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Review article

Clinical effects and mechanisms of a Chinese patent medicine, Tongxinluo capsule, as an adjuvant treatment in coronary heart disease

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ABSTRACT

Coronary heart disease (CHD) is the leading cause of death globally, posing a serious threat to human health. However, the current treatment approaches available for CHD fall short of the ideal results. Tongxinluo (TXL) is a traditional Chinese medicine (TCM) that has been employed in the clinical treatment of cardiovascular and cerebrovascular diseases (such as angina pectoris, stroke, etc.) in China for many years and holds great potential as a prospective treatment. TXL either as a standalone treatment or in combination with interventions recommended in CHD guidelines has been shown to be effective and well tolerated in clinical trials for CHD. Drawing on the evidence from clinical trials and experimental studies, this review will focus on the cardiovascular protective properties and related mechanisms of TXL. By searching 8 Chinese and English databases, more than 4000 articles were retrieved. These articles were categorized, then read, and finally written into this review. In this review, the pharmacological properties of TXL include regulation of blood lipids, improvement of endothelial function, anti-inflammatory, antioxidant, inhibition of apoptosis and regulation of autophagy, anti-fibrosis, promotion of angiogenesis, and modulation of exosome communication. The information provided in this review will help the reader to comprehend better the insights that TCM has developed over time in practice and provide new perspectives for the treatment of CHD.

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of human mortality and ranks first in the global burden of disease. Over the last three decades, the number of people with CVD has doubled globally from 270 million to 520 million, and the number of deaths from CVD has steadily increased from 12.1 million to 18.6 million [1]. Population growth and aging are the main drivers of CVD growth.

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Abbreviations

AMI	acute myocardial infarction
ANGPTL	angiopoietin-like protein
CMECs	cardiac microvascular endothelial cells
CMs	cardiomyocytes
CVD	cardiovascular disease
CCS	chronic coronary syndrome
CTGF	connective tissue growth factor
CHD	coronary heart disease
ECs	endothelial cells
eNOS	endothelial nitric oxide synthase
HCMECs	human cardiac microvascular endothelial cells
H/R	hypoxic reperfusion
I/R	ischemia/reperfusion
MSCs	mesenchymal stem cells
MF	myocardial fibrosis
MI	cyocardial infarction
NO	nitric oxide
OS	oxidative stress
ox-LDL	oxidized low-density lipoprotein
PCI	percutaneous coronary intervention
TXL	Tongxinluo capsule
TCM	traditional Chinese medicine
TGF-β1	transforming growth factor-β1
TNF-α	tumor necrosis factor-α
UA	unstable angina
VEGF	vascular endothelial growth factor

Currently, China is experiencing the dual pressures of population aging and risk factor prevalence, and the incidence and prevalence of CVD are in a continuous rise. The number of people with CVD in China has been estimated to be approximately 330 million, among which 11.39 million diagnosed with coronary heart disease (CHD) [2]. According to the Yearbook of Health in the People's Republic of China 2019, CVD accounted for 46.66% of deaths in rural areas and 43.81% in urban areas, imposing heavy economic burdens on society and individuals. Therefore, it is imperative that prevailing cost-effective policies and interventions should be implemented as a matter of priority.

For thousands of years, traditional Chinese medicine (TCM) has been widely used in China for the prevention and treatment of diseases. Indeed, the essential contribution of low-cost TCM's in the fight against CVD among Chinese residents is undeniable compared to high-cost Western medicine, as the modernization process of TCM plays an increasingly critical role. In addition to China, TCM is not only popular in other parts of Asia, but is also used in some Western countries, including the United States and Australia [3, 4].

Thousands of clinical trials and experimental research articles on Tongxinluo capsule (TXL) have been published, including numerous meta-analyses summarizing the effectiveness and safety of TXL in patients with CHD [5–8]. However, the number of reviews about the specific mechanism of TXL for the treatment of CHD and its cardioprotective properties is scarce. In this review, we will focus on the cardiovascular protective properties of TXL in CHD and the potential mechanisms of its treatment (Fig. 1).

2. The constituents of TXL

TXL is a compound formulation based on choroidal theory proposed by academician Wu Yiling and manufactured by Yiling Pharmaceutical Co., Ltd. for the treatment of CVDs. It was approved by the Chinese Ministry of Health in 1996 as a new medication for the treatment of CHD and stroke (drug registration number Z1998015). According to the Chinese Pharmacopoeia 2010, the recommended dosage of TXL is 0.26 g/capsule, 2 to 4 capsules per time, three times daily. It is composed of natural ingredients from TCM, extracted from seven medicinal herbs (ginseng, red peony, sandalwood, incense, frankincense, sour jujube kernel, and borneol) as well as five medicinal herbs from animals (leech, scorpion, cicada slough, terrapin, and centipede). Although TXL is a mixture made of natural herbal ingredients, it contains many chemicals and compounds. By searching 8 databases (PubMed, Web of Science, EMBASE, the Cochrane Library, Wanfang, SinoMed databases, the VIP and the China National Knowledge Infrastructure), we retrieved more than 4000 articles and found that the number of published articles on the active ingredients of TXL was few and the tested herbs were incomplete. There are sporadic articles measuring the content of some compounds in TXL to provide a method for quality control [9]. In fact, most of the investigators have used network pharmacology to screen for key chemical components of TXL. For example, Wei and Jiang [10] used the TCMSP and BATMAN-TCM databases to screen 101 chemical components of TXL based on network

pharmacology. Li's study [11] gathered 111 chemical components in TXL prescriptions from TCMSP and TCMID databases. By comparison, we found that most of the compound components screened were similar, including flavonoids, terpenes, sterols, and phenols. All these compound components have been shown to possess anti-inflammatory and antioxidant properties and to contribute to cardiovascular protection. However, there were also some differences in the composition of the compounds, which may be explained by the fact that researchers used different databases as well as data processing methods for screening. In fact, the best way to obtain more accurate information on the biologically active components of TXL is to directly identify the compound components of TXL, which can lead to a better understanding of TXL from chemical substance to mechanism. Therefore, active ingredient identification of TXL is a worthwhile study to be conducted in the future.

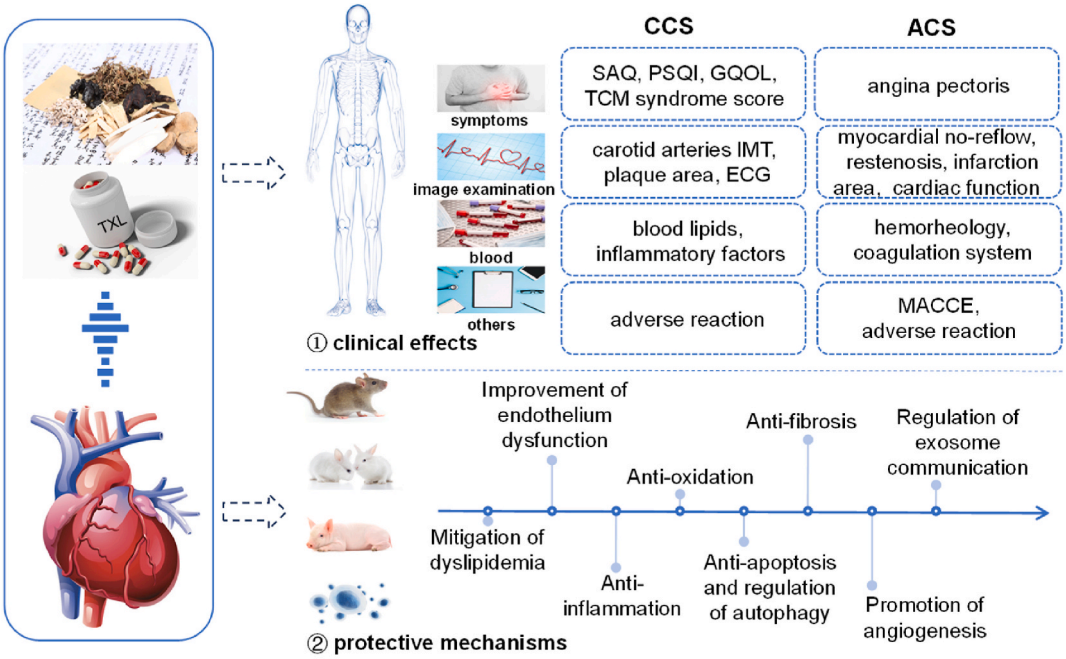
3. Clinical effects of TXL in coronary heart disease

3.1. Chronic coronary syndrome

In 2019, the European Society of Cardiology discarded the traditional concept of stable coronary heart disease and introduced the term chronic coronary syndrome (CCS) [12]. According to cardiovascular experts, CHD can remain stable for an extended period but may become unstable due to acute arterial thrombotic event resulting from plaque rupture or erosion. Therefore, to reduce the risk of CCS developing into acute coronary syndrome, controlling cardiovascular risk factors, modifying lifestyle, taking medications and performing revascularization are necessary. TCM, as an alternative medicine, has shown apparent clinical efficacy and fewer adverse reactions in CCS [13,14]. Correspondingly, TXL has demonstrated efficient therapeutic effects on CCS from various aspects (Table 1).

Angina is the most prominent manifestation of CCS. Clinical studies and meta-analyses have demonstrated that TXL in combination with conventional Western medications significantly ameliorates the symptoms of angina pectoris and improves their tolerability of activity in patients with CHD [15–22], manifesting predominantly as elevations in the Seattle Angina Scale score [23]. In addition, TXL has shown positive clinical effects in improving the TCM syndrome score [24], the pittsburgh sleep quality index score, as well as the global quality of life score [25].

ST-T segment elevation on the electrocardiograph is a gold standard indicator of myocardial ischemia in CHD. A study by D.J. Ou compared the effects of conventional treatment with conventional treatment + TXL in CHD patients with angina, which found that conventional treatment + TXL led to a significant reduction in electrocardiograph ST-segment depression compared to traditional treatment alone [26]. It is well known that CHD is primarily caused by atherosclerosis. The carotid artery is a window reflecting the health of the human blood vessels in the body. If lesions such as atherosclerotic plaque and lumen narrowing are present in the carotid artery, it means that the same lesions have occurred in other locations, especially in the cardiovascular. TXL has been shown to reduce



TXL, tongxinluo capsule; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; SAQ, seattle angina questionnaire; PSQI, pittsburgh sleep quality index; GQOL, global quality of life; TCM, traditional Chinese medicine; IMT, intima-media thickness; ECG, electrocardiography; MACCE, major adverse cardiovascular and cerebrovascular event

Fig. 1. Graphical abstract ① Clinical efficacy of TXL in symptoms, image examinations, blood tests and other aspects of CCS and ACS. ② The sketch of the mechanisms for cardioprotective effects of TXL.

Table 1
Clinical trials on the effects of Tongxinluo or Tongxinluo combined with Western medicine in the treatment of cardiovascular diseases.

Citation	Type of study	Type and number of subjects (observation group:control group)	Main observation indicators	Main findings
S. Van Hoang [15]	Open-label clinical trial	Stable ischemic heart disease, 300 Vietnamese patients	The frequency, duration and severity of angina pectoris, exercise time and MET	Reduction in frequency, duration and severity of angina pectoris attacks, improvement of exercise ability
R.T. Hou [21]	Randomized controlled trial	Coronary heart disease, 84 (42:42) patients	Exercise time, MET, RPP and ST-segment	Improvement of exercise tolerance and ST-segment depression
J.Q. Li [22]	Controlled before-after analyse	Coronary heart disease, 62 patients	Exercise time, MET, HR, ST-segment and blood lipids (TC, TG)	Improvement of exercise tolerance and ST-segment depression, lowering of blood lipid levels
S.P. Kang [23]	Randomized controlled trial	Stable angina, 80 (40:40) patients	SAQ and ST-segment	Improvement of angina symptoms and ST-segment abnormalities, enhancement of quality of life
X.H. Xing [24]	Randomized controlled trial	Coronary heart disease, 86 (42:44) patients	Angina symptoms, TCM syndrome score, electrocardiograph and blood lipids (TC, TG, LDL-C)	Relief of angina pectoris, improvement of electrocardiograph and blood lipids, decline of TCM syndrome score
M.W. Yang [25]	Randomized controlled trial	Coronary heart disease, 60 (30:30) patients	Angina symptoms, quality of life, quality of quality, electrocardiograph, cardiac function (LVEF, SV, CI, E wave AT) and blood lipids (TC, TG, LDL-C, HDL-C)	Relief of angina pectoris, enhancement of quality of sleep and life, modification of electrocardiograph and cardiac function, improvement of blood lipid levels
D.J. Ou [26]	Stratified randomized controlled trial	Stable angina, 97 (51:46) patients	The frequency, duration and severity of angina pectoris, ST-segment, and hemorheology (WBV, PV, FIB)	Improvement of angina pectoris and ST-segment depression, lowering of hemorheological parameters
M. Zhang [27]	Multicenter randomized double-blind parallel-group placebo-controlled study	Atherosclerosis, 1212 (607:605) patients	Carotid arteries IMT, plaque area, RI of the bilateral common carotid arteries, blood lipids (TC, TG, LDL-C, HDL-C), hs-CRP, and MACE	Delay of progression in carotid arteries IMT, plaque area and vascular remodeling
C. Huang [28]	Randomized controlled parallel-group trial	Coronary heart disease, 68 (34:34) patients	Blood lipids (TC, TG, LDL-C, HDL-C) and hemorheology (WBV, WBLSV, WBHSV, PV, HCT)	Enhancement of clinical efficacy, improvement of blood lipids and hemorheological parameters
Q.D. Zhang [29]	Non-randomized controlled trial	Ischemic heart disease combined with hyperlipidemia, 60 (30:30) patients	Blood lipids (TC, TG, LDL-C, HDL-C, ApoA, ApoB, ApoA/ApoB, Lp (a)) and ET-1	Improvement of blood lipid levels and endothelial function
L.X. Bao [30]	Randomized controlled trial	Ischemic heart disease, 126 (63:63) patients	Angina pectoris, electrocardiograph and hs-CRP	Inhibition of inflammation response, improvement of clinical efficacy
Y. Tian [31]	Randomized controlled trial	Coronary heart disease, 164 (83:81) patients	TNF-α, IL-1, IL-6 and CRP	Reduction of the inflammatory factor levels
Y.H. Ren [32]	Randomized controlled trial	Coronary heart disease, 42 (21:21) patients	Hemorheology (WBLSV, WBHSV, PV), blood lipids (TC, TG, LDL-C), adipocytokines (leptin, resistin, visfatin), inflammatory factors (CRP, TNF-α, IL-18, IL-4, IL-10, IL-37, sTREM-1, MFG-E8, MMP-9) and cardiac function (LVEF, E/A ratio)	Improvement of blood lipid levels and hemorheological parameters, inhibition of inflammation response, amelioration of the patient's illness state
P.K. Zhang [43]	Randomized controlled trial	Unstable angina, 80 (40:40) patients	Angina symptoms, blood lipids (TC, TG, LDL-C, HDL-C) and inflammatory factors (hs-CRP, TNF-α, IL-6)	Relief of unstable angina, improvement of blood lipid levels, reduction of inflammation factors levels
Y.Y. Jing [44]	Randomized controlled trial	Unstable angina, 84 (42:42) patients	Angina symptoms, electrocardiograph, blood lipids (TC, TG, LDL-C, HDL-C) and inflammatory factors (hs-CRP、IL-6)	Promotion of clinical efficacy ， improvement of blood lipids ， inhibition of inflammatory response
Q.P. He [47]	Randomized controlled trial	Unstable angina, 80 (40:40) patients	Angina symptoms, electrocardiograph and hemorheology (WBV, WBRV, PV, FIB, HCT)	Control of angina attacks, improvement of hemorheology
Q. Wang [48]	Randomized controlled trial	Unstable angina, 90 (45:45) patients	The frequency and duration of angina pectoris, and hemorheology (PV, FIB, HCT)	Promotion of clinical efficacy, control of angina attacks, improvement of hemorheology disorder
X.C. Li [49]	Randomized controlled trial	Unstable angina, 110 (55:55) patients	clinical effective rate, electrocardiograph, blood lipids (TC, TG, LDL-C, HDL-C) and the coagulation system (APTT, PT)	Improvement of clinical efficacy, regulating of blood lipid levels and coagulation function
H.L. Zhou [50]	Randomized controlled trial	Unstable angina, 60 (30:30) patients	clinical effective rate, PAI-1, 6-keto-PGF1α, TXB2	Improvement of the prethrombotic state, promotion of clinical efficacy

(*continued on next page*)

Table 1 (*continued*)

Citation	Type of study	Type and number of subjects (observation group:control group)	Main observation indicators	Main findings
Y.J. Yang [51]	Multi-center, randomized, double-blinded clinical trial	St segment elevation myocardial infarction, 3777 (1889:1888) patients	MACCE at 30 days (cardiac death, repeat MI, stroke or urgent revascularization) and secondary endpoints included 30-day rates of MACCE components, STEMI complications, 1-year MACCE, all-cause death, bleeding, rehospitalization rate and incidence of myocardial no-reflow	Improvement of clinical outcomes in patients with STEMI at 30-day and 1-year, lowering of sudden cardiac death and severe STEMI complications, high security
H.T. Zhang [52]	Randomized double-blind placebo-controlled multicenter clinical trial	Acute myocardial infarction, 219 (108:111) patients	Electrocardiogram and the infarct area	Significant reduction of myocardial no-reflow and infarction area
P.G. Zhang [53]	Randomized controlled trial	Acute myocardial infarction, 100 (50:50) patients	The number of cases with non-reflow, CTFC, LVEF and NT- proBNP	Faintly effectiveness in the treatment of no-reflow phenomenon in AMI stenting, significant promotion of forward coronary blood flow, enhancement of cardiac function
J.L. Liu [54]	Randomized controlled trial	Acute myocardial infarction, 120 (48,72) patients	The number of cases with non-reflow, CTFC, LVEF and NT- proBNP	Promotion of forward coronary blood flow, enhancement of cardiac function
Z.L. Yu [55]	Randomized controlled trial	Acute myocardial infarction, 120 (60:60) patients	TIMI classification, sCD40L, MMP-9, and inflammatory factors (CRP, IL-6)	Significant enhancement the classification of TIMI blood flow, reduction of sCD40L and MMP-9 levels, inhibition of inflammatory response
H.B. Xiao [56]	Randomized controlled trial	Coronary artery disease, 132 (62:70) patients	MACE, CRP	Decrease of the CRP level, improvement of clinical efficiency
Y. Kai [58]	Randomized controlled trial	Acs undergoing intracoronary stent placement, 72 (36:36) patients	Blood lipids (TC, TG, LDL-C, HDL-C), hemorheology (WBV, PV, FIB, HCT, platelet aggregation rate) and restenosis rate	Improvement of blood lipids and hemorheology, reduction of restenosis rate
Y. Zhang [59]	Randomized controlled trial	Patients undergoing percutaneous coronary intervention, 120 (60:60) patients	Restenosis rate and inflammatory factors (hs-CRP, IL-6, TNF-α)	Reduction of restenosis rate, lowering of serum inflammatory factor levels
M.X. Tang [60]	Randomized controlled trial	Patients undergoing percutaneous coronary intervention, 147 (77:70) patients	Restenosis rate and inflammatory factors (NF-κB, IL-6)	Inhibition of inflammatory response, prevention of restenosis
H.W. Lu [61]	Randomized controlled trial	Patients undergoing percutaneous coronary intervention, 180 (90:90) patients	Restenosis rate, recurrence of angina and MACCE	Prevention of restenosis, reduction of angina recurrence, decrease of MACCE rate

6-keto-PGF1α, 6-keto-prostaglandin F1α; AMI, acute myocardial infarction; ApoA, apolipoprotein A; ApoB, apolipoprotein B; APTT, activated partial thromboplastin time; CI, cardiac index; CRP, C-reactive protein; CTFC, corrected thrombolysis in myocardial infarction frame count; E wave AT, E wave acceleration time; E/A ratio, early to late peak diastolic mitral flow velocity ratio; ET, endothelin-1; FIB, fibrinogen; HCT, hematocrit; HDL-C, high density lipoprotein-cholesterol; HR, heart rate; hs-CRP, high sensitivity C-reactive protein; IL-1, interleukin 1; IL-10, interleukin-10; IL-18, interleukin 18; IL-37, interleukin-37; IL-4, interleukin-4; IL-6, interleukin 6; IMT, intima-media thickness; LDL-C, low density lipoprotein-cholesterol; Lp (a), lipoprotein (a); LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular event; MACCE, major adverse cardiovascular and cerebrovascular event; MET, metabolic equivalent; MFG-E8, milk fat globule-epidermal growth factor-factor 8; MMP-9, matrix metalloproteinase-9; NF-κB, nuclear factor kappa-B; NT-proBNP, N terminal pro brain natriuretic peptide; PAI-1, plasminogen activator inhibitor-1; PT, prothrombin time; PV, plasma viscosity; RI, remodeling index; RPP, rate pressure product (systolic blood pressure × heart rate); s 40L, soluble CD40 ligand; SAQ, seattle angina questionnaire; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; SV, stroke volume; TC, total cholesterol; TCM, traditional Chinese medicine; TG, triglycerides; TIMI, thrombolysis in myocardial infarction; TNF-α, tumor necrosis factor-α; TXB2, thromboxane B2; WBHSV, whole blood high shear viscosity; WBLSV, whole blood low shear viscosity; WBRV, whole blood reduced viscosity; WBV, whole blood viscosity.

carotid intima-media thickness, atherosclerotic plaque area, degree of vascular remodeling, and incidence of major cardiovascular events in the CAPITAL study of 1212 subjects carried out in 35 clinical centers across 18 provinces of China [27].

The doctrine of lipid infiltration is the mainstay of CHD caused by coronary atherosclerosis. Studies have shown that TXL has a positive impact on lipid metabolism in patients with CHD, reducing the levels of total cholesterol, triglycerides, low-density lipoprotein cholesterol, apolipoprotein B, and lipoprotein (a) [28,29]. Inflammation plays a critical role in the disease process of CHD. Numerous clinical trials have shown that TXL can decrease the levels of C-reactive protein, high sensitivity C-reactive protein, tumor necrosis factor-α (TNF-α), interleukin-1, interleukin-6 and interleukin-18, and increase the levels of interleukin-4 and interleukin-10 in patients with CHD, leading to a slower progression of inflammation [30–32]. Furthermore, experimental studies have shown that TXL significantly inhibits inflammation-related factors [33,34].

It is important to emphasize that while most studies obtained their conclusions by comparing the efficacy of conventional treatment versus TXL, they did not directly compare the efficacy of placebo versus TXL. However, this does not prevent us from concluding that TXL is efficacious for CCS.

3.2. Acute coronary syndrome

Acute coronary syndrome is a common and severe complication of CHD. It is a series of clinical syndromes characterized by rupture or invasion of coronary atherosclerotic plaques secondary to complete or incomplete occlusive thrombosis, including unstable angina (UA), non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction [35]. More than a decade ago, clinical studies [36,37] have shown that TXL is safe and effective for the prevention of cardiovascular and cerebrovascular events in patients with acute coronary syndrome. Subsequently, an experimental article [38] was published indicating that TXL can reduce lipid levels, inhibit inflammation, increase the stability of atherosclerotic plaques, and prevent their rupture.

3.2.1. Unstable angina

Several meta-analyses have reported that TXL in combination with routine angina management is effective in decreasing the risk of subsequent acute myocardial infarction (AMI), percutaneous transluminal coronary angioplasty, and coronary artery bypass graft surgery, reducing attacks and severity of angina pectoris, as well as improving ischemic symptoms and changes on electrocardiograph [39–41]. In addition to the above, TXL has been found to decrease the level of high sensitivity C-reactive protein and increase the levels of nitric oxide (NO) [5,42]. UA is mainly caused by plaque rupture and thrombosis, leading to partial or complete occlusion of the coronary arteries, resulting in myocardial ischemia and angina pectoris. TXL is effective in stabilizing plaque and inhibiting thrombosis. Excessive inflammatory responses and lipid levels are among the factors that promote plaque destruction. The combination of TXL with Western medicine can significantly suppress the inflammatory response and decrease blood lipid levels in patients with UA compared to Western medicine alone [43,44]. Hemorheological factors such as high blood viscosity and high platelet aggregation rate can also increase the risk of plaque rupture and thrombosis [45]. In contrast, TXL has been shown to improve hemorheological indicators, including whole blood viscosity, plasma viscosity, hematocrit, and fibrinogen in patients with UA [46–48]. Moreover, TXL can inhibit abnormal activation of platelets, which may help to control the activation and aggregation of platelets, ultimately preventing the formation of thrombus and the deterioration of UA. The coagulation-fibrinolytic system is intimately related to thrombosis, and imbalance in this system may lead to thrombosis-related diseases. TXL plays an essential role in enhancing coagulation function and promoting the balance of the coagulation-fibrinolytic system [49,50].

3.2.2. Myocardial infarction

Myocardial infarction (MI) is a cardiovascular event that poses serious threats to human life and is caused by the further deterioration of UA. In recent years, experimental animal models and clinical trials have demonstrated that TXL can effectively reduce the infarction area, shorten the recovery time after infarction, and improve the cardiac function in patients with CHD. A CTS-AMI trial [51] conducted in China showed that the addition of TXL to guideline-recommended basic therapy could significantly improve the short-term and long-term clinical outcomes of ST-segment elevation myocardial infarction patients, especially in reducing cardiac deaths and severe complications, without severe adverse reactions such as massive bleeding. The results of this trial validated the clinical efficacy and safety of TXL in patients with MI. Percutaneous coronary intervention (PCI) is a proven method of restoring myocardial blood supply, but failure to reflow in patients with MI treated with PCI is strongly associated with poor prognosis. Recent research [52] has shown that TXL + conventional medication can significantly reduce myocardial no-reflow and infarct size after emergency PCI treatment of ST-segment elevation myocardial infarction. At the same time, it has also been noted that TXL is less effective in reducing the no-reflow phenomenon during AMI stenting, but facilitates forward coronary blood flow [53,54]. In contrast, in patients with lower TIMI blood flow grades after PCI, postoperative administration of TXL can improve TIMI blood flow grades [55]. Xiao HB conducted a 6-month follow-up of patients taking TXL after PCI and found that the incidence of major adverse cardiovascular events was significantly reduced in the TXL group compared with the conventional treatment group, nevertheless, there was no significant difference between the two groups in terms of coronary artery restenosis [56]. However, it can be found that the combination of TXL and essential Western medicine can reduce the incidence and degree of coronary restenosis after PCI in other studies [57–61]. To evaluate the clinical application value of TXL after AMI reperfusion, the researchers concluded from a meta-analysis that the addition of TXL to secondary preventive medication was found to be effective in the treatment of patients after AMI reperfusion and could reduce the incidence of cardiovascular adverse events rate, the incidence of no-reflow, restenosis rate, lower inflammatory factors, low-density lipoprotein cholesterol levels, increase left ventricular ejection fraction and improve left ventricular remodeling and prognosis [7,62,63]. In general, the addition of TXL to essential treatment benefits patients with MI (Table 1).

4. Protective mechanism of TXL in treating coronary heart disease

4.1. Mitigation of dyslipidemia

Disorder of lipid metabolism is a high-risk factor for CHD and the major contributor to CHD, and reducing circulating lipids is of great significance for the prevention and treatment of CHD. As mentioned above, TXL has been documented to be effective in improving dyslipidemia in numerous clinical trials. The effect of TXL on lowering lipid levels has also been confirmed in experimental study [64]. Yu YH found from rabbits fed with high cholesterol diet that the mechanism of TXL lowering cholesterol and low-density lipoprotein levels might be related to the downregulation of the expression level of lectin-like oxidized low-density lipoprotein (ox-LDL) receptor-1 gene and protein in vascular intima, and the weakened binding of ox-LDL and lectin-like ox-LDL receptor-1 [65]. Similar conclusions were reached by Li YH through her research [66]. It has been observed that ApoE-/-mice have significantly elevated blood lipid levels, particularly cholesterol, compared to C57BL/6J wild-type mice [67]. Han's research showed that ApoE polymorphisms influence TXL intervention in CHD [68]. This implies that the mechanism by which TXL improves blood lipid levels may be related to gene polymorphisms affecting ApoE. ATP binding cassette transporter A1 and its regulator Retinoid X Receptor, play crucial roles in mediating HDL formation and cholesterol efflux from macrophages [69]. Studies have shown that TXL effectively reduces lipid levels, while upregulating mRNA levels and protein expressions of ATP binding cassette transporter A1 and Retinoid X Receptor [70,71].

4.2. Improvement of endothelium dysfunction

Coronary vascular endothelial dysfunction is a critical pathogenic factor in the development of CVD, and restoring and maintaining normal endothelial function is considered a potentially viable approach for the treatment of cardiovascular diseases. The vascular endothelial function includes several aspects, such as secretion of various active substances, including prostaglandin, NO, endothelin, thromboxane, etc., maintenance of vascular permeability, regulation of immune cell migration and accumulation, and prevention of thrombosis. A meta-analysis showed that TXL has a significant improvement in vascular endothelial function in patients with CHD [72].

Evidence shows that TXL can promote NO and prostaglandin production and reduce endothelin and thromboxane levels [73–78]. Researchers discovered that there was a correlation between endothelial barrier dysfunction and myocardial necrosis after myocardial ischemia/reperfusion (I/R) in mini-swine and TXL significantly improved endothelial barrier function, which was manifested as enhanced activities of PKA and endothelial nitric oxide synthase (eNOS), and increased expressions of eNOS, vascular endothelial-cadherin, β-catenin, and γ-catenin [79]. It concluded from an experiment that TXL could improve endothelium-dependent vasodilation by upregulating the expression of eNOS and increasing the content of NO in human umbilical vein endothelial cells through the PI3K/Akt/HIF-dependent signaling pathway [80]. In addition, Dai WD applied principal component analysis to compare the metabolic patterns of endothelial dysfunction rats and healthy control rats and found that the metabolic pathways of adenine, tryptophan, phenylalanine, riboflavin, and porphyrin were disturbed in endothelial dysfunction rats and that endothelin-1 and NO were improved in endothelial dysfunction rats after applications of TXL, suggesting that TXL may also improve endothelial dysfunction by regulating various metabolic pathways to restore the above substances to a normal state [81].

Vascular permeability is critical to maintaining vascular function and is affected by the connections between vascular endothelial cells (ECs). Vascular hyperpermeability due to altered connections between ECs has been associated with various CVDs, including CHD. After the endothelium damage, abnormalities in occludin, claudin, junctional adhesion molecule, and Zonula Occludens-1 appear in the endothelial cell-cell junction region, and these changes lead to upregulation of paraendothelial permeability, which manifested as increased intercellular substance transport [82]. In contrast, TXL can reverse the vascular hyperpermeability response caused by changes in EC connections, and the mechanism may be related to the activation of ERK1/2 in ECs [83]. There was a study that separately investigated the effects of TXL on the claudin protein family and found that a high dose of TXL increased the distribution and content of histone H3K9 acetylation in the claudin-9 gene promoter. It resulted in transcriptional activation of Claudin-9 and decreased endothelial permeability of human cardiac microvascular endothelial cells (HCMECs) [84]. Additionally, several studies have concluded that TXL can induce phosphorylation of Kruppel-like factor (for example, KLF4, KLF5) in HCMECs to increase the level of tight junction protein [85–87]. Vascular endothelial-cadherin and angiopoietin-like protein (ANGPTL) also provide barrier integrity to ECs. The PPARα signaling pathway is a possible mechanism by which TXL maintains the level of vascular endothelial-cadherin and promotes the expression of ANGPTL [88–91].

The von Willebrand factor and fibronectin expression in ECs can mediate the connection between vascular endothelium and platelet, promote platelet adhesion, activation, and aggregation, and participate in the coagulation process. TXL can inhibit the expression of von Willebrand factor and fibronectin in vascular ECs [92], but the specific mechanism of regulating these proteins has yet to be studied in depth. Vascular-cell adhesion molecule-1, intercellular adhesion molecule-1, β-catenin, and P-selectin are molecules or regulators representing endothelial adhesion function and TXL can regulate the expression of these molecules to reduce immune cell infiltration, platelet aggregation, and avoid inflammation and thrombosis [91,93].

In addition to all mentioned above, the research showed that the effects of TXL in attenuating HCMECs damage were similar to but better than that of peroxynitrite decomposition catalyst [94]. TXL can also protect against endothelial barrier breakdown caused during oxygen-glucose-serum deprivation and restoration under high glucose conditions partly via the PPAR-α/ANGPTL4 pathway [95]. In conclusion, these results suggest TXL achieves its protective effects on endothelial function through multiple pathways.

4.3. Anti-inflammation

The occurrence and development of CHD are closely related to the continuous inflammatory response, whether the CHD is in the early stage, already formed, or after treatment. Like soil "breeding" seeds, inflammation always affects the occurrence and development of CHD. The inflammatory factor is a core factor in the formation of atherosclerosis, which is the pathological basis of CHD. TXL has been proven to inhibit mRNA and protein expression of common inflammation-related factors such as NF-κB, TNF-α, interleukin-6, and other inflammatory factors in experiments [96]. Dendritic cells play a pathogenic role in immune processes associated with the pathological formation of atherosclerosis. TXL could significantly reduce the maturation-associated markers induced by ox-LDL, such as CD40, CD86, CD1a, and human leukocyte antigen-DR, as well as the secretions of cytokine interleukin-12 and TNF-α by silencing PPARγ expression in dendritic cells [97]. NF-κB also plays a crucial role in cellular inflammatory and immune responses. Multiple studies [89,98] have shown that TXL has an apparent inhibitory effect on the release of interleukin-1β and TNF-α induced by the activation of NF-κB, alleviating the inflammatory response in CHD as well as I/R-induced inflammatory endothelial damage. In addition to directly reducing the level of inflammatory factors, TXL also shows superior characteristics in the aggregation of inflammatory cells, inhibiting the expression of monocyte chemoattractant protein-1 and intercellular adhesion molecule-1 and reducing the chemotaxis of inflammatory cells to the site of endothelial injury [73]. For myeloid-derived macrophages, TXL can inhibit the expression of miR-155 mediated by Akt1 and block the feedback loop between miR-155 and TNF-α, which in turn play an important role in vasoprotection [99]. In addition, there are numerous experiments confirming the anti-inflammatory mechanism of TXL, such as inhibition of the NLRP3 inflammatory pathway [100] and regulation of the TLR2/TLR4 – NF-κB pathway [101].

4.4. Anti-oxidation

Oxidative stress (OS) is one of the most critical pathological factors contributing to endothelial injury.In addition to participating in the formation of atherosclerosis in the early stage of CHD, OS can also cause platelet aggregation, which is the basis for the formation of CHD and a crucial catalyst for the development of CHD. Superoxide dismutase and maleic dialdhyde are essential indicators of OS status in the body, which can indirectly reflect the severity of OS in CHD. TXL can attenuate OS damage to a certain extent [102]. TXL can inhibit the elevated levels of ROS and maleic dialdhyde and the decreased Superoxide dismutase activity caused by OS, both at the cellular level, animal level and in clinical patients [96,103–108]. Wu XL found that TXL pretreatment could abrogate the up-regulation of ROS and maleic dialdhyde induced by C16, and its antioxidant effect may be related to inhibiting the expression of p22 (phox), p47 (phox), and HO-1 in HCMECs [98]. The study have also observed that TXL inhibition of angiotensin II-induced vascular oxidative injury is associated with the reduction of NADPH oxidase subunit P22 (phox) [109]. In addition, other studies have shown that TXL inhibits OS and enhances intracellular antioxidant capacity through the AMPK [110] and the ppar-γ pathway [103], which in turn improves endothelial function. In summary, these results reasonably explain the TXL-mediated cardiovascular protective effect.

4.5. Anti-apoptosis and regulation of autophagy

The relationship between cardiomyocyte apoptosis and CHD is currently widely studied, especially in the development of MI, where apoptosis is an essential factor involved. Inhibition of myocardial apoptosis can help prevent the occurrence or reduce the severity of MI. TXL can increase the phosphorylation level of AMPK/mTOR, upregulate the expression of autophagy protein LC3, and downregulate the expression of apoptotic proteins Bax and caspase-3. However, these effects are canceled when the AMPK inhibitor is added, demonstrating that the protective effect of TXL in AMI model rats is related to inhibiting myocardial cell apoptosis and promoting myocardial autophagy, which may occur through the AMPK signaling pathway [111,112]. Myocardial apoptosis induced by I/R or hypoxic reperfusion (H/R) is the predominant cause of sustained myocardial injury after MI. TXL can regulate the expression of eNOS and apoptotic proteins (Bcl2, Bax, caspase-3) in returnee and non-returnee myocardium through the PKA signaling pathway to reduce I/R injury and myocardial cell apoptosis [113,114]. The miR-128-3p/p70s6k1 signaling pathway is also involved in protective effect of TXL against human cardiac myocytes apoptosis during I/R [115]. Autophagy, specifically mitophagy, is an important mechanism of mitochondrial quality control. It is activated to remove damaged or aged mitochondria, maintain a healthy mitochondrial pool, and finally sustain the physiological function of cells. Recent research shows that TXL ameliorates myocardial ischemia reperfusion injury by activating PINK1/Parkin-mediated mitochondrial autophagy in model rats [116].

Currently, most studies have focused on the effects of I/R or H/R injury on myocardial cells, and only a few studies have been conducted on vascular ECs, which play an important role in the maintenance of normal cardiovascular function. Therefore, the I/R-induced or H/R-induced EC injury and vascular damage should not be neglected. In I/R-injured ECs, TXL was found to upregulate six proteins and downregulate five proteins. These proteins are crucial in cell proliferation, stress response, and metabolic regulation [117]. I/R had a significant impact on the induction of autophagy in cardiac microvascular endothelial cells (CMECs), as evidenced by an increased number of monotansine positive cells, increased formation of autophagosomes, and a higher ratio of type II to type I light chain 3. 3-methyladenine induced autophagy is associated with pro-apoptosis. In contrast, rapamycin-induced autophagy is connected with anti-apoptosis. Comparing 3-methyladenine, rapamycin, and MEK inhibitor PD98059, Cui HH found that autophagy is a protective mechanism for CMECs against I/R injury, and that TXL can promote the aforementioned autophagic response in a dose-dependent manner by activating the MEK/ERK pathway [118]. Besides, the RISK pathway [119] and the JAK/STAT pathway [120] have also been shown to be possible mechanisms by which TXL protects HCMECs from H/R injury.

In addition to the above mentioned signaling pathways, the secretory function of CMECs is also vital for antagonizing H/R injury-induced apoptosis. A study has elucidated the paracrine function of CMECs in I/R injury and also introduced the protective mechanism

of TXL [121]. Cui HH also observed the regulatory role of paracrine function of CMECs under H/R conditions. Their finding suggests that the mechanism of TXL inhibiting apoptosis of CMEC after H/R is related to the factors affiliated with proliferation, growth, and differentiation secreted by ECs [122]. It has also been confirmed in other literature that TXL inhibits the apoptosis of CMECs induced by H/R and is accompanied by significant changes in the concentration of cytokines secreted by CMECs, such as Human Heme Oxygenase 1, angiopoietin 2, sequestosome1 and connective tissue growth factor (CTGF), and these factors have been reported as an important player in the regulation of cell proliferation, stress response, metabolism. This result again suggests that TXL anti-apoptosis may be achieved by regulating the secretory function of ECs [123].

The effect of TXL on the antagonism of apoptosis is also reflected in the prevention and treatment of CHD. Macrophage apoptosis plays a vital role in secondary plaque necrosis. Chen YF et al. found that TXL can inhibit ox-LDL-induced apoptosis of macrophages, increase the expression of Beclin-1, and promote the dissociation of Bcl-2 Beclin-1 complex through enhanced autophagy [124,125], thereby stabilizing plaques and avoiding the occurrence of thrombotic cardiovascular events. For decades, researchers have considered stem cell transplantation as a potential therapeutic approach that can truly promote the repair and regeneration of infarcted myocardium and reverse the decline in heart function. A growing number of studies are being conducted to investigate the feasibility of bone marrow mesenchymal stem cells (MSCs) for the treatment of MI. Bone marrow MSCs are expected to provide great potential for the treatment of MI. However, the actual therapeutic effect of MSCs is not satisfactory due to the bottleneck problem of the low survival rate of transplanted cells. Owing to this contradiction, researchers are still exploring ways to improve the survival rate of MSCs. Until now, multiple studies have shown that TXL can protect MSCs from hypoxia and serum deprivation through MEK/ERK1/2 pathway and AMPK/eNOS pathway and reduce the apoptosis of MSCs [126–128]. This result provides some possible explanations for the protective mechanism of TXL on the survival of MSCs.

4.6. Anti-fibrosis

Following the death of myocardial cell caused by ischemia, hypoxia, or other stimuli, the resulting void is often filled with the extracellular matrix, ultimately forming scar tissue. Subsequently, it can lead to myocardial fibrosis (MF) and structural changes in the heart, which in turn affect heart function and reduce quality of life for patients, even to the point of being life-threatening. TXL can reduce interstitial fibrosis after MI [129,130]. Endothelial-to-mesenchymal transition is an important mechanism of MF and TXL can reduce MF after AMI by inhibiting endothelial-to-mesenchymal transition and activating NRG-1/ErbB-PI3K/AKT signaling cascade [131]. In addition, it was shown that TXL can inhibit MF by reducing the expression of transforming growth factor-β1 (TGF-β1) and CTGF, improve the left ventricular structure of MI model rats, and protect heart function by a mechanism related to the inhibition of the Hif/1α/TGF-β1/Smad2/CTGF signaling pathway [132,133]. Collagen is a common type of collagen in myocardial tissue, and its high expression may exacerbate MF [134]. Therefore, interventions to regulate collagen synthesis and degradation may be one of the potential strategies for the treatment of MF. It was observed that collagen I, collagen III, and TGF-β1 levels were decreased in patients with stable angina pectoris in the treatment of TXL compared with the control group [135]. At the animal level, TXL can shrink the thickness of rat myocardial basement membrane, reduce the density of collagen I and collagen IV, and thus improve the left ventricular myocardial morphology and inhibit myocardial collagen remodeling [34]. This suggests that regulating collagen synthesis and degradation may also be one of the anti-fibrosis mechanisms of TXL.

4.7. Other novel mechanisms

4.7.1. Promotion of angiogenesis

In the treatment of myocardial infarction, promoting myocardial tissue repair and angiogenesis is an important strategy. TXL is a Chinese patent medicine proven to promote angiogenesis. It has been observed that the coronary-artery-ligation-induced MI rabbits model appeared to have compensatory angiogenesis at six weeks postoperatively, and the application of TXL resulted in a significant increase in the number of capillaries and a corresponding decrease in infarct size [130,136], indicating that TXL has a role in promoting angiogenesis. EC proliferation plays a vital role in the formation and repair of blood vessels and is one of the critical steps of angiogenesis. Many growth factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor, TGF-β, and multiple signaling pathways interacting can facilitate this process. Various studies have demonstrated that TXL can promote the "proliferation", "migration", and "tube formation" of CMECs and act like a vascular bypass, and the mechanism may be related to the up-regulation of VEGF and basic fibroblast growth factor expression [33,137,138]. Besides, activation of the Notchl/Jaggedl/VEGF signaling pathway, promotion of microangiogenesis at the edge of infarction, and increase in microvascular maturation rate may also be the mechanism by which TXL improves myocardial blood supply [133]. In addition, TXL can activate important factors of the angiogenic pathway in MI mice, such as PI3K/AKT, ERK, HIF-1α, VEGF, and *p*-eNOS, thus suggesting that its protective effect on the heart may be accomplished through the activation of the angiogenic signaling pathway [139]. Further analysis revealed that the SDF-1a/CXCR4 system is vital in mobilizing and recruiting endothelial progenitor cells to promote angiogenesis after MI.

4.7.2. Regulation of exosome communication

As described in 4.5, MSCs are the most promising candidates for the treatment of AMI. However, the low retention and survival rates of MSCs in ischemic hearts limit their therapeutic effectiveness. Thus, researchers speculate that regulating the balance between MSCs and ischemic myocardium and promoting the survival of transplanted MSCs may resolve this contradiction. Previous research has found that combined application with TXL can significantly reduce MF and inflammatory cell infiltration with more surviving myocardia than direct transplantation of MSCs, suggesting that TXL may achieve the above effects by improving the transplantation

microenvironment of MSCs [140], nevertheless, the specific mechanism needs to be further explored. Subsequently, experiments have confirmed that the signaling of exosomes between MSCs and other cells may be the key for TXL to play its role. CXCR4 is a cytokine that plays a vital role in the homing of stem cells, mediating the homing of stem cells to damaged tissues. Researchers injected exosomes from MSCs intramyocardially into the infarcted heart in AMI rats on the third day followed by intravenously infused MSCs and found that the expression level of CXCR4 increased, which promoted the homing and retention of MSCs and reduced the occurrence of apoptosis. The cardiac repair effect after MI was more obvious if TXL were used to pretreat MSC [141]. Further exosomal miRNA analysis suggested that miR-146a-5p was a participant in the superior effect of MSCs (TXL) -exo, as exosomal miR-146a-5p could target IRAK1 reduction and inhibit nuclear translocation of NF-κB p65, thereby protecting rat cardiomyocytes from hypoxia-induced injury [142]. These results show that TXL plays a positive role in the transfer of exosome miR-146a-5p through the IRAK1/NF-κB p65 pathway to facilitate cardiac repair.

It has been observed that TXL can reduce the apoptosis rate of CMECs from 43% to 34% after H (18h)/R (2h). The degree of apoptosis inhibition of MECs is more significant (from ~44% to ~20%) when TXL pretreated cardiomyocytes (CMs), which are co-cultured with MECs after H/R. In addition to direct inhibition of MECs apoptosis through some mechanisms, TXL may also achieve a protective effect on MECs by promoting the secretion of certain substances by pretreated CMs that can be eliminated by exosome release inhibitors (GW4869) [143]. Further study has shown that TXL can stimulate CMs to release exosomes, which contain high levels of long intergenic non-protein-coding RNA and reprogramming regulators (Linc-ROR). After the uptake of Linc-ROR by CMECs, linc-ROR activates the eNOS pathway by promoting the expression of p145s5k70 in cells to downregulates mir-6-1P [144]. eNOS secreted by CMECs contributes to improve the survival of CMECs and CMs, thereby alleviating myocardial ischemia reperfusion injury.

5. Safety concerns of TXL

The reported rate of TXL adverse reactions recorded by the Chinese National Adverse Drug Reaction Monitoring System was approximately 5.6/100,000, belonging to a rare adverse reaction [145]. This data confirms the safety of TXL in clinical practice. Although less frequent and mild, some adverse events with TXL have been reported, including mild abdominal pain, bloating, nausea, and rash [146,147]. These adverse reactions can be alleviated and eliminated by dose reduction, adjustment of administration schedule, and symptomatic treatment [5]. In general, TXL has played a beneficial role in the treatment of CHD, both in animal studies and in various clinical trials, where it has been shown to have relatively safe properties [148].

6. Conclusions and perspectives

In summary, TXL has good effectiveness and safety for the prevention and treatment of CHD at different stages, such as reducing cardiovascular events, slowing disease progression, relieving patients' pain, and improving pathological indicators. In terms of mechanism, TXL can participate in the whole process of CHD treatment, from regulating blood lipids to improving endothelial function, anti-inflammatory, antioxidant, and other aspects. Anti-apoptosis and regulation of autophagy, anti-fibrosis, angiogenesis promotion, and exosome communication regulation are mainly protective mechanisms for TXL against MI. This shows that TXL is a multi-component, multi-target Chinese medicine preparation with a possible broader range of uses compared with single-target Western medicine.

It should be noted that most of the clinical trials mentioned in this paper were conducted in China with limited sample sizes, so the efficacy and safety of TXL will still need to be revalidated through high-quality, large-scale, multicentre, and randomized controlled clinical trials in the future. In accordance with the above results, the combination of TXL with basic Western medicine for CHD is an important direction to improve the curative effect. However, due to the multi-component nature of TXL, many target mechanisms in CHD are not fully understood. Until now, most studies on the protective mechanism of TXL against CHD have detected the effects of TXL on disease phenomena and downstream effector molecules, without exploring the key upstream signaling pathway by which TXL affects disease progression, resulting in a certain ambiguity of TXL functional signal network. Therefore, it is necessary to conduct further molecular, cellular, and animal studies in the future to elucidate its multidrug ecological characteristics and specific pathways of cardiac protection mechanism, to lay a reliable theoretical foundation for the therapeutic potential of TXL in cardiovascular protection and to provide a new perspective for the development of other TCM.

Ethics statement

Review and approval by an ethics committee was not needed for this study because this was a literature review and no new data were collected and analysed. For the same reason, informed consent was not required.

Additional information

No additional information is available for this paper.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Jing Wang: Writing – original draft. **Tian Li Li:** Writing – original draft. **Pei Fen Chang:** Writing – review & editing. **Yu Qian Gao:** Visualization. **Jia Sai Fan:** Visualization. **Chen Hao Zhang:** Funding acquisition. **Hai Yan Zhu:** Writing – review & editing.

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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