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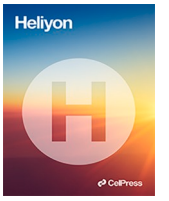

Review article

Tongxinluo capsule as a multi-functional traditional Chinese medicine in treating cardiovascular disease: A review of components, pharmacological mechanisms, and clinical applications

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ABSTRACT

Cardiovascular diseases (CVDs) are one of the most significant diseases that pose a threat to human health. The innovative traditional Chinese medicine Tongxinluo Capsule, developed under the guidance of the theory of traditional Chinese medicine, has good clinical efficacy in various cardiovascular diseases, this medicine has effects such as blood protection, vascular protection, myocardial protection, stabilizing vulnerable plaques, and vasodilation. However, CVDs are a multifactorial disease, and their underlying mechanisms are not fully understood. Therefore, exploring the mechanism of action and clinical application of Tongxinluo Capsule in the treatment of various cardiovascular diseases is beneficial for exerting its therapeutic effect from multiple components, targets, and pathways. At the same time, it provides broader treatment ideas for other difficult to treat diseases in the cardiovascular event chain, and has significant theoretical and clinical significance for improving the treatment of cardiovascular diseases with traditional Chinese medicine.

1. Introduction

Cardiovascular disease (CVD) is a general term for a group of heart and vascular diseases, which refers to ischemic or hemorrhagic diseases in the heart and whole body tissues caused by hyperlipidemia, blood viscosity, atherosclerosis, hypertension, etc. [1]. The high prevalence, high disability, and high mortality rates of CVD pose significant challenges to the public health system. According to

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the latest data from the 2019 Global Burden of Disease (GBD), cardiovascular disease accounts for 32 % of global deaths, 85 % of them die from heart attacks and strokes [2].。 At present, the incidence rate and prevalence rate of CVD in China continue to increase, which has become the first cause of death among residents. According to the report on cardiovascular health and disease in China in 2022, CVD will account for 48.00 % and 45.86 % of the causes of death in rural and urban areas respectively in 2020, and two out of every five deaths will die from CVD [3], the economic burden this brings to society and residents is increasing day by day. It is estimated that if the current trend of risk factors continues, 7.8 million people will die prematurely from cardiovascular disease by 2025 [4]. At present, the treatment of cardiovascular diseases in China is based on the guidelines of the American Heart Association (AHA)/American College of Cardiology (ACC), European Society of Cardiology (ESC), as well as the Chinese Society of Cardiology (CSC) and Cardiovascular Physicians Branch of the Chinese Medical Association (CCCP), combined with the clinical experience of physicians, It presents a treatment model mainly based on Western medicine. However, there are many risk factors for cardiovascular disease, and its pathological and physiological processes are closely related to the body's own immunity. Western medicine has a single treatment target, making it difficult to comprehensively intervene in diseases. In addition, Western medicine inevitably has side effects and drug resistance issues. Therefore, exploring new ideas and methods for preventing and treating cardiovascular diseases has become a focus of international medical attention.

Thanks to the extensive development of modern research in traditional Chinese medicine, advances in scientific technology and research methods, the multi component, multi target, and multi pathway regulation characteristics of traditional Chinese medicine have further demonstrated advantages in the treatment of cardiovascular diseases [5]. The innovative traditional Chinese medicine Tongxinluo (TXL) developed under the guidance of traditional Chinese medicine theory of collateral diseases has good therapeutic effects on various cardiovascular diseases. Research has shown that this medicine has effects such as blood protection, vascular protection, myocardial protection, stable vulnerable plaques, and vasodilation [6–8]. In recent years, research on the treatment of cardiovascular diseases with TXL has gradually increased both domestically and internationally. Therefore, this article reviews the formulation, pharmacological components and mechanisms of action, network pharmacology analysis, and clinical application of TXL based on current research progress both domestically and internationally, in order to provide reference for the prevention and treatment of cardiovascular diseases with TXL.

Fig. 1. The insect and herbal medicines contained in Tongxinluo (TXL) capsules. The TXL prescription consists of twelve insects and herbs: one monarch drug (JUN) - Ginseng Radix et Rhizoma. (Ren-Shen), two ministerial drug (CHEN) - Hirudo (Shui-Zhi), scorpio (Quan-Xie), eight adjuvant drug (ZUO)- Ground beetle (Tu-Bie-Chong), Scolopendra (Wu-Gong), Cicadae Periostracum (Chan-Tui), Paeoniae Radix Rubra (Chi-Shao), Lignum Santali Albi Santalum album L (Tan-Xiang), Lignum Dalbergiae Odoriferae (Jiang-Xiang),and Olibanum (Ru-Xiang), Semen ziziphi spinosae, (Suan-Zao-Ren), conductant drug (SHI) - Borneolum Syntheticum (Bing-Pian). TXL is orally administered as capsules. The picture of this patent medicine has been permitted to be presented in the manuscript by YILIG PHARMACEUTICAL, INC.

2. The composition principle and main active ingredients of Tongxinluo capsules

2.1. Principles of TXL composition

Regarding the same pathological characteristics of cardiovascular diseases: phlegm, blood stasis, weakness, toxicity, guided by the theory of meridians, the treatment principle of "tonifying qi and promoting blood circulation, searching wind and unblocking collaterals" was proposed. And the treatment method of "tonifying qi and warming yang, promoting blood circulation and dispersing stasis, unblocking collaterals and relieving pain" was determined. On this basis, an innovative traditional Chinese medicine called Tongxinluo Capsule was developed, which is composed of 12 types of insect herbs (Fig. 1). Ginseng in the formula is a medicinal herb for monarchs, which is good at tonifying vital energy and nourishing the heart to aid blood circulation. Leeches are good at promoting blood circulation and meridians, dispelling stasis and removing blood stasis; Scorpion, good at searching for wind and unblocking meridians, Both serve as ministerial medicines. Ground beetle beetle, promoting blood circulation and unblocking collaterals; Centipede, good at unblocking meridians and relieving pain; Cicada molting, good at calming the wind and stopping spasms; Red peony, good at clearing heat and cooling blood, dispersing blood stasis and relieving pain; Sandalwood, Dalbergia, and frankincense are good at promoting blood circulation, promoting qi circulation, and relieving pain; roasted sour jujube kernels are good at nourishing the heart and calming the mind, the above eight medicines are all adjuvants. borneol is conductant drug, Skilled in opening the orifices, relieving pain, awakening the mind and transforming turbidity, and introducing various medicines into the heart meridian. The combination of various medicines plays a role in tonifying qi, warming yang, promoting blood circulation, dispersing blood stasis, and unblocking collaterals to relieve pain.

2.2. The main active ingredients of a single drug in TXL

TXL is composed of 12 insect herbs, including ginseng, leech, scorpion, ground beetle worm, centipede, cicada slough, red peony, sandalwood, dalbergia odorifera, frankincense, fried sour jujube kernel, and borneol. However, each single medicine contains multiple active ingredients.

The main active ingredients of Chinese herbal ginseng include ginsenosides, panaxadiol, panaxatriols, polyacetylenes, sesquiterpenes, fatty acids, phenolic acids, sterols, ginseng oligosaccharides, ginseng polysaccharides, etc. These are considered to be the main pharmacological active ingredients in ginseng. Numerous experimental studies and clinical observations have demonstrated that among ginsenosides, total ginsenoside (TSPG), ginsenoside Rb1, ginsenoside Rd, ginsenoside Rg1, ginsenoside Rg3, ginsenoside Re, ginsenoside Rb3, ginsenoside Rp1, ginsenoside Rp3, and ginsenoside Rc have a positive effect on the prevention and treatment of cardiovascular diseases by antioxidation, controlling vasoconstriction function, regulating ion channels and signal transduction, improving lipid status, regulating blood pressure, improving heart function, and reducing platelet adhesion [9–27]. In addition, ginseng phenolic acids, ginseng polysaccharides, and ginsenosides also play beneficial roles in the prevention and treatment of cardiovascular diseases [28–30].

Chinese medicine leech, its main active ingredients include hirudin, hirudin synthetic peptide, hirudin active peptide, hirudin anticoagulant peptide, hirudin protein, hirudinase extract, etc. Numerous in vivo and in vitro experiments have shown that it has positive effects on the prevention and treatment of cardiovascular diseases through anticoagulation, antiplatelet aggregation, antithrombotic activity, inhibition of inflammation, improvement of lipid status, regulation of blood pressure, improvement of heart function, and reduction of platelet adhesion [31–56].

The main active ingredients of traditional Chinese medicine scorpion include scorpion toxin peptides, scorpion degradation peptides, and peptides derived from scorpion venom. Experiments have shown that it has a positive effect on the prevention and treatment of cardiovascular diseases by inhibiting inflammation, improving oxidative stress in the body, anticoagulating, antithrombotic, analgesic, immune regulation, regulating vasoconstriction, regulating blood pressure, and increasing myocardial cell metabolism [57–60].

The main active ingredient of the traditional Chinese medicine ground beetle beetle is the active peptide of ground beetle beetle, which can prevent and treat cardiovascular and cerebrovascular diseases by anti thrombosis, improving blood viscosity, reducing blood lipids, etc [61–63].

The main active ingredients of Chinese medicine centipede include fungal Aspergillus, centipede toxin, centipede toxin like peptide, and centipede acidic protein extracted from the intestine of centipede. Experiments have proved that these active ingredients have positive effects on the prevention and treatment of cardiovascular diseases by protecting myocardial cells, improving oxidative stress reaction in the body, regulating blood pressure, reducing total cholesterol, triglycerides, low-density lipoprotein, increasing plasma high-density lipoprotein, improving abnormal bleeding, anti atherosclerosis and other effects [60,64–66].

The main active ingredients of traditional Chinese medicine cicada molt include cicada molt extract oleic acid (OA), palmitic acid and linoleic acid, cicada molt peptide, cicada molt chitin, cicada molt chitosan, N-acetyldopamine polymer, etc. [67–69]. Experiments have shown that its active ingredients have anti-inflammatory, immune response regulating, anti thrombotic, and anticoagulant effects [70].

The main active ingredients of the traditional Chinese medicine red peony include paeoniflorin, total glucoside of peony, total glucoside of red peony, paeoniflorin, gallic acid, etc. Its active ingredients have the functions of relieving venous plaques, reducing stress reactions, lowering serum lipid concentration, regulating immunity, inhibiting inflammation, analgesia, anticoagulation, anti myocardial remodeling, antiviral infection, reducing total cholesterol, anti platelet aggregation, and protecting the heart [71–78].

The main active ingredients of traditional Chinese medicine sandalwood include sandalwood oil, sandalwood alcohol, and

sandalwood ene. Research has found that its active ingredients have functions such as antibacterial, anti-inflammatory, hypoglycemic, lipid-lowering, antioxidant stress, and protection of myocardial cells [60,64–66,79].

The main active ingredients of traditional Chinese medicine for reducing fragrance include perilla alcohol, mangiferin, volatile oil, flavonoids, and n-butanol. Research has found that its active ingredients have effects such as regulating inflammatory response, promoting angiogenesis, inhibiting oxidative stress, promoting energy metabolism, relaxing blood vessels, increasing coronary artery flow, regulating blood lipids, lowering blood pressure, anticoagulation, antithrombotic, and anti myocardial ischemia [80–82].

The main active ingredients of traditional Chinese medicine frankincense include terpenes, frankincense acid, volatile oil, etc. [83], Studies have found that these active ingredients have effects such as promoting blood circulation, anticoagulation, and anti-inflammatory effects [84–90]. The main terpenoid active ingredients in frankincense for treating coronary heart disease are AKBA β- BA and KBA [91], the volatile oil of frankincense improves myocardial hypertrophy and protects the heart by acting on heart related targets such as ESR1, MAPK14, MAPK1, CNR1, CXCL8, etc. [92].

The main active ingredients of stir fried sour jujube kernel in traditional Chinese medicine include sour jujube kernel saponin A, sour jujube kernel saponin B, spironol, 6′′- ferulic acid spironol, etc. Research has found that these active ingredients mainly pass through PPAR, AMPK, ErbB, TGF- β、 5 signal pathways such as mTOR play a therapeutic role in coronary heart disease with diabetes [93]. Suanzaoren saponin A is a calcium channel blocker that can affect L-type Ca2+ion channels in ventricular myocytes, achieving the effect of inhibiting rapid arrhythmia [94,95].

The main active ingredients of traditional Chinese medicine borneol include borneol, isoproterenol, etc. A large number of studies have found that its active ingredients have anti-inflammatory, antioxidant, anti apoptotic, anticoagulant activity, improving energy metabolism, relaxing blood vessels, regulating blood pressure, improving intracellular lipid accumulation, sedation and pain relief, protecting myocardial tissue, and alleviating autophagy and apoptosis of myocardial cells [96–102].

3. The mechanism of Tongxinluo in preventing and treating cardiovascular diseases

At present, the drug treatment methods for cardiovascular diseases mainly involve anti platelet aggregation, anticoagulation, lipid-lowering, vasodilation, anti hypertension, and improvement of heart function [103,104]. According to the literature on the treatment of cardiovascular diseases with TXL, its mechanism of action (Fig. 2) mainly includes five aspects: blood protection, vascular protection, myocardial protection, stable vulnerable plaques, and vasodilation [105–107]. Due to the fact that cardiovascular disease is a multifactorial disease, its underlying mechanisms are not yet fully understood. Therefore, this article provides a comprehensive and

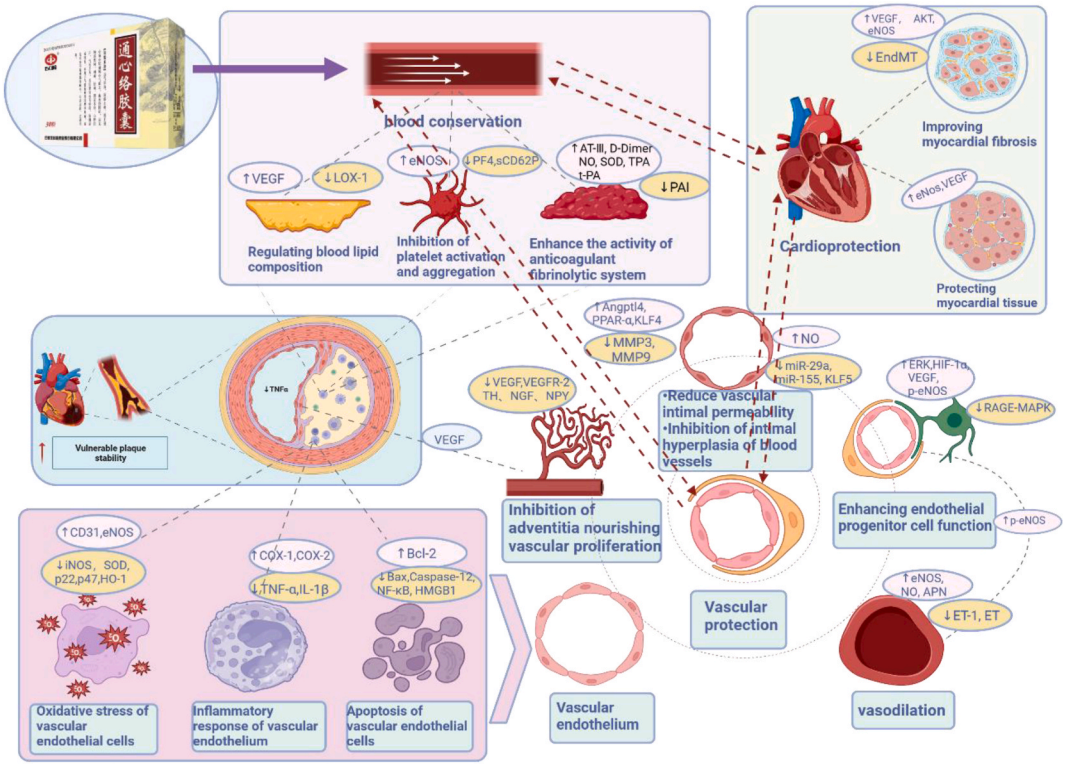

Fig. 2. Based on the above mechanism, we have drawn a mechanism diagram of TXL's action. In the above figure, → represents the action of TXL on the human body, ⇢ represents the interaction between blood, blood vessels, and heart, and ····· represents the interaction between various mechanisms.

detailed review of the mechanism of TXL in treating cardiovascular diseases from five aspects: blood protection, vascular protection, myocardial protection, stable vulnerable plaques, and vasodilation, which is of great significance.

3.1. The mechanism of TXL protecting myocardium

The mechanism of TXL in protecting myocardium mainly involves two aspects(Table 1): protecting myocardial tissue and improving myocardial fibrosis.

Table 1
The mechanism of TXL protecting myocardium.

#	Models	Involved mechanisms	Signaling pathway	Pharmacological effects	Ref
1	HCMECs: a model of cardiovascular disease in diabetes	↑:H3K9ac, claudins-5, claudin-11		Protecting myocardial tissue	[108]
2	C57BL/6J wild-type and ApoE −/− mice: a damaged heart model with hypercholesterolemia	↑: VEGF	–	Protecting myocardial tissue	[109]
3	Small pigs: ischemic heart disease model	↓Cell apoptosis and oxidative stress		Protecting myocardial tissue	[110]
4	Mini pigs: myocardial ischemia/ reperfusion injury model	↑: eNOS, cadherin		Increase local myocardial blood flow, limit myocardial infarction and no reflux size	[111]
5	Miniature pigs: models of myocardial non reflux and ischemia-reperfusion injury	↑: eNOS cadherin	↑: PKA	Reduce myocardial reflux and ischemia-reperfusion injury	[112]
6	Male SD rats: myocardial ischemia/ reperfusion (I/R) injury model	↑: Parkin mediated mitochondrial autophagy ↓: Ubiquitin proteasome	↑: PINK1/Parkin	Protecting myocardial tissue	[113]
7	Human cardiomyocytes (HCMs): ischemia/reperfusion (I/R) injury model	↑: p70s6k1, ↓: miR-128-3p	miR-128-3p/ p70s6k1	Protective effect on H/R phase HCM cell apoptosis	[114]
8	HCMEC: Ischemia/reperfusion (I/R) injury model	↑: autophagy	↑: MEK/ERK	Protecting myocardial microvascular endothelial cells (CMEC) from I/R injury	[115]
9	Mini pigs: myocardial ischemia/ reperfusion (I/R) injury model	↑: INOS activity, eNOS, VE cadherin β-Chain proteins and γ- Chain protein		Promoting endothelial barrier function of cardiac microvasculature and improving myocardial IRI	[116]
10	HCMEC: Myocardial Hypoxia Model	↑: H3K9ac ↓: claudin-9		Reduce myocardial cell damage	[117]
11	CMEC: I/R Damage Model	↑: Acyl CoA Synthase ACSM2B、CDKN1B HMOX1、SOX17、SQSTM1、TBC1D10B		Protecting CMEC from ischemia-reperfusion injury	[118]
12	CMEC and CM: I/R damage model	↑: CMEC eNOS	↑: eNOS pathway	Improve the survival rate of CMEC and CM itself	[119]
13	Wild type male C57BL/6 mice: MI model	↑: Akt phosphorylation, ERK phosphorylation, HIF-1 α, VEGF, *p*-eNOS	–	Has a protective effect on myocardial fibrosis	[120]
14	Male SD rats: acute myocardial infarction (AMI) model	↑: LC3 ↓: Bax	↑: AMPK/mTOR phosphorylation	Protective effect on myocardial infarction	[121]
15	Male SD rats: acute myocardial infarction (AMI) model	↑: CXCR4	–	Promote heart repair	[122]
16	Male SD rats: dilated cardiomyopathy (DCM) model	–	–	Improving cardiac function in rats with dilated cardiomyopathy	[123]
17	Wild type male C57BL/6 mice: an animal model of ischemic heart disease	↑: Myocardial capillary density, nitrite, VEGF, *p*-VEGFR2, p-PI3K, *p*-Akt, *p*-eNOS, HO-1, ↓: Oxidative stress injury, Nox4	VEGF/Akt/eNOS	Protective effect on heart failure caused by pressure overload in mice	[124]
18	ZDF diabetes rats: I/R injury model	↑: Angptl4	PPAR-α pathway	Protect diabetes heart from I/R damage	[125]
19	Miniature pigs: I/R injury model	↑: Angptl4	↑: PPAR-α/Angptl4	Protecting the endothelial barrier	[126]
20	Male SD rats: Myocardial fibrosis model (MF) after acute myocardial infarction (AMI)	↓: EndMT, factor-1a,transcription factor snail, ↑:NRG-1, ErbB2, ErbB4, AKT	↑NRG-1/ErbB-PI3K/AKT -	MF after weakening AMI	[127]
21	C57BL/6J mice: MIRI model	↓: EndMT	↑: PI3K/AKT	Reduce myocardial fibrosis	[128]
22	Male SD rats: myocardial fibrosis model of diabetes rats	↑: TGF-β, Smad3, Smad7		Reduce myocardial fibrosis in diabetes rats	[129]
23	Male SD rats: acute myocardial infarction (AMI) model	↑: LC3 ↓: Bax	↑: AMPK/mTOR phosphorylation	Reduced myocardial fibrosis	[121]
24	C57BL/6J mice: heart failure model	↑: VEGF, eNOS	VEGF/Akt/eNOS	Improving myocardial fibrosis in heart failure	[130]

3.1.1. The mechanism of TXL protecting myocardial tissue

Myocardial tissue injury refers to a condition in which myocardial cells are damaged due to various reasons, resulting in abnormal structure and function of myocardial cells, and even leading to heart disease. The main factors causing myocardial tissue damage are ① ischemia/reperfusion injury: ischemia/reperfusion injury, coronary heart disease, myocardial infarction (MI), myocardial hypertrophy, cardiomyopathy, heart failure [131–134]; ② Inflammatory injury: myocarditis, endocarditis, rheumatic heart disease [135–138]; ③ Toxic and drug-induced damage: drug-induced myocardial injury, septic cardiomyopathy [139,140]; ④ Other factors damage: myocardial damage caused by diabetes cardiomyopathy (DCM), hypertension, high cholesterol, obesity, etc [108,141–143]. A large number of experimental studies and clinical observations have proved that TXL protects myocardial tissue by protecting myocardial ischemia-reperfusion injury (MIRI), protecting myocardial microvascular endothelial cells (CMEC), protecting vascular endothelial function, improving myocardial infarction, improving heart failure, improving diabetes cardiovascular disease, and alleviating myocarditis [109,144].

Despite significant progress in cardiovascular treatment in previous studies, the treatment of ischemic heart disease remains an important challenge. Therefore, Qian, H. Y. et al. [110] investigated whether transplantation of mesenchymal stem cells (MSCs) after TXL treatment can improve the survival rate and subsequent activity of transplanted pig heart cells in acute myocardial infarction (AMI) and reperfusion. The research results show that TXL has significant survival and differentiation potential for implanted cells in vivo by inhibiting cell apoptosis and oxidative stress, thereby protecting myocardial tissue and having significant benefits for cardiac function. In order to further explore the mechanism of TXL in protecting against myocardial ischemia/reperfusion injury, Cheng, Y. T. et al. [111] found that TXL can significantly increase local blood flow, limit infarct area and non reperfusion area, and its mechanism may be to regulate nitric oxide synthesis by altering the activity of endothelial nitric oxide synthase. Similarly, Li, X. D. et al. [112] found that TXL can reduce myocardial ischemia/ischemia-reperfusion injury by stimulating eNOS phosphorylation through the PKA pathway, which is related to the inhibition of inflammation, edema, and cell apoptosis in both refluxed and non refluxed myocardium. In a study exploring the protective effects and mechanisms of TXL on Parkin mediated mitochondrial autophagy and ubiquitin proteasome system in a rat myocardial ischemia-reperfusion injury (MIRI) model, Yang, H. X. et al. [113] found that TXL improves MIRI by activating Parkin mediated mitochondrial autophagy and downregulating the ubiquitin proteasome system, thereby exerting a protective effect on myocardial tissue. Previous studies have shown that activation of the reperfusion injury rescue kinase (RISK) pathway can protect the heart from ischemia/reperfusion (I/R) injury, typically activated through Akt or (and) Erk1/2 and its common downstream protein ribosomal protein S6 kinase (p70s6k). In addition, TXL treatment promoted the secretion of VEGF in cells, which may be stimulated by an increase in phosphorylation of a subtype of p70s6k, p70s6k1. Therefore, Chen, G. H. et al. [114] proposed a hypothesis that TXL can protect human cardiomyocytes (HCMs) from I/R injury by activating p70s6k1. Subsequently, their team found that the miR-128-3p/p70s6k1 signaling pathway is involved in the protection of TXL against apoptosis of HCM cells during H/R.

Compared with myocardial cells, the damage of myocardial microvascular endothelial cells (CMEC) in ischemia/reperfusion (I/R) has not been fully studied. TXL is a traditional Chinese medicine with vascular protective effects. Therefore, in order to investigate the role and regulatory mechanism of autophagy in myocardial microvascular endothelial cells (CMEC) damaged by ischemia/reperfusion (I/R), Cui, H. et al. [115] exposed CMEC to different concentrations of TXL for 30 min and subjected to hypoxia/reoxygenation for 2 h. The results indicate that autophagy is a protective mechanism against I/R injury in CMEC, and TXL can promote autophagy by activating the pro mitogen activated protein kinase/ERK pathway. Previous studies have demonstrated that TXL can protect against microvascular endothelial cell (CMEC) damage caused by myocardial ischemia/reperfusion (I/R). Therefore, Qi, K. et al. [116] further explored the protective mechanism and key targets of cardiac microvascular barrier function mediated by the heart meridian against myocardial ischemia/reperfusion injury. The research results showed that TXL significantly upregulated eNOS activity, eNOS, VE cadherin β- Catenin and γ- The expression of catenin, these 5 microvascular barrier related indicators, may be key targets for TXL to reduce ischemia-reperfusion (I/R) injury (IRI). Therefore, TXL pretreatment improves myocardial IRI by simulating ischemic preconditioning (IPC) to promote microvascular endothelial barrier function in the heart. Research has found that Claudin-5, Claudin-9, and Claudin-11 are expressed in endothelial cells, forming tight junctions. Their lack may lead to high permeability, which is the initiating process and pathological basis of cardiovascular disease. Therefore, in order to investigate whether and how TXL regulates claudin-5, claudin-9, and claudin-11 in human cardiac microvascular endothelial cells (HCMEC) stimulated by hypoxia, Liu, K. et al. [117] used CoCl2 to simulate hypoxia induced HCMEC and treated it with TXL. The research results show that TXL exerts a protective effect on HCMEC by increasing its gene promoter H3K9ac, reversing the hypoxia inhibited claudin-9, thereby protecting myocardial tissue from damage caused by hypoxia stimulation. Due to the limited attention paid to the protective effect of endothelial cells against reperfusion injury. Therefore, Li, Q. et al. [118] used tandem mass spectrometry (TMT) proteomics to investigate the regulatory proteins in an in vitro model of ischemia/reperfusion (I/R) injury in cardiac microvascular endothelial cells (CMEC) and the effects of the traditional Chinese medicine TXL on them. This study provides differential proteins through proteomic analysis. The research results show that TXL regulates the expression of proteins in CMEC and has a protective effect in the response to I/R. Previous studies have shown that TXL can reduce myocardial ischemia-reperfusion injury, protect capillary endothelial function, and reduce ventricular remodeling in animal models. Yuan, G. Q. et al. [109] further investigated whether TXL can improve impaired cardiac function in hypercholesterolemia by protecting arterial endothelial function and increasing cardiac microvascular density (MVD). The research results show that TXL can significantly improve the cardiac function of ApoE −/− mice, and its action ways are: reducing blood lipids and atherosclerosis; Enhance the impulsivity, blood supply capacity, and vascular elasticity of the aorta; Improving endothelial dependent vasodilation; Inhibition of angiogenesis containing aortic plaques; Improve cardiac MVD. The molecular mechanism of MVD enhancement may be related to the increased expression of VEGF.

The crosstalk between myocardial cells (CM) and cardiac microvascular endothelial cells (CMEC) has become a key component in the development and prevention of heart diseases. However, little is known about the signals generated by CMs that can regulate the

biology of CMEC. Therefore, Chen, G. et al. [119] revealed a mechanism of alleviating myocardial ischemia/reperfusion (I/R) injury by activating CMEC eNOS using TXL. The research results show that the crosstalk between CMs and CMEC activates eNOS, leading to an increased cardiac survival rate after I/R injury, and pointing out new therapeutic targets for TXL to slow down myocardial I/R injury.

Myocardial infarction (MI) is the main cause of incidence rate and mortality in the world. TXL is a traditional Chinese medicine compound with cardioprotective effects. Bai, W. W. et al. [120] investigated the effects of TXL on post MI cardiac dysfunction and remodeling. It used ligation of the left anterior descending coronary artery (LAD) in male adult mice to create an MI model. This research result shows that TXL can enhance the phosphorylation of Akt and ERK, HIF-1 α The expression and activity of VEGF and *p*-eNOS, as well as the protein levels of VEGF and *p*-eNOS, increase the formation of new blood vessels, thereby improving cardiac function and remodeling after myocardial infarction. In an experiment to observe the therapeutic effect of TXL on a rat model of acute myocardial infarction (AMI), in order to investigate whether TXL activates autophagy and reduces cardiomyocyte apoptosis through the AMPK pathway, promotes cardiomyocyte survival and improves cardiac function, Li, Q. et al. [121] found that TXL's cardioprotective effect on myocardial infarction is related to inhibiting cardiomyocyte apoptosis and promoting autophagy in rats after acute myocardial infarction, this effect may be related to the phosphorylation of AMPK/mTOR, upregulation of autophagy protein LC3 expression, and downregulation of apoptotic protein Bax expression. Research has shown that bone marrow mesenchymal stem cells have immunomodulatory properties and are candidate cells for the treatment of acute myocardial infarction (AMI). However, the low retention and survival rates of mesenchymal stem cells in ischemic hearts limit their therapeutic efficacy. Therefore, Xiong, Y. et al. [122] explored the efficacy of sequential transplantation of extracellular vesicles and combined pre-treatment of bone marrow mesenchymal stem cells in the treatment of AMI. The research results show that sequential administration of extracellular vesicles and pretreated bone marrow mesenchymal stem cells is beneficial for cardiac repair after AMI, and the combination of hypoxia and TXL pretreatment can better enhance cardiac protection.

To verify the hypothesis that TXL may exert its cardioprotective effect by preventing ventricular remodeling and improving coronary microvascular function in a rat model of doxorubicin induced dilated cardiomyopathy (DCM), Shen, F. et al. [123] administered TXL by gavage to DCM induced surviving rats for four weeks. The research results showed that the high-dose TXL group significantly improved myocardial functional parameters, increased microvascular density (MVD), and prevented left ventricular remodeling. Therefore, the results of this experiment suggest that high-dose TXL has a significant improvement effect on the cardiac function of DCM rats.

To investigate whether TXL has a protective effect on pressure overload induced heart failure in mice, Wang, B. et al. [124] used a mouse aortic constriction induced heart failure model. The research results indicate that TXL has a protective effect on pressure overload induced heart failure in mice, and its mechanism may be related to the activation of the VEGF/Akt/eNOS signaling pathway.

TXL has been widely used in the treatment of coronary heart disease in China, because it can reduce the myocardial infarction area and ischemia/reperfusion injury in non diabetes and diabetes patients. Claudins-5, -9, and -11 are tight junction proteins primarily expressed in endothelial cells. Their deficiency may lead to dysfunction of cell barrier, which is considered as the initial process and pathological basis of cardiovascular disease in diabetes. Therefore, Li, B. et al. [108] investigated whether high glucose (HG) affects claudins-5, -9, and -11 in human cardiac microvascular endothelial cells (HCMECs), and examined the effect of TXL on these tight junction proteins. Their team exposed HCMECs to HG with and without TXL, and then detected the mRNA and protein levels of claudins-5, -9, and -11. The results indicate that HG inhibits claudins-5 and -11 in HCMEC, and TXL can reverse the HG induced inhibition of claudins-5- and −11 by increasing H3K9ac in their respective gene promoters. It has been shown that TXL has a protective effect on myocardial ischemia/reperfusion (I/R) injury and endothelial barrier function, and TXL can induce human cardiac microvascular endothelial cells to secrete angiopoietin-like 4 (Angptl4) during hypoxia/reoxygenation. Therefore, in order to prove whether TXL can alleviate the myocardial I/R injury in diabetes patients characterized by microvascular endothelial barrier destruction by inducing Angptl4 mediated endothelial barrier integrity protection, Qi, K. et al. [125] used the ZDF diabetes and non diabetes control rats' coronary artery ligation to cause I/R injury model. The research results show that TXL passes PPAR- α The pathway activates Angptl4-mediated endothelial barrier integrity recovery, thus protecting the heart from I/R injury in diabetes. Research shows that TXL can regulate peroxisome proliferator activated receptor in diabetes rats- α (PPAR)- α), It is a positive regulator of angiopoietin like 4 (Angptl4). Therefore, Qi, K. et al. [126] proposed that cellular intrinsic and endothelial specific Angptl4 can be expressed through PPAR- α The pathway mediates the protection of TXL against endothelial barrier under high glucose conditions to counter the hypothesis of ischemia/reperfusion injury. The research results indicate that the innate and endothelial specific Angptl4 components of cells are mediated through PPAR- α/Angptl4 pathway mediates the protective effect of TXL against endothelial barrier damage during hypoxia and recovery under high glucose conditions.

The above research shows that TXL can reduce myocardial ischemia reperfusion injury (MIRI), protect myocardial microvascular endothelial cells (CMEC), protect vascular endothelial function, improve myocardial infarction, improve heart failure, improve diabetes cardiovascular disease, reduce myocardial inflammation, and play a role in protecting myocardial tissue.

3.1.2. The mechanism of TXL in improving myocardial fibrosis

Myocardial fibrosis (MF) is mainly divided into alternative fibrosis and reactive fibrosis. Alternative fibrosis often occurs after myocardial infarction, caused by damage and death of myocardial cells, forming focal fibrotic scars in necrotic myocardium. Reactive fibrosis is often present in non ischemic cardiomyopathy, surviving myocardium after myocardial infarction, valvular heart disease, and normally aging hearts. Its fibrous tissue diffusely deposits around the interstitium and blood vessels, also known as diffuse myocardial fibrosis [145].

Endothelial mesenchymal transition (EndMT) is an important mechanism of myocardial fibrosis (MF). TXL has a protective effect on endothelial cell reperfusion injury after acute myocardial infarction (AMI). However, it is still unclear whether TXL can inhibit MF

Table 2
The mechanism of Tongxinluo in protecting blood vessels.

#	Models	Involved mechanisms	Signaling pathway	Pharmacological effects	Ref
1	A model of human heart microvascular endothelial cell injury	↓:COX-2, iNOS, HIF-2α, VEGF		Protecting human heart microvascular endothelial cells	[146]
2	Human cardiac microvascular endothelial cells (HCMEC); Wild type male C57BL/6 mice: atherosclerotic model	↑: CD31, eNOS ↓: ROS, MDA, p22(phox), p47(phox), HO-1, IL-1β, TNFα	↓: NF-κB	Inhibiting inflammatory response and oxidative stress, protecting endothelial cell function	[147]
3	Human aortic endothelial cells (HAEC): An endothelial cell model of palmitic acid (PA) injury		↑: AMPK	Protecting cardiovascular system	[148]
4	Human umbilical vein endothelial cells: a model of endothelial dysfunction	↓: PPARγ	–	Inhibiting endothelial oxidative stress in blood vessels	[149]
5	A model of human heart microvascular endothelial cell injury	↓:COX-2		Protecting Hx induced HCMEC injury	[146]
6	Male SD rats: a model of vascular endothelial injury caused by Qi deficiency and Qi stagnation	↓: iNOS、SOD		Protecting vascular endothelium	[150]
7	Rabbits: Vulnerable Plaque Model	↓: NF-κB		Inhibiting endothelial inflammatory response and stabilizing vulnerable plaques	[151]
8	Patients undergoing percutaneous coronary intervention (PCI)	↑: hs-CRP ↓: NO		Inhibition of endothelial inflammatory response in blood vessels	[152]
9	Hypertension patients with diabetes	↓:hs-CRP, FIB-C, CD62p、GPIIb/IIIa, ET-1		Inhibition of endothelial inflammatory response in blood vessels	[153]
10	CMEC: I/R Damage Model	↑: Autophagy ↓: Apoptosis of endothelial cells in blood vessels	↑: Protein kinase/ERK pathway activated by mitogen	Inhibiting apoptosis of vascular endothelial cells	[115]
11	Myocardial I/R injury in patients with diabetes	↓: Apoptosis of endothelial cells in blood vessels	-	Inhibiting apoptosis of vascular endothelial cells	[125]
12	Male SD rats: intestinal ischemia/reperfusion injury model	↑:ANGPTL4,VE Cadherin ↓: HMGB1, NF-κB		Inhibiting apoptosis of vascular endothelial cells	[154]
13	ApoE (−/−) mice: AS model	↓: ROS	-	Inhibition of endothelial cell pyroptosis	[155]
14	RCMEC: Hcy induced ERS induced cell apoptosis model	↓: ERS	↓: PI3K/Akt	Inhibiting apoptosis of RCMEC	[156]
15	HAEC: Palmitic acid (PA) induced cell apoptosis model	↓:p38 MAPK	↓:p38 MAPK Stress pathways	Inhibiting apoptosis of vascular endothelial cells	[148]
16	Peripheral blood EPCs in patients with coronary heart disease	↑: EPCs	-	Enhance the number and function of endothelial progenitor cells	[157]
17	AGEs mediated abnormal differentiation model of hEPCs	–	↓: RAGE-MAPK	Improving endothelial differentiation abnormalities in hEPCs	[158]
18	Human peripheral blood EPCs	↑: Nitric oxide synthase mRNA and protein	-	Improving endothelial differentiation abnormalities in hEPCs	[159]
19	Patients with carotid atherosclerosis: EPCs	–	-	Improve the quantity and functionality of EPCs	[160]
20	Endothelial progenitor cells in patients with coronary heart disease	↑: CXCR4	↑: CXCR4 Signal pathway	Increase the number of EPCs	[161]
21	Endothelial progenitor cells in patients with coronary heart disease	–	↑: CXCR4/JAK-2	Improving endothelial progenitor cell function	[162]
22	Endothelial progenitor cells in patients with coronary heart disease	↑: VEGF	-	Improving endothelial progenitor cell function	[163]
23	Male SD rats: A model of arterial intimal hyperplasia after balloon injury	↓: MCP-1, ICAM-1	–	Inhibiting intimal hyperplasia of blood vessels	[164]
24	Male C57BL/6 mice: Carotid artery ligation model	↓: miR-155	miR-155/TNF-α	Inhibiting intimal hyperplasia of blood vessels	[165]
25	C57BL/6 mice: carotid artery induced intimal hyperplasia model	↓: Macrophage infiltration	–	Inhibiting intimal hyperplasia of blood vessels	[166]
26	KLF5ly −/− mice: carotid artery ligation model	↓: KLF5	↓:PI3K/AKT,NF-κB	Inhibiting intimal hyperplasia of blood vessels	[167]
27	Dog: A model of vascular intimal injury after femoral artery angioplasty	↓: C-MYC、C-FOS	-	Inhibiting intimal hyperplasia of blood vessels	[168]
28	Male C57BL/6 mice: left common carotid artery ligation model	↓: miR-155	-	Inhibiting intimal hyperplasia of blood vessels	[169]
29	Rabbit: model of carotid artery injury in the early stage of atherosclerosis	↓: p38 MAPK	↓: p38 MAPK	Inhibition of outer membrane nourishing vascular proliferation	[170]

after AMI by inhibiting EndMT. In order to investigate the role of EndMT in MF after AMI, as well as the protective effect and potential mechanism of TXL on MF, Yin, Y. et al. [127] established a rat AMI model by ligating the anterior descending branch of the left coronary artery. Then, rats were given high-dose, medium dose, and low-dose TXL and Benazepril for 4 weeks. The research results show that TXL weakens MF after AMI by inhibiting EndMT and activating the NRG-1/ErbB-PI3K/AKT signaling cascade. In order to further explore the potential role of TXL in reducing myocardial fibrosis after myocardial ischemia-reperfusion injury (MIRI) in mice, Wei, Y. R. et al. [128] established a MIRI mouse model using left anterior descending coronary artery ligation, with a ligation time of 45 min. On the second day after modeling, TXL and benazepril (BNPL) were administered by gavage for 4 consecutive weeks. The research results show that TXL activates the PI3K/AKT signaling pathway, inhibits EndMT after MIRI in mice, and reduces myocardial fibrosis. In order to explore the effect of TXL on myocardial fibrosis in diabetes rats and its possible mechanism, Wang, X. et al. [129] established a diabetes rat model and divided it into control group, diabetes group and TXL group. The results showed that TXL had significant preventive and therapeutic effects on myocardial fibrosis in diabetes rats. Its mechanism may mediate TGF in rat cardiomyocytes- β 1. The expression of Smad3 and Smad7 can reduce the occurrence of myocardial fibrosis in diabetes rats. In an experiment observing the therapeutic effect of TXL on acute myocardial infarction (AMI), Li, Q. et al. [121] found that TXL treatment significantly reduced myocardial fibrosis in a rat acute myocardial infarction (AMI) model, which was associated with increased AMPK/mTOR phosphorylation, upregulation of autophagy protein LC3 expression in infarcted myocardium, and downregulation of apoptotic protein Bax expression. In an experiment to investigate whether TXL has a protective effect on pressure overload induced heart failure in mice and explore its possible mechanisms of action, Zhou, H. et al. [130] induced heart failure using mouse aortic transverse constriction (TAC) surgery. The results of their study showed that low-dose and high-dose TXL treatment at 12 weeks after TAC surgery improved cardiac systolic and diastolic function, as well as left ventricular hypertrophy, fibrosis, and myocardial ultrastructural disorder. Therefore, TXL has a protective effect on pressure overload induced heart failure in mice. The activation of the VEGF/Akt/eNOS signaling pathway may be involved in the improvement of TXL in heart failure.

The above evidence indicates that TXL can play a multi component, multi-target, and multi pathway role in improving myocardial fibrosis by improving cardiac microcirculation, endothelial mesenchymal transition, myocardial ischemia-reperfusion injury (MIRI), acute myocardial infarction (AMI), anti apoptosis and promoting autophagy, and inhibiting oxidative stress.

3.2. The mechanism of action in protecting blood vessels

The mechanism of the protective effect of TXL on blood vessels is mainly through seven aspects(Table 2): inhibiting oxidative stress of endothelial cells, inhibiting inflammatory response of endothelial cells, inhibiting endothelial cell apoptosis, enhancing endothelial progenitor cell function, reducing vascular intimal permeability, inhibiting vascular intimal proliferation, and inhibiting outer membrane nourishing vascular proliferation.

3.2.1. The mechanism of TXL inhibiting oxidative stress in vascular endothelial cells

Oxidative stress can be defined as an imbalance between the levels of oxidants and antioxidants, which favors the pro oxidative environment in cells and tissues [171,172]。Oxidative stress is caused by an increase in ROS production and the failure of antioxidant mechanisms to neutralize these ROS. Research has shown that endothelial damage caused by oxidative stress plays a crucial role in the occurrence and progression of cardiovascular diseases [149].

Oxidative stress response is considered one of the main driving factors for endothelial dysfunction. Li, Y. N. et al. [146] used CoCl2 to simulate hypoxia (Hx) to treat human cardiac microvascular endothelial cells (HCMECs), and the oxidative marker nitrotyrosine (NT) and inflammatory effector molecule prostaglandin E2 (PGE2) were used to reflect HCMEC damage. The research results show that TXL can inhibit oxidative stress-related iNOS and HIF-2 α/VEGF and the inflammatory factor COX-2, to counteract Hx induced HCMEC damage. Oxidative stress and inflammation are the important pathological basis of atherosclerosis. Reducing oxidative stress and inflammation is of great significance for the prevention and treatment of atherosclerosis. Therefore, Wu, X. L. et al. [147] further explored whether the anti atherosclerosis effect of TXL is related to its antioxidant and anti-inflammatory effects on human cardiac microvascular endothelial cells (HCMEC). The results showed that TXL could reduce the formation of atherosclerotic plaque and improve endothelial cell function by inhibiting oxidative stress and inflammation in HCMEC. This discovery provides a new molecular mechanism for the anti atherosclerotic effect of TXL.

Palmitic acid (PA) is elevated in metabolic syndrome and associated with cardiovascular complications. To investigate the protective effect of TXL on endothelial cells damaged by PA, Zhang, L. et al. [148] pretreated human aortic endothelial cells (HAEC) with TXL extract before 24 h of exposure to PA. Their research suggests that TXL protects endothelial cells from PA induced damage, and its protective mechanism may be mediated by the AMPK pathway to enhance intracellular antioxidant stress capacity.In an experiment to investigate whether TXL has a beneficial effect on endothelial dysfunction induced by homocysteine thiolactone (HTL) and its potential mechanisms, Zhang, Y. et al. [149] treated cultured human umbilical vein endothelial cells with HTL (1 mM) for 24 h, significantly reducing cell viability measured by MTT and enhancing the production of reactive oxygen species. Pretreatment of cells with TXL for 1 h can reverse these effects induced by HTL. The research results show that TXL improves endothelial function in HTL fed rats, which is consistent with PPAR γ Dependent inhibition of endothelial oxidative stress is related.

In order to explore the expression profiles of seven genes related to oxidative stress in vascular endothelial injury of rats with Qi deficiency and Qi stagnation, as well as the effect of TXL on their expression profiles, Wu, Y. L. et al. [150] established models of vascular endothelial injury in rats with Qi deficiency and Qi stagnation using methods such as high L-methionine, weight-bearing swimming, and restraint. The research results show that the expression of 7 genes related to vascular endothelial injury in rats with Qi deficiency and Qi stagnation is inconsistent. TXL can regulate the expression disorder of this gene, protect the vascular

endothelium from damage, and its mechanism may be related to the increased expression of iNOS and SOD genes related to oxidative stress.

The above studies indicate that oxidative stress-induced endothelial damage plays a crucial role in the occurrence and progression of cardiovascular diseases. The mechanisms by which TXL inhibits oxidative stress response in vascular endothelial cells to treat cardiovascular diseases include: TXL inhibits oxidative stress-related factors, enhances intracellular antioxidant stress capacity through the AMPK pathway, and promotes PPAR γ Dependent inhibition of vascular endothelium downregulates oxidative stress response, promotes increased expression of iNOS and SOD genes related to oxidative stress, and fully leverages the advantages of TXL's multi-component, multi target, and multi pathway intervention in the treatment of cardiovascular diseases.

3.2.2. The mechanism of TXL inhibiting endothelial inflammation

Inflammatory reactions exist in both acute and chronic cardiovascular diseases, vascular endothelial cells are the main site of systemic inflammation or local inflammatory response [173]. Numerous studies have shown that inflammation is one of the main driving mechanisms of cardiovascular disease [174,175]. However, the inflammatory response of endothelial cells plays a crucial role in the pathogenesis of cardiovascular diseases. Therefore, reducing the inflammatory response level of endothelial cells is of great significance for the prevention and treatment of various cardiovascular diseases.

Endothelial dysfunction is considered to be the process and pathological basis of cardiovascular disease. Cyclooxygenase-2 (COX-2) and prostacyclin synthase (PGIS), inducible nitric oxide synthase (iNOS), and endothelial NOS (eNOS) are key enzymes that have opposite effects in inflammation and oxidative stress, and are considered the main driving factors for endothelial dysfunction. Due to whether and how TXL regulates COX-2, PGIS, iNOS, eNOS, and HIF-1 in human cardiac microvascular endothelial cells stimulated by hypoxia (Hx) α、 HIF-2 α As VEGF has not yet been elucidated, Li, Y. N. et al. [146] used CoCl2 to simulate Hx treatment of HCMEC, using inflammatory effector molecule prostaglandin E2 (PGE2) and oxidative marker nitrotyrosine (NT) to reflect HCMEC damage. The research results show that TXL can inhibit inflammation related COX-2 factors to counteract Hx induced HCMEC injury.

In order to explore the expression profiles of seven genes related to inflammation in vascular endothelial injury in rats with Qi deficiency and Qi stagnation, as well as the effect of TXL on their expression profiles, Wu, Y. L. et al. [150] established models of vascular endothelial injury in rats with Qi deficiency and Qi stagnation using methods such as high L-methionine, weight-bearing swimming, and restraint. The research results show that the expression of 7 genes related to vascular endothelial injury in rats with Qi deficiency and Qi stagnation is inconsistent. TXL can regulate the expression disorder of this gene, protect the vascular endothelium from damage, and its mechanism may be related to the increased expression of inflammation related COX-1 and COX-2 genes. Zhang, L. et al. [151] proposed the hypothesis that TXL enhances the stability of vulnerable plaques in a dose-dependent manner through lipid-lowering and anti-inflammatory effects. To verify this hypothesis, their team treated rabbit abdominal aortic balloon injury with low, medium, and high doses of TXL for 8 weeks. At the end of week 16, adenovirus containing p53 was injected into the abdominal aortic plaque. Two weeks later, medication triggered plaque rupture. The research results show that TXL dose-dependent reduces serum lipid levels and inhibits systemic inflammation. Therefore, we can speculate that TXL also inhibits the inflammatory response of vascular endothelium, thereby enhancing the stability of vulnerable plaques and preventing plaque rupture.

In a clinical study observing the effects of TXL on endothelial function and high-sensitivity C-reactive protein (hs CRP) in patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI), Ma, Q. et al. [152] treated 33 patients with unstable angina and 6 patients with acute myocardial infarction with PCI. The patients were randomly divided into a conventional group and a TXL group. The former received conventional treatment, while the latter received TXL on the basis of conventional treatment after PCI for 3 months. The research results show that TXL Capsule directly acts on the endothelial cells of PCI patients with acute coronary syndrome, indirectly inhibits inflammatory response, and has significant beneficial effects on the endothelial function and anti-inflammatory properties of patients. In a clinical observation to explore the effect of TXL on platelet activating factor, vascular inflammatory factor and vascular endothelial function in patients with essential hypertension (EH) and diabetes (DM), Zhang, C. Q. et al. [153] randomly divided 100 EH patients with DM into TXL group and control group for 8 weeks. The research results show that TXL can inhibit platelet activation and vascular inflammatory response in EH patients with DM, improve endothelial function, and have a certain effect on preventing and treating thrombotic complications.

Inflammation is one of the important pathological bases of atherosclerosis, and reducing inflammatory reaction is of great significance for the prevention and treatment of atherosclerosis. Therefore, in order to explore whether the anti atherosclerotic effect of TXL is related to its anti-inflammatory effect on human cardiac microvascular endothelial cells (HCMECs), Wu, X. L. et al. [147] showed that TXL can reduce the formation of atherosclerotic plaque and improve the function of endothelial cells by inhibiting the inflammatory reaction in HCMECs. This discovery provides a new molecular mechanism for the anti atherosclerotic effect of TXL.

The above studies indicate that endothelial damage caused by inflammation plays a crucial role in the occurrence and progression of cardiovascular diseases. The mechanism of TXL in treating cardiovascular diseases by inhibiting the inflammatory response of endothelial cells includes inhibiting inflammation related COX-2 factors, promoting inflammation related COX-1 and COX-2 gene expression, inhibiting endothelial inflammatory factors, improving endothelial function, etc., thus fully leveraging the advantages of TXL's multi-component, multi-target, and multi pathway intervention in the treatment of cardiovascular diseases.

3.2.3. The mechanism of TXL inhibiting apoptosis of vascular endothelial cells

Apoptosis is type I programmed cell death, which is one of the core mechanisms of cardiovascular and cerebrovascular injury [176]. Increased apoptosis of endothelial cells is one of the main characteristics of endothelial dysfunction, which can promote smooth muscle cell proliferation and migration, increase leukocyte infiltration into the endothelium, lead to endothelial dysfunction, and cause cardiovascular and cerebrovascular diseases [177].

Compared with myocardial cells, the apoptosis of myocardial microvascular endothelial cells (CMEC) during ischemia/reperfusion (I/R) injury has not been fully studied. TXL is a traditional Chinese medicine with vascular protective effects. In a study exploring the role and regulatory mechanism of TXL in autophagy in CMEC with I/R injury, Cui, H. et al. [115] found that TXL can promote autophagy and reduce apoptosis in CMEC by activating the pro mitogen activated protein kinase/ERK pathway, thereby exerting a cardioprotective effect. In another experiment to explore whether TXL can alleviate myocardial I/R injury in diabetes patients characterized by microvascular endothelial barrier destruction by inducing the integrity of Angptl4 mediated endothelial barrier, Qi, K. et al. [125] showed that in diabetes hearts with I/R injury, TXL treatment significantly reduced the infarct area, and protected the integrity of vascular endothelial barrier by reducing vascular endothelial cell apoptosis, microvascular permeability, etc., thus protecting diabetes hearts from I/R injury. Therefore, this experiment proves that TXL plays a role in protecting diabetes heart from I/R injury by reducing the apoptosis of vascular endothelial cells. In order to investigate the preventive effect of TXL on microvascular function and endothelial cell survival in a rat intestinal I/R injury model, Zhang, J. X. et al. [154] used an acute superior mesenteric artery occlusion model pre treated with TXL for intestinal ischemia-reperfusion (I/R) injury in rats. The research results show that TXL pretreatment can significantly prevent I/R induced apoptosis of endothelial cells, microvascular integrity damage, and inflammatory response.

TXL plays an important role in the treatment of atherosclerosis (AS). Endothelial cell (EC) pyroptosis plays a crucial role in the development of atherosclerosis. Previous studies have revealed the inhibitory effects of TXL on EC apoptosis and autophagy. However, whether TXL can inhibit the pyroptosis of endothelial cells has not been determined. Therefore, in order to investigate the effect of TXL on EC pyroptosis and determine its potential mechanism of action in AS, Jiang, X. et al. [155] established a disease model of AS using ApoE (−/−) mice and treated it with TXL. The research results show that TXL has an inhibitory effect on EC pyroptosis in AS, and reducing the accumulation of ROS may be an important mechanism by which TXL inhibits AS.

In an experiment exploring the protective effect of TXL on apoptosis of rat cardiac microvascular endothelial cells (RCMECs) induced by homocysteine (Hcy) - induced endoplasmic reticulum stress (ERS), Wei, G. et al. [156] found that TXL can inhibit apoptosis of RCMECs induced by Hcy induced ERS, and its mechanism may be related to the activation of the PI3K/Akt signaling pathway. Therefore, this experimental result demonstrates that TXL can exert a therapeutic effect on cardiovascular diseases by inhibiting RCMEC apoptosis. The risk factor palmitic acid (PA) is elevated in metabolic syndrome and associated with cardiovascular complications. To investigate the protective effect of TXL extract on endothelial cells damaged by PA, Zhang, L. et al. [148] used TXL extract to pretreat human aortic endothelial cells (HAEC) before 24 h of exposure to PA. The research results found that PA exposure induced 73 % apoptosis of endothelial cells. However, when ethanol extracted TXL was used to pretreat HAEC, PA only induced 7 % of endothelial cell apoptosis. Therefore, we can speculate that TXL can exert a therapeutic effect on cardiovascular diseases by inhibiting endothelial cell apoptosis, and its mechanism may be related to TXL weakening the activation of PA induced p38 MAPK stress pathway.

The above studies indicate that endothelial cell apoptosis is one of the core mechanisms underlying the occurrence and development of cardiovascular diseases. The mechanism of TXL in treating cardiovascular diseases by inhibiting endothelial cell apoptosis includes activating the pro mitogen activated protein kinase/ERK pathway, protecting the integrity of the endothelial barrier, preventing I/R induced endothelial cell apoptosis, reducing ROS accumulation, and inhibiting Hcy induced ERS induced RCMEC apoptosis. This fully leverages the advantages of TXL's multi-component, multi target, and multi pathway intervention in the treatment of cardiovascular diseases.

3.2.4. The mechanism of TXL enhancing the number and function of endothelial progenitor cells

Endothelial progenitor cells (EPCs) are precursors of endothelial cells, playing an important role in angiogenesis and maintaining the integrity of endothelial function. The differentiation of vascular EPCs into mature endothelial cells is involved in repairing damaged endothelium. Evidence has shown that the downregulation of the quantity and function of EPCs is believed to be closely related to the occurrence of various cardiovascular diseases [178–181].

The reduction and dysfunction of endothelial progenitor cells are considered predictive factors for future cardiovascular events. Therefore, Zong, X.M. et al. [157] investigated the effect of TXL on the adhesion and proliferation function of human peripheral blood EPCs cultured in vitro. The research results show that TXL can significantly improve the adhesion and proliferation ability of peripheral blood EPCs in a certain dose-response and time-dependent relationship, which may be a new mechanism for the prevention and treatment of cardiovascular and cerebrovascular diseases through TXL. In an experiment to investigate the effect of TXL on the induction of endothelial differentiation of human endothelial progenitor cells (hEPCs) by advanced glycation end products (AGEs) and its molecular mechanism, Wu, S.P. et al. [158] cultured hEPCs from healthy human peripheral blood in vitro and administered AGEs and/or different concentrations of TXL stimulation. The research results show that TXL intervention can significantly improve AGEs mediated endothelial differentiation abnormalities in hEPCs by downregulating the RAGE-MAPK signaling pathway, which may be the role of TXL in protecting blood vessels and treating cardiovascular diseases.

Previous studies have found that TXL can promote NO synthesis and improve endothelial diastolic function. In order to further study the effect of TXL on the number and function of EPCs and the expression of endothelial nitric oxide synthase in EPCs, and further clarify and improve the mechanism of TXL in anti atherosclerosis and protecting vascular endothelial function. The research results of Liang, X.W. et al. [159] showed that TXL can significantly increase the number of human peripheral blood EPCs, improve their proliferation, migration, and adhesion abilities, and increase the expression of endothelial nitric oxide synthase mRNA and protein in EPCs. Therefore, TXL can treat ischemic cardiovascular disease by improving the number and function of EPCs. In order to further investigate the effect of TXL on the proliferation, migration, and adhesion of human peripheral blood EPCs in vitro, Miao, W. et al. [160] found that different levels of TXL improved the proliferation, migration, and adhesion functions of EPCs, and at 500 μ The effect is most significant at g/ml. Therefore, TXL can significantly improve the proliferation, migration, and adhesion ability of peripheral

blood EPCs, which may be a new mechanism for the prevention and treatment of cardiovascular and cerebrovascular diseases through TXL.

Coronary heart disease (CHD) is one of the diseases with high mortality, and its incidence rate is still rising significantly. Studies have shown that the decrease in the number of EPCs in the peripheral blood of patients with coronary heart disease is closely related to various risk factors for coronary heart disease. Increasing the number of endothelial progenitor cells in patients can improve their vascular endothelial condition and prognosis. In order to investigate the number of endothelial progenitor cells in patients with different degrees of coronary heart disease and the effects of TXL and statins on endothelial progenitor cells in patients with coronary heart disease, Li, B.Q. et al. [161] conducted a clinical observation experiment. The research results showed that the combination of TXL and fluvastatin improved the number of endothelial progenitor cells more significantly. On the basis of conventional western medicine treatment, patients with coronary heart disease benefit more from TXL capsule, a traditional Chinese patent medicines and simple preparations that can promote menstruation and blood circulation. The impaired function of endothelial progenitor cells is closely related to the onset and prognosis of coronary heart disease, and the CXCR4 signaling pathway is an important molecular mechanism for regulating endothelial progenitor cell function. In order to further investigate the effect of TXL treatment on endothelial progenitor cell function in coronary heart disease patients and its relationship with the CXCR4 signaling pathway, Ding, M.L. et al. [162] randomly divided 60 coronary heart disease patients into two groups, with group A receiving standardized treatment; Group B received standardized treatment + TXL treatment, with a treatment period of 3 months. The research results show that TXL treatment can improve endothelial progenitor cell function in patients with coronary heart disease, which is related to the upregulation of the CXCR4/JAK-2 signaling pathway. In another experiment to investigate the effect of TXL on the blood concentration of vascular endothelial growth factor (VEGF) and endothelial progenitor cells (EPCs) in peripheral blood of coronary heart disease patients, Liu, X. C et al. [163] used a dual antibody sandwich ELISA detection method to detect VEGF levels before and after taking TXL capsules in coronary heart disease patients. Density gradient centrifugation was used to obtain mononuclear cells from peripheral blood of coronary heart disease patients before and after 7 days of cultivation, and immunofluorescence and flow cytometry were used to identify EPCs. The research results show that TXL has a positive regulatory effect on the function of VEGF and EPCs in patients with coronary heart disease.

The above evidence indicates that the downregulation of the quantity and function of EPCs is closely related to the occurrence and development mechanisms of various cardiovascular diseases. The mechanism of TXL in treating cardiovascular diseases by enhancing the quantity and function of EPCs includes improving the proliferation, migration, and adhesion ability of peripheral blood EPCs, downregulating the RAGE-MAPK signaling pathway, and upregulating the CXCR4/JAK-2 signaling pathway, thus fully leveraging the advantages of TXL's multi-component, multi target, and multi pathway intervention in the treatment of cardiovascular diseases.

3.2.5. The mechanism of TXL inhibiting vascular intimal hyperplasia

Endovascular proliferation is a natural repair process after vascular damage, but excessive proliferation can lead to the occurrence of vascular restenosis. Endometrial proliferation of blood vessels originates from the excessive proliferation, migration, and phenotypic transformation of smooth muscle cells in the intima of blood vessels, which are stimulated by local or circulatory oxidative stress and inflammatory factors [182,183]. The entire process includes endothelial damage, platelet aggregation, inflammatory cell infiltration, smooth muscle cell proliferation and migration to the subintima, etc [184] Endovascular hyperplasia is the central link in the pathological process of vascular remodeling.

TXL is often used to treat coronary heart disease and atherosclerosis. Therefore, Yao, E. H. et al. [164] conducted a study to investigate the effects of TXL on neointimal formation and inflammatory cytokine expression after carotid balloon injury in rats. His team randomly divided male Sprague Dawley rats into four groups: sham surgery group, balloon injury group, TXL low-dose group, and TXL high-dose group. The research results indicate that TXL can effectively improve endothelial function, reduce the proliferation of arterial intima after balloon injury, and reduce the expression of inflammatory cytokines MCP-1 and ICAM-1. Studies have shown that microRNA-155 (miR-155) is related to vascular inflammation and atherosclerosis. However, the direct relationship between TXL and miR-155 in the development of vascular inflammation and remodeling has not been confirmed. Therefore, Zhang, R. N. et al. [165] conducted an experiment to investigate whether TXL inhibits vascular inflammatory response and endometrial hyperplasia by regulating the expression of miR-155. The research results show that TXL inhibits vascular inflammation and intimal hyperplasia caused by carotid artery ligation in mice. Akt1 mediated inhibition of miR-155 expression and the relationship between miR-155 and TNF- α Blocking the feedback loop between TXL is an important pathway for TXL to exert vascular protective effects.

In order to investigate the inhibitory effect of TXL on intimal hyperplasia and local inflammatory response induced by carotid artery ligation, Zhang, N. N et al. [166] used a C57BL/6 mouse model of intimal hyperplasia induced by ligation of the left common carotid artery near the bifurcation. The research results show that TXL can significantly inhibit intimal hyperplasia induced by carotid artery ligation in mice, and its effect is related to reducing macrophage infiltration and alleviating local inflammatory response. The proliferation and migration of macrophages play an important role in the intimal hyperplasia induced by vascular endothelial injury. Therefore, in order to investigate whether inhibiting macrophage proliferation and migration has a therapeutic effect on vascular remodeling cardiovascular diseases characterized by intimal hyperplasia, Jiang, W. et al. [167] randomly divided KLF5ly −/− mice into a control group, a carotid artery ligation group, and a carotid artery ligation + TXL treatment group. The research results show that TXL passes through PI3K/AKT and NF- κ The B signaling pathway inhibits KLF5 mediated macrophage proliferation, migration, and vascular intimal hyperplasia. Therefore, TXL can play a therapeutic role in vascular remodeling cardiovascular disease by inhibiting intimal hyperplasia.

In an experiment to investigate the effect of TXL on post angioplasty vascular intimal hyperplasia and C-MYC and C-FOS gene expression in dogs, Wei, F. et al. [168] established a model of post angioplasty vascular intimal injury in 24 dogs and randomly divided

them into a control group and a TXL treatment group, with 12 in each group. The research results show that the C-MYC and C-FOS genes are involved in the regulation of vascular endothelial cells. TXL has the effect of promoting endometrial cell apoptosis and downregulating the expression of C-MYC and C-FOS genes, which can reduce the degree of vascular intimal hyperplasia and luminal stenosis. In order to investigate the effects of TXL on intimal hyperplasia, macrophage infiltration, and related miR-155 expression induced by carotid artery ligation in mice, Zhang, N.N. et al. [169] randomly divided male C57BL/6 mice with left common carotid artery ligation for 7, 14, and 21 days at each time point into four groups: model group and TXL small, medium, and high-dose groups. The research results show that TXL inhibits the proliferation of vascular intima and macrophage infiltration in mice after ligation, partially through the inhibition of miR-155 expression.

The above evidence indicates that intimal hyperplasia of blood vessels is closely related to the occurrence and development mechanisms of various cardiovascular diseases. The mechanism of TXL in treating cardiovascular diseases by inhibiting intimal hyperplasia includes reducing the expression of inflammatory cytokines MCP-1 and ICAM-1, promoting Akt1 mediated miR-155 expression, reducing macrophage infiltration, and inhibiting KLF5 mediated macrophage proliferation and migration, promoting apoptosis of vascular endothelium cells and downregulating the expression of C-MYC and C-FOS genes, inhibiting the expression of miR-155, etc., fully leveraging the advantages of TXL's multi-component, multi-target, and multi pathway intervention in the treatment of cardiovascular diseases.

3.2.6. The mechanism of TXL inhibiting outer membrane nourishing vascular proliferation

The outer membrane nourishes blood vessels by providing oxygen and nutrients, helping to maintain the survival and function of blood vessel wall cells. They can also affect the growth and repair process of blood vessels by regulating the metabolism of blood vessel walls and cell proliferation. The study also found that outer membrane nourishing blood vessels are induced by various cytokines such as vascular endothelial growth factor (VEGF) and inflammatory factors to sprout into the inner and middle membranes, ultimately forming new microvessels within the plaque [185].

In an experiment to explore the effect of TXL ultrafine powder on the angiogenesis of adventitia at the early stage of atherosclerosis in rabbits and its possible mechanism, Liu, M.Z. et al. [170] used carotid cannulation combined with high-fat diet to establish a model of carotid artery injury at the early stage of atherosclerosis in rabbits. The results showed that TXL superfine powder could inhibit the angiogenesis of adventitia in the early stage of atherosclerosis in rabbits, and its mechanism might be related to improving the antioxidant capacity of vascular system and adventitia tissue and inhibiting the activation of p38 MAPK pathway. In another study by Liu, M.Z [186]. exploring the role and related mechanisms of TXL in the angiogenesis of the carotid outer membrane in hyperlipidemic rabbits, the results showed that TXL has an inhibitory effect on the angiogenesis of the carotid outer membrane in hyperlipidemic rabbits, which may be related to downregulating the expression of neuroendocrine factors.

The above evidence shows that adventitious trophoblastic vascular hyperplasia is closely related to the occurrence and development mechanism of atherosclerosis, hyperlipidemia and other cardiovascular diseases. The mechanism of TXL in treating

Table 3
The mechanism of Tongxinluo protecting blood.

#	Models	Involved mechanisms	Signaling pathway	Pharmacological effects	Ref
1	C57BL/6J wild-type and ApoE −/− mice: a damaged heart model with hypercholesterolemia	↑: VEGF	–	Regulating blood lipid composition	[109]
2	New Zealand white rabbits: atherosclerotic plaque model	↓: ox-LDL receptor 1、MMP-1、MMP-3、MMP1、NF-κB		Reduce serum lipid levels	[151]
3	ApoE (−/−) mice: AS model	↓: ROS	-	Reduce oxidized low-density lipoprotein(ox-LDL)	[155]
4	Male apoE −/− mice: AS model	↓: IL-6、TNF-α、MMP-2	–	Changed lipid metabolism	[187]
5	New Zealand White Rabbit: AS Model	↓: TC, LDL, LOX-1		Reduce serum lipid levels	[188]
6	DC: AS model derived from human monocytes	↑: PPARγ	↑: PPAR-gamma	Reduce OX-LDL	[189]
7	ACS patients	↑: eNOS	L-arg/NO	Inhibition of platelet activation and aggregation	[190]
8	CHD patients	↓: ADP、COL	–	Inhibition of platelet activation and aggregation	[191]
9	New Zealand White Rabbit: AS Model	↓: PF4、sCD62P、Calcium concentration	–	Inhibition of platelet activation and aggregation	[192]
10	New Zealand White Rabbit; HUVEC: AS model	↓: CD40L/CD40	↓: CD40L/CD40	Inhibition of platelet activation and aggregation	[109, 193]
11	Male SD rats: myocardial infarction model	↓: ADP和collagen	–	Inhibition of platelet activation and aggregation	[194]
12	Male SD rats: blood stasis model	↑:t-PA活性, ↓: PAI	–	Regulating the coagulation-fibrinolysis system	[195]
13	Patients after coronary stent placement surgery	↑:AT-III、t-PA, ↓:FIB、PAI-1、Angiotensin II	–	Regulating the coagulation-fibrinolysis system	[196]
14	After PCI in patients with coronary heart disease	↑:AT-III、t-PA, ↓:FIB、PAI-1	–	Regulating the coagulation-fibrinolysis system	[197]
15	DM-CHD patients	↓: vWF、F1+2、Fib、PAI-1, ↑: t-PA	–	Regulating the coagulation-fibrinolysis system	[198]

cardiovascular diseases by inhibiting outer membrane nourishing vascular proliferation includes improving the antioxidant capacity of the vascular system and outer membrane tissue, inhibiting the activation of the p38MAPK pathway, downregulating the expression of neuroendocrine factors, etc., thus fully leveraging the advantages of TXL's multi-component, multi target, and multi pathway intervention in the treatment of cardiovascular diseases.

3.3. The mechanism of TXL in protecting blood

The mechanism of TXL in protecting blood mainly involves three aspects(Table 3): regulating blood lipid composition, inhibiting platelet activation and aggregation, and regulating the coagulation fibrinolysis system.

3.3.1. The mechanism of TXL regulating blood lipid composition

Hyperlipidemia is one of the risk factors for cardiovascular disease. The main components of blood lipids include cholesterol (TC) and triglycerides (TG), as well as phospholipids and free fatty acids. Lipids are insoluble in water and must bind with proteins to form lipoproteins in order to function in the bloodstream. Therefore, the content of lipoproteins (LPa) in the blood is also an important indicator of whether blood lipids are elevated. More important lipoproteins include low-density lipoprotein (LDL) and high-density lipoprotein (HDL) [199]. Hyperlipidemia is one of the main causes of atherosclerosis. Studies have found that high blood lipids can cause atherosclerosis, resulting in insufficient blood supply to tissues and organs, which can lead to coronary heart disease, myocardial infarction, hypertension, etc. [200,201]. Therefore, reducing blood lipid composition is of great significance for the prevention and treatment of various cardiovascular diseases.

Both basic research and clinical observation show that TXL has obvious therapeutic effect on atherosclerosis (AS). However, its mechanism research is not yet clear. Therefore, in order to comprehensively evaluate the potential mechanism of TXL on atherosclerosis, Ma, J. et al. [187] randomly divided 100 apoE −/− mice (male, 12 weeks old) into 5 groups. The control group mice were fed a normal diet, while the other four groups (intervention group) mice were fed a high-fat diet. The intervention group was randomly divided into a saline group and a TXL treatment group, with an intervention period of 16 weeks. The results showed that TXL could inhibit the development of atherosclerosis and stabilize plaque. Its mechanism mainly involves inflammation and lipid metabolism. In an experiment to explore the preventive effect of TXL on vascular disease in atherosclerotic rabbits and its effect on lectin like oxidized low-density lipoprotein receptor-1 (LOX-1) protein and gene expression in vascular wall, Yu, Y. H. et al. [188] showed that TXL has an inhibitory effect on blood lipids, can prevent the occurrence of vascular disease and treat the development of vascular disease, and its protective effect on AS may be related to reducing the expression of LOX-1 in vascular wall. In order to verify whether endothelial cell (EC) pyroptosis plays a crucial role in the development of atherosclerosis, Jiang, X. et al. [155] conducted an in vitro experiment, which showed that TXL significantly reduced the degree of damage to aortic endothelial cells (MAEC) caused by oxidized low-density lipoprotein (ox LDL).

To verify the hypothesis that TXL enhances the stability of vulnerable plaques in a dose-dependent manner through lipid-lowering and anti-inflammatory effects, Zhang, L. et al. [151] fed 75 rabbits with a 1 % cholesterol diet after abdominal aortic balloon injury for 10 weeks, and divided them into a control group, a low-dose TXL group, a medium dose TXL group, a high-dose TXL group, and a high-dose simvastatin group for 8 weeks of treatment. At the end of week 16, inject adenovirus containing p53 into the abdominal aortic plaque. The research results show that TXL dose-dependent reduces serum lipid levels and inhibits systemic inflammation. TXL has the effect of enhancing the stability of vulnerable plaques and preventing plaque rupture. In order to investigate the effects of TXL on the maturation and immune function of dendritic cells (DCs) induced by oxidized low-density lipoprotein (OX-LDL) and its possible mechanisms, Su, W. et al. [189] incubated human monocyte derived DCs with TXL or sitagliptone, followed by OX-LDL stimulation to induce maturation. The research results show that TXL can inhibit OX-LDL induced DC maturation by activating the PPAR gamma pathway.

Previous studies have shown that TXL has good clinical efficacy in the treatment of acute myocardial infarction (AMI), but there is a lack of systematic research. Li, M. et al. [202] included 19 randomized controlled trials in this study and conducted a meta-analysis based on 16 studies. The research results showed that the TXL treatment group reduced primary cardiovascular events, recurrent myocardial infarction, arrhythmia, recurrent angina, improved heart function, and regulated blood lipid TC. In order to investigate whether TXL can improve the impaired cardiac function caused by hypercholesterolemia by protecting arterial endothelial function and increasing cardiac microvascular density (MVD), Yuan, G. Q. et al. [109] measured serum total cholesterol, high-density lipoprotein cholesterol, extremely low density lipoprotein (VLDL) cholesterol, triglycerides, and blood glucose levels after gastric administration of TXL to C57BL/6J wild-type and ApoE −/− mice. The research results show that TXL can significantly improve the cardiac function of ApoE −/− mice, and can increase the cardiac microvessel density (MVD) by reducing blood lipids and atherosclerosis. The molecular mechanism of MVD enhancement may be related to the increased expression of VEGF.

The above evidence shows that blood lipid composition is closely related to the pathogenesis of various cardiovascular diseases such as atherosclerosis, hyperlipidemia, coronary heart disease, myocardial infarction, etc. The mechanism of TXL in treating cardiovascular diseases by regulating blood lipid composition includes increasing lipid metabolism, reducing the expression of LOX-1 in the vascular wall, reducing oxidized low-density lipoprotein (ox LDL), lowering serum lipid levels, activating the PPAR gamma pathway, etc., thus fully leveraging the advantages of TXL's multi-component, multi-target, and multi pathway intervention in the treatment of cardiovascular diseases.

3.3.2. The mechanism of TXL inhibiting platelet activation and aggregation

Platelet activation and aggregation are complex processes mediated by different signaling pathways. Modern pharmacological

research shows that TXL has a good inhibitory effect on platelet activation and aggregation, and has been widely used in the prevention and treatment of various cardiovascular diseases (including coronary heart disease, atherosclerosis, myocardial infarction, etc.) [190].

It is currently clear that platelet activation and aggregation are central processes in the pathogenesis of acute coronary syndrome (ACS). However, there is currently little research on the mechanism of TXL's anti platelet activation and aggregation effects. Therefore, Liu, J. et al. [190] conducted a clinical observational study to verify whether the antiplatelet aggregation effect of TXL is related to the platelet's own L-arg/NO system. The research results show that in the treatment of ACS patients, TXL may achieve antiplatelet aggregation by activating the platelet L-arg/NO pathway and increasing platelet eNOS activity. In another clinical observation experiment to observe the effect of TXL on platelet aggregation in patients with aspirin resistant coronary heart disease (CHD), Yin, C. H. et al. [191] screened aspirin resistant (AR) patients from 330 CHD patients who regularly took aspirin (100 mg/d) for more than a month by detecting platelet aggregation levels induced by adenosine diphosphate (ADP) and collagen (COL). Randomly divided into TXL + aspirin combination treatment group, TXL group, and AS group, three times a day, with a course of treatment of one month each. Measure the patient's platelet aggregation before and after one month of treatment. The research results show that TXL has a certain inhibitory effect on ADP + COL induced platelet aggregation, and its mechanism of inhibiting platelet aggregation may be related to the inhibition of ADP and COL.

In an experiment to explore the protective effect of TXL on platelets in atherosclerosis (AS) New Zealand rabbits, Liu, H.L. et al. [192] used 42 SPF grade New Zealand rabbits, half male and half female, and randomly divided them into normal group, model group, Tongxinluo ultramicro powder low, medium and high dose groups, atorvastatin group, and aspirin group. The normal group was given normal diet for 12 weeks, the model group was given high-fat diet for 12 weeks to establish atherosclerosis model, and the other groups were given high-fat diet at the same time by gavage for 12 weeks. The research results show that TXL can significantly inhibit the activation status of platelets during the AS process, and its mechanism is related to reducing platelet expression of PF4, sCD62P levels, and decreasing platelet calcium ion concentration. Therefore, TXL has important clinical therapeutic value in delaying AS thrombosis formation. In order to investigate whether TXL has a protective effect and mechanism against platelet induced endothelial cell injury in AS, Liu, H.L. et al. [193] validated it through animal and cell experiments. The research results show that TXL has a certain therapeutic and protective effect on endothelial cell damage induced by activated platelets in AS, which is related to its inhibition of platelet activation and reduction of platelet endothelial cell adhesion ability. The mechanism may be to inhibit CD40L/CD40 activity.

n order to investigate the effects of TXL ultrafine grinding on experimental myocardial infarction and platelet aggregation in rats, Zhang, Y.F. et al. [194] randomly divided the rats into a sham surgery group, a model group, diltiazem, TXL, and thromboxane Lu. Then ligate the left anterior descending branch of the rat coronary artery to induce experimental myocardial infarction. The research results show that TXL ultrafine powder can protect rat myocardial ischemic injury by antioxidation and inhibiting platelet aggregation, and its mechanism of action may be related to the inhibition of ADP and collagen.

The above research shows that the activation and aggregation of platelets are closely related to the pathogenesis of coronary heart disease, atherosclerosis, myocardial infarction and other cardiovascular diseases. The mechanism of TXL in treating cardiovascular diseases by inhibiting platelet activation and aggregation includes activating the platelet L-arg/NO pathway, increasing platelet eNOS activity, inhibiting ADP and COL, reducing platelet expression of PF4 and sCD62P levels, lowering platelet calcium ion concentration, inhibiting CD40L/CD40 activity, inhibiting ADP and collagen, etc., fully leveraging the advantages of TXL's multi-component, multi-target, and multi pathway intervention in the treatment of cardiovascular diseases.

3.3.3. The mechanism of TXL regulating the coagulation fibrinolysis system

When anticoagulant function is elevated, it can inhibit thrombus formation. The main function of the fibrinolytic system is to remove fibrin clots deposited on the blood vessel wall, dissolve blood clots, and maintain smooth blood flow. Therefore, enhancing the activity of the anticoagulant fibrinolytic system can help prevent and treat various ischemic cardiovascular diseases. Multiple studies have found that TXL has the function of regulating the activity of the coagulation fibrinolysis system.

Animal studies and clinical observations have demonstrated that TXL is used for the treatment of coronary artery atherosclerotic heart disease (coronary heart disease) and has significant anti myocardial ischemia and lipid-lowering effects [203,204]. Therefore, in order to investigate the effects of TXL on microcirculation and coagulation fibrinolysis system, as well as its role in promoting blood circulation and removing blood stasis, the research results of Ma, X.Y. et al. [195] showed that TXL can improve microcirculation disorders in blood stasis model rats, regulate abnormal fibrinolysis system function, and have the effect of promoting blood circulation and removing blood stasis. Its mechanism may be related to enhancing t-PA activity and reducing PAI activity.

In a clinical study on the effects and mechanisms of TXL on the coagulation fibrinolysis system and angiotensin II in patients after coronary stent implantation, Zhang, W. et al. [196] randomly divided 58 patients after coronary stent implantation into conventional drugs and conventional drugs plus TXL treatment, and observed the coagulation fibrinolysis related indicators in postoperative patients. The research results show that TXL regulates the balance of the coagulation fibrinolysis system by increasing the levels of AT - III and t-PA in the body, and reducing the levels of FIB, PAI-1, and angiotensin II. In another study exploring the effects of TXL on the coagulation and fibrinolysis system in patients with coronary heart disease undergoing percutaneous coronary intervention (PCI) and the mechanism of drug action, Liu, M. et al. [197] divided 52 patients with coronary heart disease into an observation group and a control group. After surgery, two groups of patients were given conventional oral medication treatment, while the observation group was given TXL orally. The research results show that TXL can regulate the balance of the coagulation fibrinolysis system in patients with coronary heart disease after PCI, and its mechanism may be to increase the levels of AT-III and t-PA in the body and reduce the levels of FIB and PAI-1.

In a clinical observation experiment to explore the effect of TXL on the coagulation and fibrinolysis function of patients with type 2 diabetes and coronary heart disease (DM-CHD), Ma, T. et al. [198] randomly divided 120 patients with DM-CHD into a conventional

treatment group and a conventional treatment plus TXL group, with 60 cases in each group for 2 months. The research results show that TXL can improve the coagulation fibrinolysis function of DM-CHD patients, and its mechanism may be related to the decrease in vWF, F1+2, FIB, PAI-1 levels and the increase in t-PA activity.

The above evidence shows that the regulation of coagulation fibrinolysis system is closely related to the pathogenesis of coronary heart disease, coronary stent implantation, type 2 diabetes with coronary heart disease and other cardiovascular diseases. The mechanism by which TXL regulates the coagulation fibrinolysis system to treat cardiovascular diseases includes enhancing t-PA activity, reducing PAI activity, increasing levels of AT - III and t-PA in the body, lowering FIB, PAI-1, angiotensin II levels, increasing levels of AT - III and t-PA, lowering FIB and PAI-1 levels, lowering vWF, F1+2, FIB, PAI-1, and increasing t-PA activity. This fully leverages the advantages of TXL's multi-component, multi target, and multi pathway intervention in the treatment of cardiovascular diseases.

3.4. The mechanism of TXL stabilizing vulnerable plaques

Vulnerable plaques with a certain degree of coronary stenosis are more prone to acute cardiovascular events. Therefore, stabilizing vulnerable plaques has become a key issue in scientific research on the prevention and treatment of cardiovascular diseases. Multiple studies have found that TXL can effectively stabilize vulnerable plaques through various mechanisms(Table 4).

In an experimental study to explore the stabilizing effect of TXL on vulnerable plaque, Zuo, F [205]. used 46 New Zealand purebred male rabbits to damage the abdominal aorta endothelium with PTCA filling balloon traction method, and then fed them with high cholesterol diet for 8 weeks. At the end of 8 weeks, 16 rabbits were randomly selected as the validation group, and intravascular ultrasound was used to prove the formation of atherosclerotic plaque. The remaining 30 rabbits were randomly divided into a high-fat diet group, a regular diet group, and a TXL group as the intervention group. The TXL group was treated for 12 weeks, during which a high cholesterol diet was continued. At 12 weeks, medication was triggered to cause plaque rupture. The experimental results showed that TXL could selectively change the expression of MMPs and TIMPs in atherosclerotic plaques, reduce matrix decomposition and destruction, increase the stability of local plaques, and play a role in stabilizing atherosclerotic plaques and delaying the progression of atherosclerosis to a certain extent; TXL can reduce the levels of plasma inflammatory factors such as P-selectin, hsCRP, MMP-1, inhibit the adhesion of monocytes and T lymphocytes to vascular endothelial cells, reduce the inflammatory environment around the fibrous cap of atherosclerotic plaque, strengthen the fibrous cap of plaque, and help stabilize atherosclerotic plaque. In another experiment to compare the stabilizing effect of TXL and simvastatin on vulnerable plaques in rabbits, Lu, X.T. et al. [206] established atherosclerosis models in 30 experimental rabbits by using balloon injured abdominal aorta + high-fat feeding. At the end of 10 weeks, they were fed with normal diet and randomly divided into natural regression group, Tongxinluo group, and simvastatin group, with 10 rabbits in each group. They continued drug intervention for 12 weeks and drug triggering at the end of 22 weeks to create plaque instability models. The research results show that TXL, like simvastatin, has the same stabilizing effect on vulnerable plaques and has comparable therapeutic effects. Its mechanism may be related to reducing serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C).

Similarly, in an experimental study by Academician Zhang, Y [207]. exploring the role and mechanism of TXL in stabilizing vulnerable plaques, 30 male purebred New Zealand rabbits were randomly divided into three groups after receiving abdominal aortic balloon injury and high-fat diet for 8 weeks to establish a model of stable plaques in the abdominal aorta. TXL + high-fat diet group, regular diet group, high-fat group, intervention for 3 months. Trigger medication at the end of the third month to create an unstable plaque model. The research results show that TXL can effectively prevent plaque rupture in the AS vulnerable plaque rabbit model. Its main molecular biology mechanisms include: TXL significantly reduces LDL-C and TC levels, generally inhibits the expression of inflammatory factors in plaques, and exerts anticoagulant effects by reducing fibrinogen concentration. The main morphological mechanism is that TXL significantly reduces plaque load and positive vascular remodeling, significantly increases fiber cap thickness and plaque density, and prevents plaque rupture.

Inflammation is one of the important mechanisms for the occurrence and development of vulnerable atherosclerotic plaques. However, at present, the clinical treatment of vulnerable plaques mainly stays in the level of lipid reduction, and there is no targeted

Table 4
The mechanism of Tongxinluo in stabilizing vulnerable plaques.

#	Models	Involved mechanisms	Signaling pathway	Pharmacological effects	Ref
1	New Zealand White Rabbit: AS Model	↓: ox-LDL receptor-1、MMP-1、MMP-3、MMP1、 NF-κB	–	Stable and vulnerable plaques	[151]
2	Male: apoE −/− Mouse: AS model	↓: IL-6, TNF-α, MMP-2	–	Stable atherosclerotic plaque	[187]
3	New Zealand purebred male rabbits: AS model	↓:P-Selectin,hsCRP,MMP-1	–	Stable atherosclerotic plaque	[205]
4	New Zealand White Rabbit: AS Model	↓: TC、LDL-C	–	Stable and vulnerable plaques	[206]
5	Male purebred New Zealand rabbits: AS model	↓: LDL-C和TC	–	Stable and vulnerable plaques	[207]
6	New Zealand White Rabbit: AS Vulnerable Plaque Model	↓: NLRP3	↓: NLRP3通路	Stable and vulnerable plaques	[208]

drug to treat inflammation. To verify the hypothesis that TXL enhances the stability of vulnerable plaques in a dose-dependent manner through lipid-lowering and anti-inflammatory effects, Zhang, L. et al. [151] fed 75 rabbits with a 1 % cholesterol diet for 10 weeks after abdominal aortic balloon injury, and then divided them into 5 groups for 8 weeks of treatment: control group, low-dose TXL group, medium dose TXL, high-dose TXL, and high-dose simvastatin group. At the end of the 16th week, adenovirus containing p53 was injected into the abdominal aortic plaque to create an unstable plaque model. The research results show that TXL dose-dependent enhances the stability of vulnerable plaques and prevents plaque rupture, possibly by reducing the oxidative low-density lipoprotein (ox LDL) receptor 1, matrix metalloproteinase 1 (MMP-1), MMP-3, MMP1 tissue inhibitor, and NF in plaques- κ The expression of B is related.

A study has found that after TXL intervention, ApoE −/− mice have reduced arterial plaque burden and reduced plaque vulnerability. However, the mechanism by which TXL stabilizes vulnerable plaques is still unclear. In recent years, research has found an undeniable link between gut microbiota and diseases. At present, there is no research on the relationship between vulnerable plaques and gut microbiota. Therefore, Yuan, Y. et al. [208] further explored whether TXL can inhibit the inflammatory response within vascular plaques by altering gut microbiota and metabolites, thereby stabilizing vulnerable arterial plaques. The research results show that in a vulnerable plaque model, TXL inhibits the NLRP3 inflammatory pathway in blood vessels by increasing the active form of indistinctus bacteria in the intestine and increasing the content of metabolite TFA, thereby stabilizing vulnerable plaques.

In a study to comprehensively evaluate the potential mechanism of TXL on atherosclerosis, Ma, J. et al. [187] found that TXL can inhibit the development of atherosclerosis and stabilize plaque. In addition to inflammation and lipid metabolism, its comprehensive mechanism may also involve cellular physical functions, hormone secretion, protein binding, and immune response processes.

The above evidence shows that stable vulnerable plaque is closely related to the pathogenesis of various cardiovascular diseases such as atherosclerosis. The mechanisms of TXL in treating cardiovascular diseases by stabilizing vulnerable plaques include: reducing the expression of MMPs and TIMPs in atherosclerotic plaques, reducing the levels of plasma inflammatory factors such as P-selectin, hsCRP, MMP-1, and inhibiting the adhesion of monocytes and T lymphocytes to vascular endothelial cells, Reduce serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), increase fiber cap thickness and plaque density, and reduce oxidative low-density lipoprotein (ox LDL) receptor 1, matrix metalloproteinase 1 (MMP-1), MMP-3, MMP1 tissue inhibitor, and NF in plaques- κ The expression of B increases the intestinal metabolite TFA and inhibits the NLRP3 inflammatory pathway in blood vessels, fully leveraging the advantages of TXL's multi-component, multi-target, and multi pathway intervention in the treatment of cardiovascular diseases.

3.5. The mechanism of TXL vasodilation

Diastolic effect refers to the physiological or pharmacological effect of the relaxation of smooth muscle in the blood vessel wall, leading to the expansion of blood vessel diameter. Vasodilation plays an important role in the treatment of cardiovascular diseases such as hypertension, coronary heart disease and atherosclerosis. In addition, vasodilation can also improve blood supply, promote tissue oxygenation and nutrient supply, and help prevent and treat some organ diseases [209]. Moreover, multiple studies have found that TXL can also improve endothelial dependent vasodilation function in blood vessels [210].

In order to investigate the effect of TXL on the high conductivity calcium activated potassium channel (BKCa) in vascular smooth muscle cells and explore its possible mechanism of vasodilation at the molecular level, Tang, Y. et al. [211] randomly divided SD rats into a control group, a model group, a low-dose TXL group, and a high-dose TXL group, with 12 rats in each group. A hypertensive rat model was established using abdominal aortic ligation technique. The research results show that TXL can activate the BKCa channel in rat vascular smooth muscle cells and exert the effect of vasodilation. In an experiment exploring the molecular mechanisms by which TXL improves endothelial function, Liang, J. Q. et al. [212] induced hyperhomocysteinemia in Wistar rats using a diet rich in methionine. The rats were treated with TXL and the aortic rings were separated to measure vascular dilation and eNOS expression in the aorta. The research results show that TXL upregulates the expression of eNOS through the PI-3K/Akt/HIF dependent signaling pathway, thereby improving endothelial dependent vasodilation.

In a clinical observation experiment exploring the effects of TXL on circulating endothelial microparticles (EMPs) and endothelial function in hypertensive patients, Lu, Y. G. et al. [213] randomly divided 94 hypertensive patients into TXL group and conventional treatment group, with 20 healthy individuals as the healthy control group. The research results showed that after 6 months of treatment, the circulating endothelial microparticles (EMPs) and blood pressure in the TXL group and conventional treatment group were significantly reduced compared to before treatment, and endothelial dependent vasodilation function (FMD) was significantly increased, with the TXL group showing a more significant increase. Therefore, TXL treatment can significantly reduce endothelial microparticle levels and improve endothelial dependent vasodilation function in hypertensive patients.

In another experiment to explore the effect of TXL on vascular endothelial diastolic function in type 2 diabetes patients with coronary heart disease, He, J.B. et al. [214] showed that after treatment with TXL, fasting blood glucose (FPG), postprandial 2h blood glucose (2hPG), glycosylated hemoglobin (HbAlc), triglyceride (TG), systolic blood pressure, diastolic blood pressure and ET-1 levels were significantly reduced, and levels of nitric oxide (NO), nitric oxide synthase (NOS), endothelium-dependent diastolic function (EDD) and endothelium-independent diastolic function (EID) were significantly increased. Therefore, we can speculate that type 2 diabetes patients with coronary heart disease have obvious vascular endothelial dysfunction, and TXL can improve vascular endothelial diastolic function by affecting the release of ET-1, NO and NOS.

In order to explore the drug intervention effect on vascular inflammation response and endothelial function changes after coronary intervention, Liu, M [215]. randomly divided 100 patients undergoing coronary intervention treatment into a control group (conventional treatment) and a treatment group (conventional treatment + TXL), with 50 cases in each group. Through Doppler ultrasound

examination, C-reactive protein (CRP), ICAM-1, interleukin-10 (IL-10), and brachial artery endothelial diastolic function (NMD) were observed and compared between the two groups before and after treatment. The research results showed that the levels of CRP and ICAM-1 were significantly reduced in the treatment group, while the levels of IL-10 and NMD were significantly increased. Therefore, TXL can significantly improve vascular inflammation and endothelial dilation function after coronary intervention, improve patient prognosis, and is worthy of clinical promotion.

In an experiment to explore the effect of TXL on vascular diastolic function and atherosclerosis, Xiao, W.G. et al. [216] randomly divided 240 New Zealand rabbits into normal group, model group, atorvastatin group and TXL high, medium and low dose groups, with 40 rabbits in each group. The normal group was fed with regular feed, while the other groups were fed with high-fat feed to establish a hyperlipidemia model. At the same time, the atorvastatin group was given atorvastatin solution by gavage, while the high-dose, medium, and low-dose groups of TXL were given TXL capsule solution by gavage for 6 weeks. The research results show that TXL can improve the vasodilation function by reducing the blood lipid level and inhibiting the growth of microvessels in the arterial wall, thus delaying the further development of atherosclerosis.

The above evidence shows that vasodilation is closely related to the pathogenesis of various cardiovascular diseases such as hypertension, coronary heart disease, atherosclerosis, etc. The mechanisms by which TXL treats cardiovascular diseases through vasodilation include(Table 5): Activating the BKCa channel in vascular smooth muscle cells, upregulating the expression of eNOS, affecting the release of ET-1, NO, and NOS, reducing CRP, ICAM-1, increasing IL-10 levels, lowering blood lipid levels, inhibiting the proliferation of microvessels in arterial walls, etc., thus fully leveraging the advantages of TXL's multi-component, multi-target, and multi pathway intervention in the treatment of cardiovascular diseases.

4. Network pharmacological study on the mechanism of TXL in treating cardiovascular diseases

Traditional Chinese medicine has the characteristics of multiple components, targets, and pathways [217].In recent years, network pharmacology has been widely recognized as an effective research strategy for exploring traditional Chinese medicine from the perspective of biological network balance [218–220]. Here, we use a network pharmacology approach that combines chemical and therapeutic properties to explore the molecular mechanism of TXL in treating cardiovascular disease (CVD). Using "cardiovascular disease" as the search term, CVDs genes were retrieved from six sources including DisGeNET [221], Open Target Platform [222], MalaCards [223], CTD [224], GeneCards and text mining [225]。Using Database for Annotation, Visualization, and Integrated Discovery (DAVID) 2021(https://david.ncifcrf.gov/)Used to standardize gene names [226]. To ensure the reliability of the data, only genes that appear in three or more databases are retained as the core gene set for cardiovascular disease. Analyze the gene set related to cardiovascular disease and potential targets of TXL to identify functional targets for TXL in the prevention and treatment of cardiovascular disease. Then submit the target data to STRING version 12.0(https://string-db.org/)Protein interaction background network for constructing PPI network (confidence level 0.7) [227]. The obtained PPI network is visualized in Cytoscape v3.9.0 [228]. The comprehensive target spectrum of TXL is crucial for studying its substantial basis and mechanism of action in treating cardiovascular diseases. We collected targets [229],TTD [230], ChEMBL [231], PubChem from DrugBank and standardized their names through UniProt [232–234]. In order to further explore the key active compounds and targets of TXL in the treatment of cardiovascular diseases, we collected literature on targets and therapeutic targets from the PHARMACODIA database(https://www.pharmacodia.com/). To explain the mechanism of TXL in combating cardiovascular disease from a systemic perspective, we conducted gene ontology (GO) and KEGG pathway enrichment analysis using Metascape(https://metascape.org)ClueGO plugin in Cytoscape [235].

Based on the pathogenic genes reported in CVDs literature and the therapeutic targets of approved drugs, a PPI molecular network was constructed for the specific pathogenesis of CVDs, and its mechanism was explored. TXL has 224 adjustable targets, and 35 key targets were selected through network parameters, such as EGFR, HSP90AA1, SNCA, CDK5, NR3C1, CACNA1C, KDR, TNF, MMP9, EDN1, NFKB1, etc. (threshold: degree>11, intermediate centrality>0.009, near centrality>0.348) (Fig. 3A). In addition, key biological processes regulated by TXL include membrane potential regulation, single atom ion transport regulation, and response to lipopolysaccharides(Fig. 3B). The calcium signaling pathway, cAMP signaling pathway, HIF-1 signaling pathway, cell apoptosis, and MAPK signaling pathway are potential key signaling pathways regulated by TXL to exert CVD effects(Fig. 3C).

Table 5
The mechanism of action of Tongxinluo in relaxing blood vessels.

#	Models	Involved mechanisms	Signaling pathway	Pharmacological effects	Ref
1	SD rats: hypertensive model	↑: BKCa	↑: BKCa	Dilate blood vessels	[211]
2	Wistar rats: a model of hyperhomocysteinemia	↑: eNOS	PI-3K/Akt/HIF	endothelium-dependent vasodilation	[212]
3	hypertensive patients	↓: EMPs	–	endothelium-dependent vasodilation (FMD)	[213]
4	Type 2 diabetes patients with coronary heart disease	↓: ET-1, ↑: NO及NOS	–	Improving endothelial dilation function	[214]
5	Patients undergoing coronary intervention treatment	↓: CRP、ICAM-1 ↑: IL-10、NMD	–	Improving endothelial dilation function	[215]
6	New Zealand White Rabbit: Hyperlipidemia Model	↓: Blood lipid levels, Growth of microvasculature in arterial wall	–	Improving endothelial dilation function	[216]

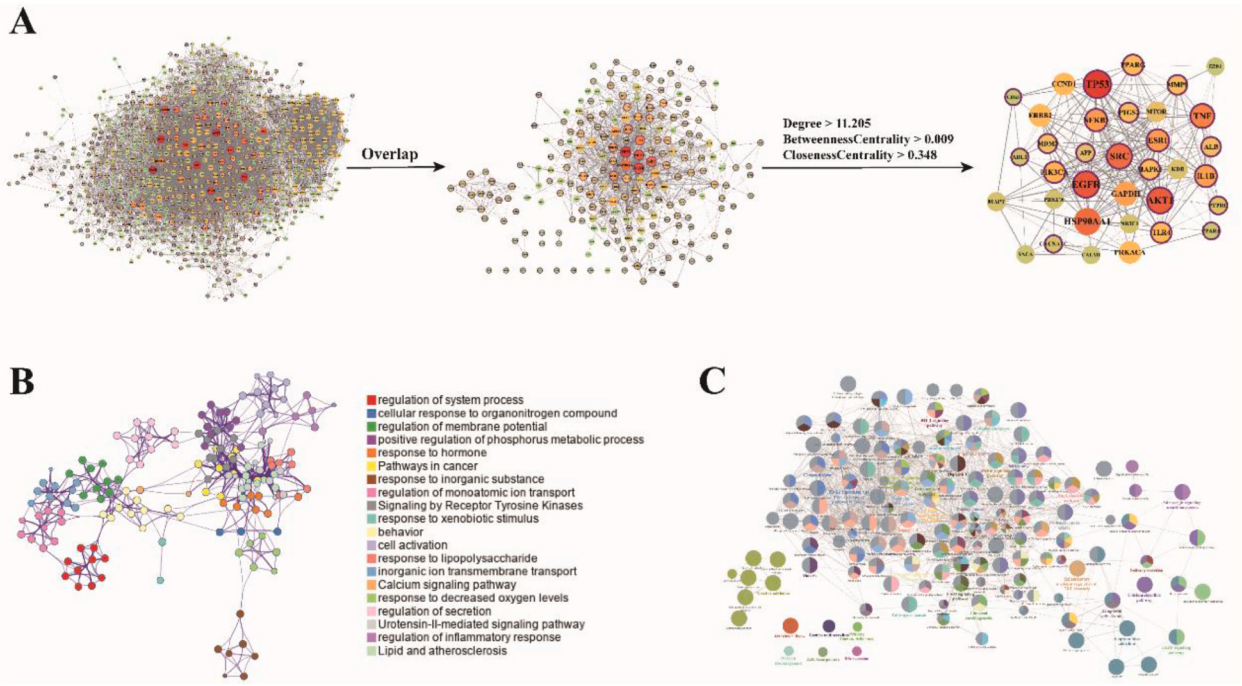

Fig. 3. The PPI network of cardiovascular diseases and the mechanism by which Tongxinluo exerts cardiovascular disease effects. (A) The key targets of cardiovascular disease PPI network and TXL's anti cardiovascular disease effects. Bioprocess and KEGG pathway enrichment analysis of targets regulated by TXL to exert anti CVDs effects.

5. Clinical research on the prevention and treatment of cardiovascular diseases through TXL

Retrieve Chinese and English databases such as PubMed, China Journal Full Text Database (CNKI), Wanfang Database, and VIP Chinese Science and Technology Journal Database (as of August 2023). Chinese search terms: "Tongxinluo", "Cardiovascular disease", "Randomized controlled clinical research", "Clinical controlled research", etc. English search terms: "Tongxinluo", "cardiovascular disease", "randomized double blind", "Clinical study", using subject words combined with free words for retrieval. A total of 2107 clinical literatures were obtained, including atherosclerosis, coronary angina, myocardial infarction, no reflow after PCI for acute myocardial infarction, coronary heart failure, coronary syndrome, etc. Atherosclerosis includes coronary atherosclerosis and carotid atherosclerosis.

5.1. Clinical study of TXL in prevention and treatment of atherosclerosis

Atherosclerosis is a chronic and progressive vascular disease, which is mainly caused by the thickening of the vascular wall and the formation of fibrous plaque caused by the lipid deposition of the arterial inner wall and inflammatory reaction. It is a common cardiovascular disease that mainly occurs in large and medium-sized arteries such as coronary arteries, carotid arteries, cerebral arteries, and lower limb arteries [236]. At present, some basic and clinical studies strongly indicate that TXL may have a strong anti atherosclerosis effect, but the evidence of large-scale clinical trials of TXL in treating atherosclerosis patients is still lacking.

The CAPITAL study is a multicenter, randomized, double-blind, parallel group, placebo-controlled clinical trial. In order to determine whether TXL can effectively delay the progression of carotid atherosclerosis, Zhang, M. et al. [237] conducted a CAPITAL study on 35 hospitals in 18 provinces of China. 1212 eligible patients were randomly divided into a TXL group and a placebo group, with 204 exfoliated patients removed, and the remaining 1008 participants, including 499 in the TXL group and 509 in the placebo group. The CAPITAL study of his team shows that in addition to conventional treatment, TXL treatment can delay the progress of carotid artery mean intima-media thickness (IMT), plaque area and vascular remodeling in subclinical carotid atherosclerosis patients, with good safety. Therefore, it is necessary to conduct further randomized clinical trials to confirm the long-term efficacy of TXL treatment in patients at high risk of cardiovascular events.

5.2. Clinical study on TXL in the prevention and treatment of angina pectoris

Angina Pectoris is a clinical syndrome characterized by paroxysmal chest pain or discomfort caused by insufficient coronary artery blood supply and sudden temporary ischemia and hypoxia of the myocardium. The coronary artery is a blood vessel that supplies the myocardium. When the coronary artery is narrowed or blocked, the myocardium will experience hypoxia, leading to chest pain [238].

In order to explore the efficacy indicators of TXL and KX in treating angina pectoris and determine the indications for traditional Chinese medicine Qi deficiency and blood stasis syndrome, Yan, S. Y. et al. [239] analyzed data from a multicenter, randomized, double-blind study in five centers in China. Their team randomly divided 239 patients with angina pectoris and qi deficiency and blood stasis syndrome into TXL group (119 cases) and KX group (120 cases) in a 1:1 ratio. Choose the effectiveness of angina and improvement in electrocardiogram (ECG) as treatment outcomes. The research results showed that after 4 weeks of treatment with TXL and KX, the effective rates were 43.70 % and 25.00 %, respectively. Serum low-density lipoprotein (LDL) levels have an impact on the therapeutic effect of TXL, and TXL has a higher effective rate for patients with low LDL levels. Heart rate affects the efficacy of KX in treating angina pectoris with Qi deficiency and blood stasis syndrome. KX has a higher effective rate for patients with a heart rate of 80 beats per minute. Therefore, the indications for TXL and KX in treating angina pectoris with Qi deficiency and blood stasis syndrome are low-density lipoprotein levels and heart rate, respectively.

5.3. Clinical study on TXL in the prevention and treatment of myocardial infarction

Myocardial infarction refers to a disease in which insufficient coronary artery blood supply leads to myocardial ischemia and necrosis. Myocardial infarction is usually caused by narrowing or obstruction of coronary arteries, resulting in insufficient blood supply to the myocardium and ultimately leading to myocardial cell death [240]. American Heart Journal: Acute ST segment elevation myocardial infarction (STEMI) remains a serious life-threatening event. Despite coronary artery revascularization, patients may still experience adverse outcomes due to myocardial non reperfusion and ischemia/reperfusion injury.

TXL has been preliminarily proven to reduce myocardial non reperfusion and ischemia/reperfusion injury. Xu et al. [241] further hypothesized that TXL treatment is also effective in reducing clinical endpoints in patients with acute ST segment elevation myocardial infarction (STEMI), Therefore, a randomized, double-blind, placebo-controlled, multicenter clinical trial was conducted on 3796 eligible STEMs from approximately 120 centers. All selected patients were orally administered 8 TXL or placebo and dual antiplatelet drugs upon admission, followed by 4 tablets three times a day until 12 months. This experiment evaluated the clinical efficacy and endpoint safety of oral TXL in reperfusion treatment of STEMI patients or patients with reperfusion deficiency. This research result is expected to validate and provide new evidence-based treatment options for myocardial non reperfusion and reperfusion injury, and may further improve the prognosis of STEMI patients during reperfusion.

5.4. A clinical study on TXL in the prevention and treatment of postoperative non reflow after PCI

Non reflow after percutaneous coronary intervention (PCI) refers to the failure of coronary artery blood flow to return to normal after PCI, resulting in the myocardium remaining in an ischemic state. This may be due to the incomplete dissolution or re formation of blood clots [242]. TXL is one of the preventive strategies for cardiovascular events after PCI and is widely used in China, but its effectiveness and safety have not been systematically evaluated.

No reflow after emergency percutaneous coronary intervention (PCI) in acute ST segment elevation myocardial infarction (STEMI) is associated with severe prognosis. In order to evaluate the therapeutic effect of TXL traditional Chinese medicine on non reflow and infarct size after STEMI emergency PCI, Zhang, H. T. et al. [243] conducted a randomized, double-blind, placebo-controlled, multicenter clinical trial involving 219 patients who underwent STEMI emergency PCI from 9 clinical centers. All patients were randomly divided into the TXL group and the control group, and were given TXL or placebo, aspirin, and clopidogrel in combination before emergency PCI. The research results show that TXL, as a traditional Chinese medicine, can significantly reduce myocardial non reflow and infarct size after STEMI emergency PCI in addition to conventional drug treatment.

In an experiment to observe the risk of no reflow during emergency coronary stent surgery and the impact on short-term prognosis in patients with acute myocardial infarction treated with TXL Capsules, Liu, J. L. et al. [244] randomly divided 120 patients with acute myocardial infarction into a TXL group and a non TXL group. The treatment group received TXL continuously for more than 1 week (2–4 capsules, 3 times a day) before surgery, while the control group did not receive TXL before surgery and underwent emergency stent implantation using conventional methods. The research results show that preoperative use of TXL does not reduce the incidence of no reflow during stent placement in acute myocardial infarction, but it can still improve forward coronary blood flow and improve heart function. In another clinical observation on the protective effect of TXL on no reflow after acute myocardial infarction reperfusion, as well as the long-term efficacy and safety evaluation of the drug, Gao, L [245]. selected 40 hospitalized patients with acute myocardial infarction and randomly divided them into a TXL group and a control group. The TIMI blood flow grading of the two groups of patients in no reflow after acute myocardial infarction reperfusion was compared. The research results show that TXL has a protective effect on the occurrence of no reflow after acute myocardial infarction reperfusion, helping to improve coronary artery forward blood flow, improve ventricular wall motion abnormalities, accelerate ST segment regression, and long-term use can reduce plasma brain natriuretic peptide levels, reduce left ventricular end diastolic volume, increase left ventricular ejection fraction, and improve heart function. The clinical effect is safe and effective.

Similarly, in order to investigate the impact of TXL on myocardial microcirculation and its long-term safety and effectiveness in patients without reflow after percutaneous coronary intervention (PCI), He, N. et al. [246] randomly divided 128 patients without reflow after PCI into two groups. The control group ($n = 63$) received standardized drug treatment, while the treatment group ($n = 65$) received oral TXL on the basis of standardized drug treatment. Compare the baseline clinical conditions between two groups, including intraoperative surgical procedures, inflammatory and oxidative stress indicators, cardiac function indicators, myocardial contrast-enhanced echocardiography images, and myocardial micro perfusion at 7, 30, and 90 days postoperatively. Follow up for 24 months was conducted on adverse cardiac events (MACE) and adverse reactions caused by the use of TXL capsules in patients. The

observation results show that early use of TXL in non reflow patients can reduce inflammatory response, inhibit oxidative stress, increase myocardial micro perfusion, improve heart function, and ultimately improve patient prognosis. Long term observation has good safety.

5.5. Clinical study on TXL in the prevention and treatment of coronary heart disease and heart failure

Heart failure refers to a disease in which the heart is unable to pump blood effectively, resulting in insufficient blood and oxygen supply to various organs of the body [247].

To systematically evaluate the clinical efficacy and safety of TXL in the treatment of heart failure, Zhu et al. [248] used computer searches on databases such as CNKI, Wanfang, and PubMed Library Clinical Controlled Trial Database. At the same time, reference materials for the included literature were screened, and randomized controlled trials (RCTs) of TXL in the treatment of heart failure were included according to the inclusion and exclusion criteria. Two evaluators will independently evaluate the quality of the literature, extract data, cross check, and finally conduct meta-analysis using RevMan5.3 software. A total of 27 research articles were included, all of which were Chinese literature. There were a total of 2222 heart failure patients, and 27 articles with a Jadad score of 1 were all Chinese literature. After using meta-analysis, it was found that the combination of TXL and Western medicine treatment can improve overall efficacy compared to conventional Western medicine treatment. The conclusion of this study is that compared with the simple Western medicine group, TXL can further improve clinical efficacy and have a certain effect on improving heart function in the treatment of heart failure. However, due to the low quality, limited length, and small sample size of the included articles, more high-quality and large-scale RCTs are needed for further validation.

5.6. Clinical study on TXL in the prevention and treatment of coronary syndrome

Coronary syndrome refers to a series of symptoms and signs caused by insufficient coronary blood supply, including angina, acute coronary syndrome, and myocardial infarction. The coronary artery is the main blood vessel supplying the heart. When the blood flow of the coronary artery is blocked, the oxygen supply to the myocardium is insufficient, leading to a series of cardiovascular symptoms [249].

Zhang et al. [250] conducted a multicenter, randomized, double-blind, placebo-controlled study on the role of TXL in patients with acute coronary syndrome (ACS) with high platelet reactivity (HPR) in 136 patients from three clinical research centers in China. All selected patients were randomized into two groups at three locations in China, with eligible patients receiving TXL or placebo for 1 year. The dosage used in this study was 3TXL or 3 placebo capsules, three times a day. Patients participated in follow-up appointments at 30 days of treatment and telephone follow-up at 180 and 360 days. Although the results of this experimental study showed that the difference in clinical endpoints between the TXL group and the placebo group was not significant in this study, the TXL group had better numerical values for ischemic events and the composite incidence of ischemic events and ST phase.

6. Conclusions

The innovative traditional Chinese medicine TXL developed under the guidance of the theory of traditional Chinese medicine collateral diseases has a solid theoretical foundation and precise clinical efficacy in the treatment of cardiovascular diseases, which is of great significance for improving the prevention and treatment of cardiovascular diseases with traditional Chinese medicine. TXL can be used to treat various cardiovascular diseases through multiple components, targets, and pathways, leveraging the advantages of comprehensive interventions such as blood protection, vascular protection, myocardial protection, stable vulnerable plaques, and vasodilation. This improves the problem of a single target of Western medicine, while reducing side effects and drug resistance. However, cardiovascular disease is a pathological development process involving multiple factors, and there are still some issues in the basic and clinical research of TXL, and its mechanism has not been fully elucidated. It is necessary to integrate systems biology, bioinformatics, computational biology, and pharmacogenomics to explore the potential interactions that occur during the overall treatment process. Based on widely adopted network pharmacology techniques, combined with chemical and therapeutic characteristics, a network correlation analysis was conducted on the dispersion mechanism information reported in the literature, providing a comprehensive understanding of the pharmacology of TXL in treating cardiovascular diseases from a systemic perspective. We hope that the systematic evaluation and prospective analysis in this article can also provide new directions and insights for the further research of TXL in the field of multi potency material basis and mechanism. With the improvement of research technology and the expansion of research fields, on the one hand, it is necessary to conduct more in-depth theoretical research, more experimental and clinical studies on TXL, and explore the mechanisms of multi-component, multi target, and multi pathway effects. On the other hand, it is necessary to further deepen and expand the therapeutic effect of traditional Chinese medicine on cardiovascular diseases, and provide broader treatment ideas for other difficult to treat cases in the cardiovascular event chain.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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