Review Article

Holistic Regulation of Angiogenesis with Chinese Herbal Medicines as a New Option for Coronary Artery Disease

Rong Yuan,1,2 Wei-Li Shi,1 Qi-Qi Xin,1 Ke-Ji Chen,1 and Wei-Hong Cong1

1Laboratory of Cardiovascular Diseases, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing 100091, China
2Graduate school, Beijing University of Chinese Medicine, Beijing 100029, China

Correspondence should be addressed to Ke-Ji Chen; kjchenvip@163.com and Wei-Hong Cong; congcao@188.com

Received 13 March 2018; Accepted 5 August 2018; Published 13 August 2018

Academic Editor: Youn C. Kim

Copyright © 2018 Rong Yuan et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Effectively improving myocardial blood flow and controlling atherosclerotic plaque have always been key and difficult points in the prevention and treatment of coronary artery disease (CAD). Although “therapeutic angiogenesis” is regarded as a promising approach for ischemic heart disease by improving blood flow, angiogenesis itself can induce the destabilization of atherosclerotic plaque, which reflects the double-edged role of angiogenesis. Modulating the balance of angiogenesis can be an important target for CAD treatment. Traditional Chinese medicine (TCM) emphasizes the holistic view and dynamic balance of the body. Furthermore, the principle of activating blood circulation and removing blood stasis (ABCRS) is closely connected with angiogenesis and CAD. Recent research suggests that Chinese herbal medicines for ABCRS are effective in balancing the regulation of angiogenesis. This review presents the progress of recent research on the angiogenesis regulation with Chinese herbal medicines for ABCRS in CAD. Moreover, this review demonstrates that Chinese herbal medicines for ABCRS can not only promote angiogenesis in the ischemic area to improve myocardial blood flow but also alleviate angiogenesis to stabilize plaque in atherosclerosis, which reflects the holistic regulatory role in CAD treatment.

1. Introduction

Coronary artery disease (CAD), also known as coronary atherosclerotic heart disease, coronary heart disease, and ischemic heart disease (IHD), is the most common cause of heart attacks [1]. According to the World Health Organization, CAD is the leading cause of death worldwide among all noncommunicable diseases [2]. Current therapeutic options are limited to pharmacological therapy, percutaneous coronary intervention, and bypass surgery. However, a large number of patients do not qualify for surgical or intervention procedures [3], and these patients mainly present with refractory angina with severe atherosclerosis in the clinic. At present, a number of studies have indicated that promoting angiogenesis is a promising approach for IHD [4], while angiogenesis in atherosclerosis induces plaque destabilization and hemorrhage [5]. Therefore, more attention should be paid to balancing the regulation of angiogenesis in myocardial ischemia and atherosclerosis.

The holistic theory of traditional Chinese medicine (TCM) aims to modulate the dynamic balance of the body. Among the different TCM therapies, activating blood circulation and removing blood stasis (ABCRS) therapy is effective in CAD treatment, with antiplatelet function, vascular endothelium protection, myocardial remodeling, and microcirculation improvement [6]. Recently, an increasing number of studies have focused on the effects of Chinese herbal medicines for ABCRS on angiogenesis in myocardial ischemia and atherosclerosis. Given the double-edged role of angiogenesis, this review aims to present the recent research progress on the regulatory role of angiogenesis by Chinese herbal medicines for ABCRS, which may provide a new angle of view with regard to the prevention and treatment of CAD.

We searched the PubMed, Chinese National Knowledge Infrastructure and Chinese Scientific Journal Database with the following keywords: “angiogenesis” OR “neovascularization” AND “coronary disease” OR “atherosclerosis” OR “myocardial ischemia/infarction” OR “Chinese medicine”
2. The Dual Role of Angiogenesis in CAD

2.1. Angiogenesis. Angiogenesis refers to the formation of new blood vessels from the preexisting vasculature [7]. Under certain conditions, various angiogenic factors are produced, and vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and their receptors are the key molecular factors. The binding of VEGF/FGF to VEGF receptor (VEGFR)/FGF receptor (FGFR) induces multiple signaling networks, such as mitogen-activated protein kinase (MAPK), phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt), extracellular regulated protein kinase (ERK), and notch pathways, and the signaling cascades result in endothelial cell (EC) survival, proliferation, migration, and tube formation [7–11]. A brief overview of the angiogenesis and the activation pathways is provided in Figure 1.

2.2. Angiogenesis in Myocardial Ischemia. Improving blood flow to the ischemic myocardium plays a critical role in the treatment of CAD, and angiogenesis is an important and promising means of increasing blood flow [12]. Numerous studies have shown that promoting angiogenesis therapy can improve myocardial ischemia by stimulating formation of collateral networks and increasing blood supply [4, 13]. Nox4 alleviated hypoxia/reoxygenation injury by inhibiting apoptosis and promoting angiogenesis via upregulation of HIF-1/VEGF signaling pathway [14]. Activation of the notch pathway also promoted coronary neoangiogenesis and revascularization, limited the extent of ischemic damage, and improved heart function [15]. Additionally, secreted VCAM-1 induced EC migration and prevented cardiomyocyte death through activation of Akt, ERK, and p38 MAPK [16]. In short, promoting angiogenesis therapy is beneficial to myocardial ischemia.

2.3. Angiogenesis in Atherosclerosis. Acute coronary syndrome may be related to atherosclerotic plaque rupture and thrombosis, while angiogenesis is a key factor in plaque destabilization leading to rupture [17]. Plaque neovascularization consists of a network of capillaries that arise from the adventitial vasa vasorum and extend into the intimal layer of atherosclerotic lesions, which promotes the growth of atherosclerotic lesions and plaque destabilization. Furthermore, excessive adventitial neovascularization is also one of the hallmarks of atherosclerotic plaque progression [18, 19]. Increased IL-8, IL-1, TNF-α, CRP, and MMP levels enhanced plaque progression and destabilization and caused intraplaque hemorrhage and rupture [20, 21]. FGFR2 overexpression in ECs resulted in increased expression of VCAM-1, which aggravated atherosclerosis [22]. The HIF pathway was associated with angiogenesis in plaque [23]. Therefore, inhibiting plaque and adventitial angiogenesis is beneficial to atherosclerosis.

2.4. Double-Edged Role of Angiogenesis. The "Janus phenomenon" illustrates the double-edged role of angiogenesis: when an intervention benefits proangiogenesis and collateral development, it has the potential to increase atherosclerosis, and when an intervention has antiatherosclerotic effects, it has the potential to inhibit collateral development [20, 24]. Although proangiogenesis therapy can improve blood supply in animal models, several clinical studies have not shown definite evidence of clinical efficacy of proangiogenesis in CAD, and adverse effects, including edema, inflammation, and cancer, were turned up [25, 26]. Although antiangiogenesis
therapy can stabilize plaques in animal models, there has been no clinical study on antiangiogenesis therapy in atherosclerosis until now, and antiangiogenesis therapy in cancer can lead to myocardial ischemia, hypertension, and stroke [27]. Therefore, neither promotive nor inhibitory angiogenesis therapy alone is an ideal option for the treatment of CAD, and a drug that holistically regulates angiogenesis in CAD would have great potential.

3. The Holistic Regulatory Effects of Chinese Herbal Medicines on ABCRS

In TCM, myocardial ischemia and atherosclerotic plaque are collectively caused by blood stasis, and the ABCRS method is the main therapeutic method [6]. The TCM philosophy regards the ABCRS method as promoting blood circulation and dissipating stasis. Recent studies have also verified that Chinese herbal medicines for ABCRS have effects on improving microcirculation and hemorheology indices, increasing blood flow, regulating endothelial function, and inhibiting the proliferation of vascular smooth muscle cells [28]. A large number of studies have indicated that Chinese herbal medicines for ABCRS can regulate angiogenesis in myocardial ischemia and atherosclerosis. Therefore, the ABCRS method might have holistic regulatory effects on angiogenesis in CAD.

3.1. Proangiogenic Effect. Previous studies have reported that the Xiongshao capsule and Guanxin No. 2 can promote angiogenesis in the ischemic region and increase blood supply by increasing the expression levels of VEGF and bFGF [29, 30]. Tongxinluo can promote angiogenesis in the peri-infarct area and increase blood flow to the myocardium by downregulating Nox4 and by upregulating VEGF and endothelial NOS-mediated angiogenesis through the PI3K/Akt signaling pathway [31]. In addition, Qiushen Yiqi dripping pills, Xuefu Zhiyu formula, Shu-mai-tang, Shenzhuzhuanxin granules, flowers of Panax notoginseng, salvianolic acid B, Xuesetong soft capsules, Radix paconiae rubra 801, Danhong injection, and Spatholobi caulis can also protect the ischemic myocardium through the activation of VEGF and the promotion of angiogenesis [32–42] (Table 1).

3.2. Antiangiogenesis Effect. Previous studies have determined that Tongxinluo can inhibit adventitia neovascularization and decrease microvessel density in atherosclerosis by inhibiting expression of VEGF through the p38MAPK signaling pathway [43, 44]. Simiao Yongan decoction can suppress vasa vasorum neovascularization and stabilize plaques by decreasing the expression levels of HIF-1α, MEK1/2, and ERK1/2 [45]. In addition, Xiongshao capsule, Huoxue capsule, Shumai capsule, modified salvia decoction, Panax notoginseng saponins, Ruanmailing, Salvianolic acid B, Guishao-tongluo, and red yeast rice can also alleviate angiogenesis and attenuate atherosclerosis by decreasing VEGF expression [46–54]. Moreover, Buyang Huanwu decoction can promote microvessel maturation and decrease the incidence of plaque rupture by increasing the expression levels of bFGF and PDGF [55] (Table 2).

3.3. Holistic Regulatory Effects. Chinese herbal medicine for ABCRS has a holistic regulatory effect on angiogenesis. It has been reported that Rhodiola rosea and Shexiang Baoxin Pill can promote angiogenesis and increase myocardial microvesSEL density by increasing the expression levels of HIF-1α, VEGF, VEGFR2, and CD34 while inhibiting vessel growth and decreasing plaque area in atherosclerosis by reducing these indexes in the aorta [56, 57]. Another study has shown that the Xuefu Zhiyu decoction inhibits cell proliferation at certain concentrations and induces tube formation to a limited degree at low concentrations over a short time frame, suggesting that the Xuefu Zhiyu decoction controls angiogenesis in a different manner from that of the continuous function of VEGF [58]. In short, these studies imply that Chinese herbal medicines for ABCRS may have effects on balancing the regulation of angiogenesis and are thus safe for the coexistence of both myocardial ischemia and atherosclerotic lesions.

4. Discussion

The relationship between angiogenesis and CAD is double-sided [4]; balancing the contradictory angiogenesis effects might facilitate drug efficacy in CAD. Chinese herbal medicines have an advantage over regulating the balance of the body in different pathological states. The data reviewed here suggest that Chinese herbal medicines for ABCRS result in holistic regulatory effects and providing a new option for treating CAD. The mechanisms may be related to the multicomponent nature of Chinese herbal medicines, which may exhibit different effects in different pathological tissues through multiple targets and pathways. However, the deep mechanisms are complex and have yet to be clearly elucidated.

Modern research has indicated that angiogenesis within the vasa vasorum is characterized by a network of immature and leaky vessels, which plays an important role in plaque progression. Creating a mature network and normalizing plaque vessels may potentially minimize the risk of plaque hemorrhage [59]. In addition, EC metabolism including hypoxia-related fatty acid oxidation and glycolysis has gained attention as a therapeutic target for angiogenesis [60]. Therefore, interfering with vessel normalization/maturation and EC metabolism may be new directions to study the holistic regulatory effects of Chinese herbal medicines, which will bring new ideas to the clinical prevention and treatment of CAD.

To date, numerous studies have focused on angiogenesis in a myocardial ischemia model only or an atherosclerosis model only, while studies investigating angiogenesis in the context of both pathological changes and drug interventions are rare; there are mainly a few studies in this area [3, 56, 57, 61, 62]. Therefore, a desire exists to use compound models to study the double-edged roles of angiogenesis, therapeutic interventions, and mechanisms, especially of the holistic regulatory effects of Chinese herbal medicines. In addition, we can screen the drugs and active components that can both promote ischemic angiogenesis and inhibit proliferative angiogenesis by network pharmacology and
### Table 1: Proangiogenic effects of Chinese herbal medicines for ABCRS.

| Study ID       | Objects          | Chinese herbs and formulae | Study design | Composition of formula                                                                 | Therapeutic effect and mechanism                                                                 |
|----------------|------------------|----------------------------|--------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Chen et al. [29] | 8 rats           | Xiongsha capsule           | Gavage for 6 weeks | Ligusticum chuanxiong Hort., Radix paeoniae rubra                                      | Increase the expression levels of VEGF and bFGF, promote angiogenesis, enhance myocardial blood supply, improve cardiac function |
| Zeng et al. [30] | 10 rats          | Guanxin No. 2              | Gavage with 20 g/kg/d for 28 days | Panax ginseng C. A. Meyer, Hirudo nipponia Whitman, Scrophularia paniculata L., Radix paeoniae rubra, Bupleurum chinensis DC., Ligusticum chuanxiong Hort., Achyranthes bidentata Blume, Platycoptis grandiflorus (Jacq.) A. DC. | Increase the expression levels of VEGF and bFGF, promote angiogenesis, compensate blood supply to the heart |
| Wang et al. [31] | 12 mice          | Tongxinluo                 | Gavage with 0.38 g, 1.5 g/kg/d for 7/30 days | Panax ginseng, Scrophularia paniculata L., Radix paeoniae rubra, Bupleurum chinensis DC., Ligusticum chuanxiong Hort., Achyranthes bidentata Blume, Platycoptis grandiflorus (Jacq.) A. DC. | Increase the expression levels of VEGF, HIF-1α, eNOS, PI3K, Akt and ERK, promote angiogenesis, improve cardiac function, ameliorate cardiac remodeling |
| Yao [32]       | ECs              | Qishen Yiqi dripping pills | Drug serum for 7 days | Salvia miltiorrhiza Bunge, Astragalus membranaceus (Fisch.) Bunge, Panax notoginseng (Burk.) F.H. Chen | Increase the expression level of ERK, increase proliferation, migration and tube formation of ECs |
| Zhang et al. [33] | 8 rats           | Xuefu Zhuyu formula        | Gavage with 13.68 g/kg/d for 7 days | Angelica sinensis (Oliv.) Diels, Rehmannia glutinosa Libosch, Semen Persicae, Carthamus tinctorius Linn., Radix paeoniae rubra, Bupleurum chinensis DC., Ligusticum chuanxiong Hort., Achyranthes bidentata Blume, Platycoptis grandiflorus (Jacq.) A. DC. | Increase the expression level of VEGF, promote angiogenesis, protect myocardium, increase levels of serum VEGF and bFGF, relieve angina and signs of blood stasis |
| Li et al. [34] | 40 patients      | Shu-mai-tang               | Gavage with 1.71 g/kg/d for 4 weeks | Astragalus mongholicus Bunge, Salvia miltiorrhiza Bge, Panax notoginseng (Burk.) F.H. Chen, Hirudo nipponica Whitman, Eupolyphaga sinensis Walker, Moschus berezovskii Flerov, Trichosanthes kirilowii Maxim | Increase the expression levels of VEGF and platelet-derived growth factor, increase microvessels and arterioles in ischemic areas |
| Yin et al. [35] | 24 rats          | Panax notoginseng          | Gavage with 25, 50 mg/ml/d for 2 weeks | Radix Ginseng, Radix Panacis quinqufolii, Radix Notoginseng, Hirudo, Rhizaoma Pinelliae, Rhizaoma Atractylodis, Folium Nelumbinis, | Increase the expression level of VEGF, increase microvessel density, attenuate infarct size, improve cardiac hemodynamic function |
| Xu et al. [36] | 30 rats          | ShenZhuGuanXin granules    | Gavage with 630, 1260, 3981.6 mg/kg/d for 4 weeks | Radix Ginseng, Radix Panacis quinqufolii, Radix Notoginseng, Hirudo, Rhizaoma Pinelliae, Rhizaoma Atractylodis, Folium Nelumbinis, | Increase the expression level of VEGF, increase microvessel density, attenuate infarct size, improve cardiac hemodynamic function |
| Yang et al. [37] | 12 rats          | Panax notoginseng          | Gavage with 25, 50 mg/ml/d for 2 weeks | Panax Notoginseng (Burk.) F.H. Chen | Increase the expression levels of HIF-1, VEGF and VEGFR2, increase blood vessel density |
| He et al. [38] | 15 rats          | Salvianolic acid B         | Gavage with 100 mg/kg/d for 4 weeks | Salvianolic acid B | Increase the expression level of VEGF, promote angiogenesis, improve myocardial microcirculation |
| Wang et al. [39] | 8 rats           | Xuesetong soft capsules   | Gavage with 0.4 g/kg/d for 6 weeks | Notoginseng total saponin | Increase the expression level of VEGF, increase microvessel density |
| Study ID | Objects | Chinese herbs and formulae | Study design | Composition of formula | Therapeutic effect and mechanism |
|----------|---------|-----------------------------|--------------|-----------------------|---------------------------------|
| Liu et al. [40] | 10 rats | Radix paeoniae rubra 801 | Gavage with 16.2 mg/kg/d for 14 days | Propyl gallate | Increase the expression levels of NO, VEGF and bFGF, increase capillary density, improve myocardial ischemia |
| Chen et al. [41] | 25 rats | Danhong injection | Intramuscular injection with 0.76 ml/kg/d for 28 days | Radix et Rhizoma Salviae Miltiorrhizae, Flos Carthami | Increase the expression level of VEGF, increase blood vessel density, decrease ratio of infarct, improve cardiac function |
| Zhou et al. [42] | zebrafish embryos and ECs | Spatholobi caulis | 3, 10, 30 and 100 μg/ml embryo medium for 24 h in zebrafish embryos; drug serum for 24 h in ECs | Caulis Spatholobi | Increase the expression levels of VEGFRs and MAPKs, increase subintestinal vessel sprouting, promote cell proliferation and migration, increase sprout intensity |
| Study ID | Objects | Chinese herbs and formulae | Study design | Composition of formula | Therapeutic effect and mechanisms |
|----------|---------|---------------------------|-------------|-----------------------|----------------------------------|
| Ma et al. [43] | 25 apoE-/- mice | Tongxinluo | Gavage with 0.38, 0.75, 1.5 g/kg/d for 5 weeks | Panax ginseng C. A. Meyer, Hirudo nipponia Whitman, Scorpio, Radix paonieae rubra, Periostracum Cicadae, Eupolyphaga Seu Steleophaga, Scopolandra subspinipes, Santalum album Linn. | Decrease the expression level of VEGF, inhibit vas avasorum proliferation, decrease microvessel density, reduce plaque areas |
| Liu et al. [44] | 15 rabbits | Tongxinluo | Gavage with 0.6 g, 0.3 g/kg/d for 4 weeks | Panax ginseng C. A. Meyer, Hirudo nipponia Whitman, Scorpio, Radix paonieae rubra, Periostracum Cicadae, Eupolyphaga Seu Steleophaga, Scopolandra subspinipes, Santalum album Linn. | Decrease the expression level of CD31, inhibit p38MAPK pathway, inhibit adventitia neovascularization |
| Li et al. [45] | 15 apoE-/- mice | Simiao Yongan decoction | Gavage with 11.7 mg/kg/d for 8 weeks | Lonicera japonica Thunb., Scrophularia ningpoensis Hemsl., Angelica sinensis (Oliv.) Diels, Glycyrrhiza uralensis Fisch. | Decrease the expression levels of HIF-1α, CD34, MEK1/2 and ERK1/2, suppress vasa vaso accommodation, stabilize plaques |
| Zhang et al. [46] | 10 rabbits | Xiongshao capsule | Gavage with 0.24 g, 0.48 g/kg/d for 6 weeks | Ligusticum chuanxiong Hort., Radix paonieae rubra | Decrease the expression level of VEGF in plaque, reduce plaque areas |
| Ren et al. [47] | 16 rabbits | Huoxue capsule | Gavage with 0.5 g, 1.5 g/kg/d for 20 weeks | Astragalus mongholicus Bunge, Salvia miltiorrhiza Bge, Panax notoginseng (Burk.) F.H. Chen, Hirudo nipponica Whitman, Eupolyphaga sinensis Walker, Moschus bereozvskii Flerov, Trichosanthes kirilowii Maxim | Inhibit the expression levels of VEGF and VCAM-1 in plaque, reduce intima/tonica media thickness ratio |
| Qiao [48] | 10 apoE-/- mice | Shumai capsule | Gavage with 700 mg, 3500 mg/kg/d for 12 weeks | Astragalus membranaceus (Fisch.) Bunge, Semen Persicae, Carthamus tinctorius Linn., Achyranthes bidentata Blume, Spina Date Seed, Ligusticum chuanxiong Hort., Radix paonieae rubra, Citrus aurantium L. | Decrease the expression levels of VEGF, VEGFR, HIF-1α and Nox4, reduce plaque areas |
| Pan et al. [49] | 30 patients | Modified salvia decoction | 22 g/d po for 6 months | Salvia miltiorrhiza Bunge, Santalum album Linn., Ligusticum chuanxiong Hort., Radix paonieae rubra, Angelica sinensis (Oliv.) Diels, Rehmannia glutinosa Libosch, Carthamus tinctorius Linn. | Decrease serum levels of VEGF, MMP-9 and CRP, reduce carotid intima media thickness, reduce plaque areas |
| Qiao et al. [50] | 10 apoE-/- mice | Panax notoginseng saponins | Gavage with 60 mg/kg/d for 12 weeks | Panax notoginseng (Burk.) F.H. Chen | Decrease the expression levels of VEGF, CD34 and Nox4, alleviate plaque angiogenesis, reduce plaque areas |
| Zeng et al. [51] | 10 apoE-/- mice | Ruanmailing | Gavage with 20 g/kg/d for 12 weeks | Fallopia multiflora (Thunb.) Harald., Rehmannia glutinosa (Gaertn.) Libosch. ex Fisch. et Mey, Lycium chinense Miller, Panax ginseng C. A. Meyer, Salvia miltiorrhiza Bunge, Angelica sinensis (Oliv.) Diels, Ligusticum chuanxiong Hort. | Decrease the expression levels of VEGF, bFGF and CD105, inhibit plaque angiogenesis, stabilize plaques |
| Zheng et al. [52] | 10 apoE-/- mice | Salvianolic acid B | Gavage with 80, 160 mg/kg/d for 8 weeks | Salvianolic acid B | Decrease the expression levels of CD31, reduce neovascularization in plaque and incidence of plaque erosion, stabilize plaques |
| Yin et al. [53] | 24 rabbits | Guishaotongluo | Gavage with 2.08, 4.16 g/kg/d for 4 weeks | Ramulus Cinnamomi, Radix Paonieae Alba, Salvia miltiorrhiza Bunge, Curcuma longa Linn. | Decrease the expression levels of VEGF, VEGFR-2, inhibit adventitial neovascularization |
| Study ID       | Objects | Chinese herbs and formulae | Study design                      | Composition of formula                                                                 | Therapeutic effect and mechanisms                                      |
|---------------|---------|---------------------------|-----------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Yang et al. [54] | 60 patients | Red yeast rice           | 175 mg/d po for 6 months         | Fermentum rubrum                                                                       | Decrease the serum level of VEGF, reduce the density and areas of carotid plaque |
| Pang et al. [55] | 20 rabbits   | Buyang Huanwu decoction | Gavage with 20 g/d for 4 weeks    | Astragalus mongholicus Bunge, Ligusticum chuanxiong Hort., Angelica sinensis (Oliv.) Diels, Radix paoniae rubra, Semen Persicae, Carthamus tinctorius Linn., Lumbricus | Increase the expression levels of bFGF and PDGF, promote microvessel maturation, decrease the incidence of plaque rupture, stabilize plaques  |
pharmacodynamics and further identify the targets and signaling pathways of holistic regulation on angiogenesis. Until now, clinical studies have mainly focused on promoting angiogenesis, while inhibiting angiogenesis in atherosclerosis is in the experimental stage and has not been applied in clinical practice. Hence, future work remains to be done to validate the clinical results. Meanwhile, diseases are complex in patients with medications and multiple risk factors. Therefore, clinical studies on long-term follow-up after angiogenesis-targeted therapy are worthy of investigation. In addition, although clinical trials have been conducted to evaluate the efficacy of Chinese herbal medicines in CAD, there are just a few clinical studies on the regulation of angiogenesis using Chinese herbal medicines [34, 49, 54]. Hence, more clinical trials will be required to study and to determine the best means of therapeutic angiogenesis.

In conclusion, future studies are needed to investigate the holistic regulatory effects of Chinese herbal medicines for ABCRS on angiogenesis in terms of both basic studies and clinical research, and the mechanisms of the herbs involved need to be uncovered.

Disclosure

Rong Yuan and Wei-Li Shi are co-first authors. The funding had no role in work design or preparation of the paper.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This work was partially supported by the National Natural Science Foundation of China (81373821), China Academy of Chinese Medical Sciences Foundation (ZZ11-061), and Beijing Municipal Science and Technology Commission (Z14110000221401).

References

[1] D. P. Faxon, M. A. Creager, S. C. Smith Jr. et al., "Atherosclerotic vascular disease conference: executive summary: atherosclerotic vascular disease conference proceeding for healthcare professionals from a special writing group of the American Heart Association," Circulation, vol. 109, no. 21, pp. 2595–2604, 2004.
[2] WHO, World health statistics 2016. Monitoring health for the SDGs sustainable development goals, vol. 41, WHO, Geneva, Switzerland, 2016.
[3] M. Theurl, W. Schgoer, K. Albrecht-Schgoer et al., "Secretoneurin gene therapy improves hind limb and cardiac ischaemia in Apo E-/- mice without influencing systemic atherosclerosis," Cardiovascular Research, vol. 105, no. 1, pp. 96–106, 2015.
[4] W. Wu, X. Li, G. Zuo, J. Pu, X. Wu, and S. Chen, "The role of angiogenesis in coronary artery disease: A double-edged sword: Intraplaque angiogenesis in physiopathology and therapeutic angiogenesis for treatment," Current Pharmaceutical Design, vol. 24, no. 4, pp. 451–464, 2018.
[5] C. Camaré, M. Pucelle, A. Nègre-Salvayre, and R. Salvayre, "Angiogenesis in the atherosclerotic plaque," Redox Biology, vol. 12, pp. 18–34, 2017.
[6] K.-J. Chen, "Development track of the modern activating blood circulation and removing stasis (ABCRS) school on inheritance and innovation," Chinese Journal of Integrative Medicine, vol. 21, no. 12, pp. 883–886, 2015.
[7] J. Y. Tang, S. Li, Z. H. Li et al., "Calycosin promotes angiogenesis involving estrogen receptor and mitogen-activated protein kinase (MAPK) signalling pathway in zebrafish and HUVEC," PLoS ONE, vol. 5, no. 7, p.e11822, 2010.
[8] C. A. Franco, S. Liebner, and H. Gerhardt, "Vascular morphogenesis: a Wnt for every vessel?" Current Opinion in Genetics & Development, vol. 19, no. 5, pp. 476–483, 2009.
[9] J. Folkman and M. Klagsbrun, "Angiogenic factors," Science, vol. 235, no. 4787, pp. 442–447, 1987.
[10] A.-K. Olsson, A. Dimberg, J. Kreuger, and L. Claesson-Welsh, "VEGF receptor signalling—in control of vascular function," Nature Reviews Molecular Cell Biology, vol. 7, no. 5, pp. 359–371, 2006.
[11] C. Chen, L. Li, H. Zhou, and W. Min, "The role of NOX4 and TRX2 in angiogenesis and their potential cross-talk," Antioxidants, vol. 6, no. 2, p. 42, 2017.
[12] V. Novakov, G. S. Sandhu, D. Dragomir-Daescu, and M. Klabusay, "Apelinergic system in endothelial cells and its role in angiogenesis in myocardial ischemia," Vascular Pharmacology, vol. 76, pp. 1–10, 2015.
[13] S. Mitsos, K. Katsanos, E. Koletsi et al., "Therapeutic angiogenesis for myocardial ischemia revisited: basic biological concepts and focus on latest clinical trials," Angiogenesis, vol. 15, no. 1, pp. 1–22, 2012.
[14] J. Wang, Z. Hong, C. Zeng, Q. Yu, and H. Wang, "NADPH oxidase 4 promotes cardiac microvascular angiogenesis after hypoxia/reoxygenation in vitro," Free Radical Biology & Medicine, vol. 69, pp. 278–288, 2014.
[15] S. Nistri, C. Sassoli, and D. Bani, "Notch signaling in ischemic damage and fibrosis: Evidence and clues from the heart," Frontiers in Pharmacology, vol. 8, no. 373, pp. 187, 2017.
[16] K. Matsuurra, A. Honda, T. Naga et al., "Transplantation of cardiac progenitor cell ameliorates cardiac dysfunction after myocardial infarction in mice," The Journal of Clinical Investigation, vol. 119, no. 8, pp. 2204–2217, 2009.
[17] N. K. de Koven, E. R. H. Hollander, and C. Yıldırım et al., "The emerging role of galectins in cardiovascular disease," Vascular Pharmacology, vol. 81, pp. 31–41, 2016.
[18] K. S. Moulton, "Plaque angiogenesis and atherosclerosis," Current Atherosclerosis Reports, vol. 3, no. 3, pp. 225–233, 2001.
[19] I. Bot, J. W. Mukena, I. M. Lankhuizen, T. J. C. van Berkel, and E. A. L. Biessen, "Atorvastatin inhibits plaque development and adventitial neovascularization in ApoE deficient mice independent of plasma cholesterol levels," Atherosclerosis, vol. 214, no. 2, pp. 295–300, 2011.
[20] M.-H. Liu, Z.-H. Tang, G.-H. Li et al., "Janus-like role of fibroblast growth factor 2 in arteriosclerotic coronary artery disease: Atherogenesis and angiogenesis," Atherosclerosis, vol. 229, no. 1, pp. 10–17, 2013.
[21] J. F. Bentzon, F. Otsuka, R. Virmani, and E. Falk, "Mechanisms of plaque formation and rupture," Circulation Research, vol. 114, no. 12, pp. 1852–1866, 2014.
[22] J. Che, M. Okigaki, T. Takahashi et al., "Endothelial FGF receptor signaling accelerates atherosclerosis," American Journal of Physiology-Heart and Circulatory Physiology, vol. 300, no. 1, pp. H154–H161, 2011.
[23] J. C. Sluimer, J.-M. Gasc, J. L. van Wanroij et al., “Hypoxia, hypoxia-inducible transcription factor, and macrophages in human atherosclerotic plaques are correlated with intraplaque angiogenesis,” Journal of the American College of Cardiology, vol. 51, no. 13, pp. 1258–1265, 2008.

[24] S. E. Epstein, E. Stabile, T. Kinnaird, C. W. Lee, L. Clavijo, and M. S. Burnett, “Janus phenomenon: The interrelated tradeoffs inherent in therapies designed to enhance collateral formation and those designed to inhibit arterogenesis,” Circulation, vol. 109, no. 23, pp. 2826–2831, 2004.

[25] J. Kastrup, E. Jørgensen, S. Fuchs et al., “A randomised, double-blind, placebo-controlled, multicentre study of the safety and efficacy of BIOBYPASS (AdGVVEGF121.10NH ) gene therapy in patients with refractory advanced coronary artery disease: The NOVA trial,” EuroIntervention, vol. 6, no. 7, pp. 813–818, 2011.

[26] D. J. Stewart, M. J. Kutryk, D. Fitchette et al., “VEGF gene therapy fails to improve perfusion of ischemic myocardium in patients with advanced coronary disease: results of the NORTHERN trial,” Molecular Therapy, vol. 17, no. 6, pp. 1109–1115, 2009.

[27] G. Deray, N. Janus, B. Aloy, and V. Launay-Vacher, “Renovascular effects of antiangiogenic drugs,” Bulletin du Cancer, vol. 103, no. 7-8, pp. 662–666, 2016.

[28] K. J. Chen, Practical Blood Stasis Syndrome, People’s Medical Publishing House, Beijing, China, 2013.

[29] Y. N. Chen, P. Yan, J. M. Lin et al., “The effective influence of Xiongshao capsule on ischemic myocardium in rats with ultrasonography,” Chinese Journal of Integrative Medicine on Cardio/Cerebrovascular Disease, vol. 10, no. 2, pp. 191-192, 2012.

[30] X. Zeng, H. He, J. Yang et al., “Temporal effect of Guanxin No. 2 on cardiac function, blood viscosity and angiogenesis in rats after long-term occlusion of the left anterior descending coronary artery,” Journal of Ethnopharmacology, vol. 118, no. 3, pp. 485–494, 2008.

[31] Wen-Wu Bai, Yi-Fan Xing, Bo Wang et al., “Tongxinluo improves cardiac function and ameliorates ventricular remodeling in mice model of myocardial infarction through enhancing angiogenesis,” Evidence-Based Complementary and Alternative Medicine, vol. 2013, Article ID 813247, 9 pages, 2013.

[32] J. Yao, Effect of supplementing qi and activating blood circulation on the angiogenesis of rat ischemic cardiac microvascular endothelial cells and the expression of miR-223-3p and miR-132-5p in the plasma of patients with acute myocardial infarction, Shandong University of Traditional Chinese Medicine, Jinan, China, 2015.

[33] Q. Y. Zhang, Q. L. Wang, J. F. Su et al., “Angiogenesis effects of Xuefu Zhu ya decoction and VEGF protein expression,” Journal of Traditional Chinese Medicine, vol. 18, no. 2, pp. 53-54, 2011.

[34] Z. Wang and J. Zhi, “Controllability of discrete-time multi-agent systems with time-delay in state,” Journal of Qingdao University, vol. 24, no. 2, pp. 1-5, 2009.

[35] H. Yin, J. Zhang, H. Lin et al., “Effect of traditional Chinese medicine shu-mai-tang on angiogenesis, arteriogenesis and cardiac function in rats with myocardial ischemia,” Phytotherapy Research, vol. 23, no. 1, pp. 92–98, 2009.

[36] D.-P. Xu, D.-Z. Zou, H.-L. Qiu, and H.-L. Wu, “Traditional Chinese medicine ShenzhuGuanXin granules mitigate cardiac dysfunction and promote myocardium angiogenesis in myocardial infarction rats by upregulating PECAM-1/CD31 and VEGF expression,” Evidence-Based Complementary and Alternative Medicine, vol. 2017, Article ID 526729, 8 pages, 2017.

[37] B. R. Yang, K. K. Cheung, X. Zhou et al., “Amelioration of acute myocardial infarction by saponins from flower buds of Panax notoginseng via pro-angiogenesis and anti-apoptosis,” Journal of Ethnopharmacology, vol. 181, pp. 50–58, 2016.

[38] H. He, M. Shi, X. Yang, X. Zeng, L. Wu, and L. Li, “Comparison of cardioprotective effects using salvianolic acid B and benazepril for the treatment of chronic myocardial infarction in rats,” Naunyn-Schmiedeberg’s Archives of Pharmacology, vol. 378, no. 3, pp. 311–322, 2008.

[39] Z.-T. Wang, S.-J. Zhang, L.-H. Han, and S.-B. Chai, “Effects of Xuexetong Soft Capsules on angiogenesis and VEGF mRNA expression in ischemic myocardium in rats with myocardial infarction,” Journal of Traditional Chinese Medicine, vol. 32, no. 1, pp. 71–74, 2012.

[40] J. G. Liu, D. W. Zhang, J. Li et al., “Effect of radix paeoniae rubra 801 on angiogenesis in rats with myocardial infarction and bearing cancer,” Circulation Journal, vol. 8, no. 26, p. 52, 2011.

[41] J. Chen, Cao, P. F. Asare et al., “Amelioration of cardiac dysfunction and ventricular remodeling after myocardial infarction by danhong injection are critically contributed by anti-TGF-β-mediated fibrosis and angiogenesis mechanisms,” Journal of Ethnopharmacology, vol. 194, pp. 559–570, 2016.

[42] Z.-Y. Zhou, L.-Y. Huan, W.-R. Zhao, N. Tang, Y. Jin, and J.-Y. Tang, “Spatholobi Caulis extracts promote angiogenesis in HUVECs in vitro and in zebrafish embryos in vivo via up-regulation of VEGFRs,” Journal of Ethnopharmacology, vol. 200, pp. 74–83, 2017.

[43] L. Ma, M. Ni, P. Hao et al., “Tongxinluo mitigates atherogenesis by regulating angiogenic factors and inhibiting vasa vasorum neovascularization in apolipoprotein E-deficient mice,” Onco-target, vol. 7, no. 13, pp. 16194–16204, 2016.

[44] M. Z. Liu, Z. H. Jia et al., “Influence of Tongxinluo ultrafine powder on early atherosclerotic epicardial angiogenesis,” Journal of Traditional Chinese Medicine, vol. 56, no. 3, pp. 240–244, 2015.

[45] M. Li, J. P. Zhang, and K. Zhu, “Experimental study of Simiao Yongan decoction regulating vasa vasorum remodeling in ApoE-/- mice with atherosclerosis vulnerable plaque,” World Sci Technol/Mod Tradit Chin Med Mater Med, vol. 19, no. 12, pp. 1989–1997, 2017.

[46] L. Zhang, Y.-R. Jiang, C.-Y. Guo, C.-F. Wu, K.-J. Chen, and H.-J. Yin, “Effects of active components of Red Paeonia and Rhizoma chuanxiong on angiogenesis in atherosclerosis plaque in rabbits,” Chinese Journal of Integrative Medicine, vol. 15, no. 5, pp. 359–364, 2009.

[47] D. Z. Ren, Q. S. Liu, J. Li, and X. L. Shen, “Effects of Huoxue capsule on expression of VEGF and VCAM-1 in rabbits with arteriosclerosis,” Chinese Journal of Integrative Medicine, vol. 20, no. 21, pp. 167–170, 2014.

[48] Y. Qiao, Effect and Mechanism of Shumai Capsule on Atherosclerotic Plaque Angiogenesis, Shandong University, Jinan, China, 2014.

[49] X. P. Pan, Z. D. Huang, and W. F. Yang, “Effects of ultramicro-jiawei Danshen Yin on serum VEGF, MMP-9 of patients with primary hyperlipidemia and carotid atherosclerotic,” Journal of Traditional Chinese Medicine, vol. 21, no. 16, pp. 21–24, 2015.

[50] Y. Qiao, P.-J. Zhang, X.-T. Lu et al., “Panax notoginseng saponins inhibits atherosclerotic plaque angiogenesis by down-regulating vascular endothelial growth factor and nicotinamide adenine dinucleotide phosphate oxidase subunit 4 expression,” Chinese Journal of Integrative Medicine, vol. 21, no. 4, pp. 259–265, 2015.
[51] Y. Zeng, *Effect of Ruanmailing Oral Liquid on Angiogenesis in Experimental Atherosclerotic Plaque*, Fujian Medical University, Fuzhou, China, 2010.

[52] C. L. Liao, M. Z. Huang, H. Y. Liu, D. Liang, and G. Z. Pan, “Association of the genotype and serum level of P-selectin with acute myocardial infarction,” *Chinese Journal of Arteriosclerosis*, vol. 19, pp. 151–154, 2011.

[53] Y. J. Yin, L. Y. Ma, and G. Wei, “Influence of Guishaotongluo on angiogenesis of adventitial vasa vasorum and oxidative stress in early stage of atherosclerosis,” *Chinese Pharmacological Bulletin*, vol. 32, no. 3, pp. 416–422, 2016.

[54] J. H. Yang, Y. T. He, and A. L. Yuan, “Effect of lipid-lowering Hongqu micropowder on serum vascular endothelial growth factor level and plaque stability in patients with carotid atherosclerosis,” *Chinese Journal of Clinical Rational Drug Use*, vol. 8, no. 9A, pp. 82-83, 2015.

[55] X. L. Pang, L. Yang, and W. Y. Zeng, “Research the mechanism of Buyang Huanwu decoction on angiogenesis in vulnerable plaque in rabbits,” *Tianjin University of Traditional Chinese Medicine*, vol. 32, no. 11, pp. 672–674, 2015.

[56] W. Shen, *Empirical Study to Compare The Mechanism of Angiogenesis in Atherosclerosis And Ischemic Myocardium And to Perform The Medicine Interventions for Them*, Fudan University, Shanghai, China, 2008.

[57] W. Shen, W. H. Fan, H. M. Shi et al., “Effects of Shexiang Baoxin Pill on angiogenesis in atherosclerosis plaque and ischemic myocardium,” *Zhongguo Zhong Xi Yi Jie He Za Zhi*, vol. 30, no. 12, pp. 1284–1287, 2010.

[58] F. Lin, B. L. Chen, Y. Z. Wang et al., “In vitro angiogenesis effect of Xuefu Zhuyu Decoction and vascular endothelial growth factor: a comparison study,” *Chinese Journal of Integrative Medicine*, pp. 1–7, 2015.

[59] S. Goel, D. G. Duda, L. Xu et al., “Normalization of the vasculature for treatment of cancer and other diseases,” *Physiological Reviews*, vol. 91, no. 3, pp. 1071–1121, 2011.

[60] B. W. Wong, E. Marsch, L. Treps, M. Baes, and P. Carmeliet, “Endothelial cell metabolism in health and disease: impact of hypoxia,” *EMBO Journal*, vol. 36, no. 15, pp. 2187–2203, 2017.

[61] W. Shen, H.-M. Shi, W.-H. Fan, X.-P. Luo, B. Jin, and Y. Li, “The effects of simvastatin on angiogenesis: Studied by an original model of atherosclerosis and acute myocardial infarction in rabbit,” *Molecular Biology Reports*, vol. 38, no. 6, pp. 3821–3828, 2011.

[62] J. M. Xiao, W. H. Wan, and J. Xu, “Effect of Rhodobryum roseum Limpr. on atherosclerosis and ischemic myocardial angiogenesis in rabbits,” *Chinese Journal of Multiple Organ Diseases in the Elderly*, vol. 13, no. 12, pp. 935–940, 2014.