoming increasingly necessary. Many scholars have proved the effects of TCM on VEGF, interpreted TCM and complex recipes from a micro perspective, and opened up new ideas of development; however, there are many challenges ahead.

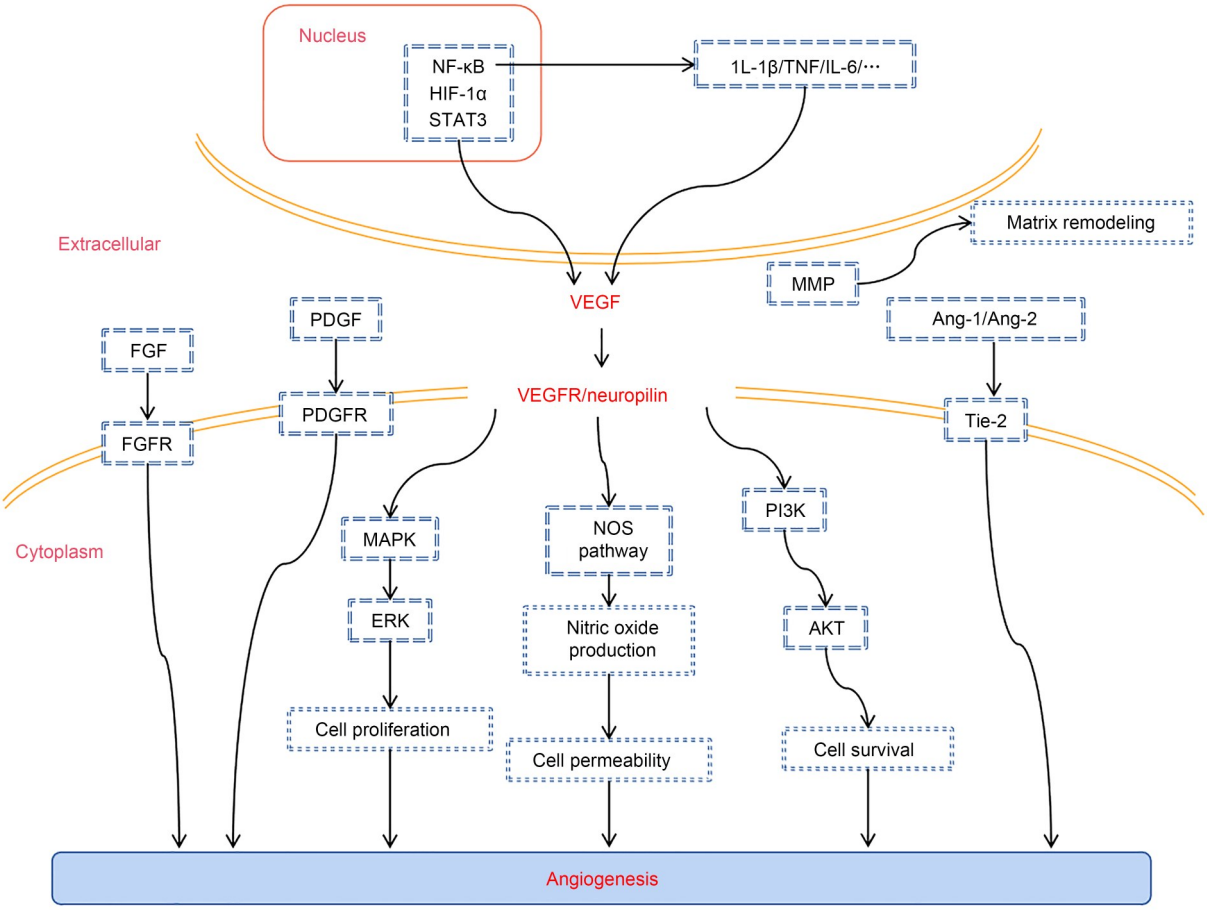

Fig. 1 Pathway map of the VEGF-related factors mentioned in this review. AKT: protein kinase B; Ang: angiopoietin; ERK: extracellular signal-regulated kinase; FGF: fibroblast growth factor; FGFR: FGF receptor; HIF-1α: hypoxia-inducible factor-1α; IL: interleukin; MAPK: mitogen-activated protein kinase; MMP: matrix metalloproteinase; NOS: nitric oxide synthase; NF-κB: nuclear factor-κB; PDGF: platelet-derived growth factor; PDGFR: PDGF receptor; PI3K: phosphoinositide-3-kinase; STAT3: signal transducer and activator of transcription 3; TNF: tumor necrosis factor; VEGF: vascular endothelial growth factor; VEGFR: VEGF receptor.

For instance, there are numerous types of TCM, and compound prescriptions have great variation. Also, the effects of such prescriptions on cells are often complicated and multi-targeted; therefore, more research is clearly needed to comprehensively clarify the mechanisms of TCM.

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Author contributions

Yijia MAO drafted the manuscript. Huayi LIU put forward the idea and revised the manuscript. Lingkai MENG, Yuting LU, Kuo YANG, and Guangze OUYANG supervised the study. Yanran BAN and Shuang CHEN edited the tables, figure, and formats. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Yijia MAO, Lingkai MENG, Huayi LIU, Yuting LU, Kuo YANG, Guangze OUYANG, Yanran BAN, and Shuang CHEN declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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