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Research Article

The Research progress of the Vessel-Collateral Theory and Organ Fibrosis

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Abstract

The Vessel-Collateral Theory is a kind of disease model theory in Traditional Chinese Medicine, that describes changes in the vascular microenvironment and microcirculatory disorders. According to this theory, the body's qi and blood run through the channels of meridians to infuse all organs and tissues of the body. And when this channel is affected by various pathological factors, its function is impaired. Fibrosis is a common pathological pathway for liver, kidney, lung and other organs to progress to end-stage diseases. Microcirculation is a place where blood, material metabolism and energy exchange are carried out by microvessels as the main structure; at the structural level, modern medicine considers microcirculation as having the characteristics of network structure, diffuse distribution, mutual penetration and fluid flow. A number of studies have confirmed that organ fibrosis is associated with sclerosis, rarefaction and decreased perfusion of the capillary network. This alteration in the vascular microenvironment is similar to the Vessel-Collateral Theory, which is called Accumulation in category of traditional Chinese medicine. The formation of accumulation is closely related to the Qi and Blood in the meridians. A variety of pathogenic factors affect the transit of Qi and Blood, causing collateral disease and eventually the accumulation of organ fibrosis. Many herbal prescriptions formed under the guidance of Vessel-Collateral Theory all work by activating blood circulation and are related to improving microcirculation, so we do an overview to dig more single and compound prescriptions to improve organ fibrosis.

Keywords: Chinese medicine, Herbal prescriptions, Chinese herbal monomer, the Vessel-Collateral Theory, Organ fibrosis.

Introduction

The Vessel-Collateral Theory first originated in the Qing Dynasty, when Ye Tianshi proposed this concept in Linzheng Zhinan Yi'an. Professor Yiling Wu inherited the traditional meridian theory and systematically constructed the Vessel-Collateral Theory to guide the prevention and treatment of vasculopathy [1]. He also proposed the concept of "vessel-vascular system diseases" based on the close correlation between collaterals and micro vessels. The collateral, as the main pathway for the transmission of qi, blood and fluid to realize the basic function and biochemical at the end of the veins, has the characteristics of network structure, diffuse distribution, bi-directional flow, and slow movement. Corresponding to collateral, the microcirculation theory under modern medical research believes that the microvessel is the main structure to carry out blood operation, material metabolism and energy exchange. According to the Vessel-Collateral. Theory, the tangible vessels of the internal organs form the vessel collaterals (blood), while the neuroendocrine immune regulation function formed by the cell signaling in the internal organs constitutes the invisible meridian collaterals (qi), and both qi and blood collaterals together complete the physiologic functions of "circulating qi and blood as well as nourishing yin and yang."

In modern medical theory, organ-specific microvascular endothelial cells, pericytes and surrounding blood cells in multiple organs including kidney constitute a relatively independent

microcirculatory whole, forming a guiding microenvironment called vascular niche, and the destruction of vascular niche is closely related to organ fibrosis. Therefore, the concept of "callateral-microvessel" was proposed based on the similarity of functions and structures of callaterals and microvessels, the treatment of fibrosis according to this theory is to treat the collateral-qi stagnation or deficient stagnation, as well as the pathological products such as phlegm, stasis and heat through the vessel-vascular system diseases by using the herbs and prescriptions, which is a combination of Chinese and Western medicine to study the theory of microvascular lesions.

Fibrosis is a protective mechanism that follows inflammation and tissue injury by cells invading the injured area secrete large amounts of extracellular matrix to reconstruct and strengthen the damaged tissue to accelerate the healing process [2]. Based on this, we propose that the vascular niche is the basic structure of organ ligaments including the kidney and is a good entry point for modern research in ligamentology. Common mechanisms involved in fibrosis include the TGF/Smads pathway [3], some inflammatory signaling pathways such as Wnt/β-catenin, MAPK, NF-κB, PI3K/Akt, and JAK-STAT pathways [4-8], the CXCL12-CXCR4/CXCR7 pathway [9], the endothelial-to-mesenchymal transformation(EMT), and the epithelial mesenchymal transition(EMT) [10,11], as well as the regulation of some inflammatory mediators and cytokines such as hypoxia-inducible factor-1 (HIF-1)、peroxisome proliferator-activated receptors (PPAR-γ), IL-10,IL-13, IL-21, TGF-β1, chemokines (MCP-1, MIP-1beta), angiogenic factors (VEGF), growth factors (PDGF), acute phase proteins (SAP), caspases, and components of the renin-angiotensin-aldosterone system (ANG II) [12-15]. The cells involved in these mechanisms include parenchymal cells of organs, vascular endothelial cells, pericytes, epithelial cells, myofibroblasts, and various immune cells [16-18].

According to current studies on the pathogenesis of organ fibrosis, the development of fibrosis is accompanied by a series of vascular changes, such as the rarefaction of peritubular capillaries [19], the defective repair of capillaries after injury [20], and divergent angiocrine signals from vascular niche [21], these factors result the proliferation of fibroblasts around blood vessels. During the progression of fibrosis, as changes in vascular tone, endothelial permeability and vascular regulation lead to inflammation, hypertension and coagulation, thus gas, solute and hormone exchange between blood and tissues is affected, subsequently affecting angiogenesis and remodeling [22,23]. Therefore, targeting the microvascular environment of injured tissues may mitigate fibrosis. Under the guidance of the Vessel-Collateral Theory, many prescriptions and Chinese medicines as well as their individual components are being studied, and these approaches have comprehensively elucidated the clinical application of Vessel-Collateral Theory from the perspective of molecular biology, such as "Dahuang Zhechong pill (DHZC)", "Buyang Huanwu decoction (BYHW)", "Qili Qiangxin capsule (QLQX)", "Xuefu Zhuyu soup (XFZY)", "Naoxintong capsule (NXT)" and so on. These prescriptions show good efficacy in the clinical application of organ fibrosis. Therefore, it is a good supplement and alternative to use the theory and methods of Vessel-Collateral Theory in treating fibrosis. Based on the above reasons, we summarized the Chinese medicine and prescriptions for the treatment of organ fibrosis based on the Vessel-Collateral Theory.

Pulmonary Fibrosis

"Buyang Huanwu decoction (BYHW)" studied by collateral disease can reduce the expression of connective tissue growth factor (CTGF) and phosphor-AKT (p-AKT) to alleviate pulmonary fibrosis in rats and can also regulate the PI3K-Akt-ENOS pathway to improve pulmonary vascular remodeling [24,25]. LHQW has an antagonistic effect on the pro-inflammatory mediator's TNF-α and IL-6 of the mechanism and reduce the degree of endothelial-mesenchymal transition (EndMT) and fibrosis [26,28]. In addition, Tetramethylpyrazine(TMP), one of TCM monomers, regulated the SDF-1/CXCR4 pathway to inhibit angiogenesis or fibrosis, and inhibited the apoptosis of pulmonary microvascular endothelial cells (PMVEC) by the PERK/eIF2α/ATF4/CHOP apoptotic signal for improving microcirculation disorders and alleviating lung injury [29,30]. Astragaloside IV can inhibit TGF-β1/Smad2/3 signaling pathway, reduce the expression of collagen I, fibronectin (FN) and α-SMA, improve pulmonary vascular remodeling and alleviate pulmonary fibrosis [31,32]. Studies show that quercetin, gambogic acid, dihydroartemisinin(DHA) can effectively inhibit TGF-β-mediated endothelial cell proliferation and EndMT in lung and skin fibrosis models [33]. Salvianolic acid B (Sal B) protected endothelial cells from oxidative stress by inhibiting endothelial cell permeability and reducing the expression of pro-inflammatory cytokines through MAPK and NF-κB signaling pathways and improves LPS-induced rat pulmonary microcirculation disorders [34,35]. Maxing Shigan Tang MXSGT ameliorated LPS-induced leukocytosis in pulmonary small veins of rats, and effectively inhibited the production of pro-inflammatory factors and pulmonary perivascular edema, which shows that MXSGT has potential therapeutic effects on pulmonary microvascular hyperpermeability and inflammatory responses [36]. Pretreatment with andrographolide pills (AP) ameliorate LPS-induced increase in cytokines, neutrophil adhesion and infiltration, oxidative stress and microvascular hyperpermeability [30]. Schisandrin (Sch), the active component of Schisandra chinensis, can attenuate LPS-induced lung endothelial and epithelial cell injury, reduce expression of vascular heme factor (vWF) and keratin, and activate cell regeneration possibly through inhibition of TLR-4/NF-κB/MAPK activation and FoxO1 signaling pathway [37].

Table 1: Chinese Medicine and Prescriptions inhibit fibrosis and inflammation through various pathways in different organs.

Organs	Chinese Medicine and Prescriptions	Via the Mechanisms or Pathways	References
	BYHW	PI3K-Akt-ENOS	[5,9]
	LHQW	TNF-α,IL-6,and EndMT	[26-28]
	TMP	SDF1/CXCR4,PERK/eIF2α/ATF4/CHOP	[29,30]
	Astragaloside IV	TGF-β1/Smad2/3	[31,32]
Lung	Quercetin, Gambogic acid, and DHA	TGF-β,EndMT	[54]
	Sal B	MAPK,NF-κB	[34,35]
	MXSGT	Reduce inflammation	[36]
	AP	Inhibit oxidative stress	[58]
	Sch	TLR-4/NF-κB/MAPK, FoxO1	[37]
	QSYQ	Wnt/β-catenin and TGF-β/Smad	[38,39]
	QCF	TGF-β1,α-SMA and E-cadherin	[40]
	YSHX	miR-126/VEGF-Notch,TGF-β/Smad	[41,42]
	Tan IIA	TGF-β/Smad, NF-κB	[43]
	Hirudin	TGF-β1/Smad, NF-κB	[44]
	Ginsenoside Rg1	TGF-β1/Smad	[44]
Kidney	TWHF	TGF-β ,Wnt/β-catenin	[46]
	Quercetin	Reduce inflammation	[47]
	YGP	Reduce inflammation	[48]
	MHCD	TGF-β/Smad	[49]
	Huangqi decoction	TGF-β/Smad	[51]
	GAS	AMPK/Nrf2/HMGB1	[6]
	HKC	p38MAPK, TLR4/NF-κB	[52,55]
	XFZY	TGF-β1,EndMT	[60]
	SSYX	TGF-β1/Smad	[61,62]
	QLQX	VEGF,p-AKT	[63,64]
	TXL	PPAR-α	[65]
	NXT	1A(TL1A), VEGF-α	[66]
	BYHW	Cav1/VEGF	[67]
	PR	PI3K/Akt,Nrf2/p38-MAPK	[68,69]
Heart	Tan IIA with PR	TLR4,TGF-β	[70]
	RAS-RH	Induce fibroblasts apoptosis	[71]
	Cur	P38 MAPK/ERK	[72,73]
	CP	TGF-β/Smads	[74]
	QSYQ	TGF-β/Smads	[75-77]
	SQ	PPAR	[78]
	CS	AMPK/mTOR/ULK1	[79]
	SCA	TGF-β1/TAK1/MAPK	[82]

	TFM	TGF-β1/Smad, NF-κB	[59]
	FSE	TLR4/MyD88/NFκB,TGFβ/smads,EMT	[84,85]
	LWWL	NF-κB,TGF-β/Smad,TIMP1 and TIMP2	[86,87]
	FZHY	PPARG	[88]
	CGA	TGF-β1/Smad,EndMT	[89]
	DHZC	PI3K/Akt	[91,136]
	Emodin	TGF-β1,EndMT	[92]
Liver	Sal B	TGF-β/Smad	[93,94]
	AU and AUG	TGF-β1	[33]
	FGP	ACE/Ang II/AT-1R,ACE2/Ang 1-7/Mas	[95]
	Yu Jin Pulvis	MAPK,PI3K/Akt	[96]
	XYXD	NF-κB,TGF-β1	[97]
	FL	EMT,Nrf2	[98]
	APE	TGF-β/Smad	[99]
	HQD	TGF-β1/Smads	[100,101]
	Artesunate	Ferritinophagy-mediated ferroptosis	[102]
	BYHW	HIF-1α/VEGF	[104,105]
	TXL	Reduce inflammation	[106,107]
	Catalpol and Puerarin	Improve cerebral microcirculation	[108,109]
	Galangin	Wnt/β-catenin,HIF-1α/VEGF	[110]
	CG	Reduce inflammation	[111-113]
	DLA	TNF-α, IL-6,CD11b/CD18	[118]
	CA	p-ERK, p38,p- JNK	[116]
	SAB	CD11b/CD18,CD62L, E-cadherin	[115]
Brain	TSI	AMPK/Akt/PKC	[117]
	Rhy	RhoA/ROCK	[119]
	IS	Regulat complex I activity	[120]
	L-THP	Inhibit the Src kinase phosphorylation	[121]
	T541	ADP/ATP⍰AMP/ATP and ATP5D	[122]
	KDZ	Inhibit the Src kinase phosphorylation	[123]
	YXQNW and SC	Maintain blood-brain barrier integrity	[124,125]
	YQFMQ	Toll-4,p- Src and caveolin-1	[103]
	QYT	NF-κB	[126]
	BSHX	RhoA/ROCK1/moesin	[127]
	DJZD	MAPK,Akt and NF-κB	[128]
	WMP	TGF-β/Smad,Wnt/β-linked	[129]
Intestine	WHTF	Protein D1 and survivin	[130]
	Baicalein	Inhibiting apoptosis and oxidation	[131]
	DHA	PI3K-ATK, EndoMT	[132]
Skin	SAB	TGF-β/SMAD, MAPK/ERK	[133]
	IT	AMPK,WNT/β-catenin	[134]

Renal Fibrosis

The TGF/Smad pathway is the classical pathway of fibrosis mechanism and is capable of causing mesenchymal changes in a variety of cells. In view of this, collateral disease prescriptions including Qishen Yiqi pill (QSYQ), Quyu Chencuo prescription (QCF) and Yishen Huoxue prescription (YSHX) have antagonistic effect on this mechanism. QSYQ is a renal protective prescription, that can inhibit EndMT by Wnt/β -catenin and TGF-β/Smad signaling pathways, thus improve renal microcirculation disorders, prevent diabetic nephropathy and alleviate renal fibrosis [38,39]. QCF, as one of the Traditional Chinese medicine TCM prescriptione that can improve blood circulation, has been proved to improve renal interstitial microvascular environment and prevent the progression of renal fibrosis by regulating the expression of TGF-β1, α-SMA and E-cadherin in UUO rats [40]. YSHX can mediate renal microvasculogenesis and improve renal microvascular injury by upregulating miR-126/VEGF-Notch signaling pathway, and also inhibit TGF-β/Smad signal transduction, both of which can alleviate renal fibrosis [41,42]. In addition, tanshinone IIA (tan IIA) can reduce the levels of inflammation and fibrosis and ameliorate the disturbance of microvascular environment by inhibiting the activation of TGF-β/Smad and NF-κB signaling pathways in CKD rats [43]. Hirudin can inhibit renal fibrosis by blocking TGF-β1/Smad and NF-κB pathways [44]. The treatment of ginsenoside Rg1 in combination with astragaloside IV can protect against microangiopathy in diabetic nephropathy by reducing oxidative stress and inhibiting TGF-β1/Smads signaling [45]. The anti-fibrosis effect of Tripterygium wilfordii Hook F (TWHF) is to ameliorate the microvascular injury of diabetic nephropathy by inhibiting TGF-β and Wnt/β-catenin signals [46]. Quercetin can not only inhibit the infiltration of M1 macrophages in renal interstitium and reduce inflammation, but also inhibit the activation of M2 macrophages and reduce the excessive accumulation of extracellular matrix, thus achieving the effect of treating renal interstitial fibrosis [47]. You-gui Pill (YGP) is a traditional prescription that has been widely used to "warm the kidney". Experiments show that YGP significantly reduce UUO-induced inflammatory cell infiltration, tubular atrophy and interstitial fibrosis [48]. Modified Huangqi Chifeng Decoction (MHCD) can inhibit secretion of extracellular matrix from glomerular thylakoid cells induced by inflammatory factor, suppress excessive activation of TGF-β/Smad signaling pathway thereby inhibiting fibrosis [49,50]. Huangqi decoction can dose-dependently downgrade the expression of collagen and inhibit the activation of TGF-β/Smad signaling pathway to improve ipsilateral renal fibrosis in UUO mice [51]. Gastrodin (GAS), the main phenolic glycoside extracted from Gastrodia elata Blume, was found that can attenuate CCl(4)-induced kidney inflammation and fibrosis via the AMPK/Nrf2/HMGB1 pathway [6]. Huangkui capsule (HKC) is an anti-inflammatory Chinese modern patent medicine. Studies showed that HKC can alleviate renal fibrosis by suppressing the activation of p38MAPK signaling pathway and inhibiting NLRP3 inflammasome activation and TLR4/NF-κB signaling pathways in the DN model rats [52-55].

Cardiac Fibrosis

Endothelial cells have the ability to convert to a smooth muscle-like phenotype, and the phenotypic transition is termed Endothelial-to-mesenchymal-transition (EndMT), which is a common mechanism in the process of organ fibrosis [56,57]. The prescription XFZY applied in collateral diseases can inhibit EndMT and fibroblast activation through TGF-β1 signaling pathway and improve myocardial fibrosis [58-60]. Shensong Yangxin capsule (SSYX) can inhibit TGF-β1/Smad signaling pathway, reduce fibrosis and improve cardiac function [61,62]. In addition, Qiliqiangxin Capsules (QLQX) can correct cardiac dysfunction and ventricular remodeling by upregulating VEGF expression and Akt phosphorylation, and its protective effect may be related to reduced apoptosis and myocardial fibrosis [63,64]. Tongxinluo (TXL) activates Angiopoietin-like 4 (Angptl4) under the regulation of PPAR-α pathway to maintain the functional and structural integrity of the endothelial barrier and protect the heart from I/R injury in diabetic rats [65]. Naoxintong capsule (NXT) has a variety of anti-thrombotic functions and can reduce the apoptosis of HUVECs by inhibiting the expression of tumor necrosis factor-like cytokine 1A(TL1A) and activating the expression of VEGF-α [66]. BYHW can reduce myocardial fibrosis and inflammation through Cav1/VEGF signaling pathway, so that can promote angiogenesis in infarct boundary area [67]. Puerarin (PR) can weaken EndMT and inhibit the activation of PI3K/Akt pathway by reactive oxygen species, so as to decelerate cardiac fibrosis [68]. PR can also rescue injured endothelial cells, improve repair function of vascular niche and prevent myocardial fibrosis by activating Nrf2 expression and inhibiting phosphorylation of p38-MAPK [69]. In addition, tan IIA combined with PR can reduce the expression of TLR4 and TGF-β, protect vascular endothelial cells, improve hemodynamics and vascular permeability, and inhibit myocardial fibrosis and ventricular remodeling [70]. Radix Angelica Sinensis and Radix Hedysari ultrafiltration extract (RAS-RH) can induce apoptosis, inhibit the levels of TGF-β1 and troponin-1(TnI), and reduce the expression of osteopontin (OPN), C-Jun, mirNA-21 and COL1α in fibroblasts, thus playing an anti-fibrosis role [71]. Curcumin (Cur) can inhibit the P38 MAPK/ERK signaling pathway to regulate the proliferation and cell cycle of cardiac fibroblasts, so as to inhibit abnormal growth of microvessels, and reduce cardiac fibrosis [72,73]. Cardiotonic pills (CP) improved myocardial fibrosis and prevented myocardial remodeling by inhibiting the expression of TGF-β1, P-Smad3, Smad4, MMP-9, α-SMA and CD68-positive cell number in rats I/ R-induced to myocardial infarction and fibrosis [74]. QiShen YiQi Pills (QSYQ) can reduce myocardial fibrosis by inhibiting the TGFβ1/Smads signaling pathways and

prevent ischemic myocardial injury by inhibiting the release of myocardial cTnI and restoring energy-regulated metabolism after myocardial ischemia [75-77]. Sang-qi Granula (SQ) is a proprietary Chinese medicine. It was found that SQ could significantly inhibit the expression of proinflammatory mediators and collagen deposition-related proteins in SHR rat cardiomyocytes and prevent cardiac fibrosis through PPAR signaling pathway [78]. Chikusetsusaponin IVa (CS) was demonstrated that can attenuate isoprenaline-induced myocardial fibrosis by activating autophagy through AMPK/mTOR/ULK1 pathway, reduce the heart index, inhibit inflammatory infiltration, and decrease collagen deposition and myocardial cell size [79].

Hepatic Fibrosis

Hepatic microcirculatory dysfunction is a key factor in causing chronic liver disease and liver fibrosis. The disruption of vascular homeostasis leads to portal hypertension, which is an important cause of compromising the liver [80,81]. Schisandra chinensis (SCA) is a traditional Chinese medicine for liver protection, and it was showed that SCA can ameliorate the liver fibrosis by inhibiting the HSCs activation and inflammatory response and inhibiting TGF-β1 mediated TAK1/MAPK signal pathways [82]. Additionaly, the main active components of SCA, schisandrin C (Sin C) and Schisandrol B (SolB) was also found to have the effect of reversing liver fibrosis in mice [8,24,83]. Total flavonoids of Mallotus apelta leaf (TFM) can alleviate CCl(4)-induced hepatic fibrosis in rats by reducing ECM accumulation, improving antioxidant and regulating TGF-β1/Smad signaling pathways and NF-κB-dependent inflammatory response [59]. The water-soluble component extracted from Forsythiae Fructuse, Forsythiae Fructuse water extract (FSE), can inhibit the development of liver fibrosis through TLR4/MyD88/NF-κB and TGF-β/smads signaling pathways. *In vivo*, studys showed FSE attenuated CCl(4)-induced liver fibrosis in mice by inhibiting hepatic stellate cells (HSCs) activation, reducing hepatic extracellular matrix (ECM) disposition and reversing epithelial-mesenchymal transition (EMT) [84,85]. There are results indicated that Liuweiwuling (LWWL) tablets, a Chinese traditional herbal prescription, can attenuate hepatic fibrosis in rats by modulating the NF-κB-dependent inflammatory response and TGF-β/Smad signaling pathway, as well as the expression levels of TIMP1 and TIMP2, which regulate extracellular matrix (ECM) degradation [86,87].

Fuzheng Huayu prescription (FZHY) have been found that its main active ingredients can directly bind to peroxisome proliferators-activator receptor PPARG to reduce the activities of HSCs, thus playing an anti-fibrosis role [88]. The prescription CGA is modified from FZHY. CGA can inhibit EndMT by antagonizing TGF-β1/Smad signaling pathway, so as to reverse the transformation of HSCs into myofibroblasts and alleviate liver fibrosis [89,90]. DHZC can play a role of anti-fibrosis in liver, which can not only inhibit macrophage recruitment to hepatocyte and reduce the accumulation of collagen in liver tissue, but also inactivate PI3K/Akt pathway for inhibiting the proliferation of HSCs [91,136]. Additionally, emodin may reduce EndMT by inhibiting TGF-β1 signaling pathway and play an anti-liver fibrosis role [92]. Sal B is a potential anti-liver fibrosis drug by inhibiting TGF-β/Smad signaling [93,94]. Aucubin (AU) and Aucubigenin (AUG), as active ingredients of eucommia ulmoides, can inhibit the activation of HSCs and ECM deposition induced by TGF-β1, so that they restore the disturbed microvascular microenvironment [33]. Fugan pill (FGP) can repair endothelial dysfunction and alleviate liver fibrosis by inhibiting ACE/Ang II/AT-1R signaling pathway and enhancing ACE2/Ang 1-7/Mas signaling pathway [95]. Yu Jin Pulvis has anti-fibrosis effect on CCL4-induced mice by blocking MAPK and PI3K/Akt signaling pathways [96]. Xia-yu-xue decoction (XYXD), a classical Collateral recipe used in China, was revealed to inhibit hepatic fibrosis by inhibiting HSC activation via inhibition of NF-κB and TGF-β1 signaling pathway [97]. The water extract of Lonicerae Japonicae Flos (FL) from carbon tetrachloride can attenuate CCl(4)-induced liver fibrosis in mice by inhibiting HSCs activation, reversing EMT and reducing liver oxidative stress injury via inducing Nrf2 activation [98]. Astragalus and Paeoniae radix rubra extract (APE) may inhibit the progression of CCl4-induced hepatic fibrosis via scavenging free radicals, decreasing TGF-β1 levels and blocking of the TGF-β/Smad signaling pathway [99]. Huangqi decoction (HQD) can alleviate DMN-induced liver fibrosis via the regulation of bile acid metabolism enzyme and inhibit CDCA-induced HSCs proliferation and activation. Moreover, the main components of HDQ, the total astragalus saponins (AST) and glycyrrhizic acid (GA), synergistically alleviated hepatic fibrosis via TGF-β1/Smads signaling pathway inhibition in hepatic stellate cells [100,101]. Artesunate, a water-soluble hemisuccinate derivative of artemisinin, could alleviate liver fibrosis by regulating ferritinophagy-mediated ferroptosis in hepatic stellate cells (HSCs) [102, 103].

Other Organ Fibrosis

Studies also found some Vessel-Collateral Theory treatment methods that can inhibit organ fibrosis in brain, intestine, skin and other organs by repairing vascular endothelial cell injury and improving the microcirculation. For example, BYHW can prevent reperfusion injury after ischemic stroke in rats by inhibiting HIF-1α and VEGF, promoting angiogenesis and repairing brain tissue [104,105]. Tongxinluo capsule (TXL) can improve ischemic cerebrovascular disease by inhibiting inflammatory response, regulating vascular endothelial function and promoting angiogenesis [106,107]. Lyophilized Powder of Catalpol and Puerarin can improve cerebral microcirculation disorders and neurological recovery after cerebral ischemia by promoting vascular renewal [108,109]. Galangin promotes vascular neogenesis and vascular remodeling

through upregulation of Wnt/β-catenin and HIF-1α/VEGF signaling pathways in MCAO model rats [110]. Cerebral care Granule (CG) is a compound Chinese medicine used to treat headache and dizziness associated with cerebrovascular diseases. It was found that CG treatment could significantly reduce microvascular ultrastructural changes in the cerebral cortex of gerbils caused by I/R injury, reduce cerebral microvascular hydrogen peroxide production, leukocyte adhesion and albumin leakage, significantly reduce blood-brain barrier permeability and brain edema, and reduce brain neuronal damage [111-114]. The active monomer components of Salvia miltiorrhiza, such as 3,4-dihydroxyphenyl lactic acid (DLA), CA, Salvianolic acid B(SAB) and Total salvianolic acid injection (TSI), can also improve cerebral microvascular hyperpermeability and inhibit thrombogenesis through anti-inflammatory and antioxidant effects [115-118]. In addition, there are many prescription and herbs as well as single components that can improve perfusion and salvage cerebrovascular and neurological damage by inhibiting vascular endothelial cell injury and cerebral microcirculatory dysfunction, such as some components of herbs: Rhynchophylline(Rhy) [119], Icariside II (IS) [120], Levo-tetrahydropalmatine(L-THP) [121], herbal monomer complex T541(AS:SAA:PNS=5:4:1) [122] and some prescriptions: Kudiezi Injection(KDZ) [123], YangXue QingNao Wan(YXQNW) and Silibinin Capsules(SC) [124,125], Yiqifumai injection(YQFMQ)[102], Qing-Ying-Tang(QYT)[126], Bushen Huoxue(BSHX) [127]. All these methods play a positive role in treating fibrosis from the perspective of Vessel-Collateral Theory.

Dajianzhong decoction (DJZD) improves intestinal fibrosis and induces intestinal blood flow by regulating mitogen-activated protein kinase (MAPK), protein kinase B (Akt) and NF-κB activity [128]. Wumei pill (WMP) inhibit intestinal fibrosis and alleviate chronic colitis by regulating TGF-β/Smad and Wnt/β-linked protein pathways [129]. Dermal fibrosis is a major pathological change in systemic sclerosis (SSc), and Wenyang Huazhuo Tongluo prescription (WHTF) may exert anti-proliferative and pro-apoptotic effects on fibroblasts by downregulating mRNA and protein levels of protein D1 and survivin in SSc cells [130]. Baicalein from Scutellaria baicalensis is able to promote flap viability by stimulating angiogenesis and inhibiting apoptosis and oxidation [131]. Dihydroartemisinin (DHA) inhibits fibroblast activation and collagen deposition via the PI3K-ATK pathway to ameliorate tissue fibrosis and protects dermal vasculature from bleomycin-induced EndoMT [132]. SAB can alleviate skin fibrosis and reduce collagen deposition in blomycin-induced SSc mouse model, reduce SSc skin fibroblast proliferation through TGF-β/SMAD and MAPK/ERK pathways, and down-regulate extracellular matrix gene transcription and collagen expression [133]. Icaritin (IT), a natural compound of epimedium herb, was found to have an anti-skin fibrotic effect through activation of AMPK signaling and inhibition of WNT/β-catenin signaling [134].

Discussion

The above studies suggested that various TCM and monomer ingredients could inhibit abnormal activation of vascular microenvironment signaling pathways in different organs to repair microcirculation, thus achieving anti-inflammatory and anti-fibrosis effects (Table1). It is especially worth pointing out that TCM prescriptions of collateral medicine can play a multi-level and multi-target role in the intervention the progression of fibrosis and protection of blood circulation system. New data from the COVID-19 pandemic suggest that there may be substantial fibrotic consequences following SARS-CoV-2 infection [135]. Thus, current therapies targeting fibrosis have value in the prevention and treatment of chronic lesions of the post-infected organ. Therefore, by studying the treatment of fibrosis with herbal compound and monomeric components under the collateral disease theory can bring richer experience for the treatment of fibrosis.

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