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Review article

A Chinese classical prescription Xuefu Zhuyu decoction in the treatment of coronary heart disease: An overview

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ABSTRACT

Background: Coronary heart disease (CHD) is the leading cause of morbidity and mortality worldwide and is a hot topic in cardiovascular disease research. Western medicine treats CHD with stent implantation, anti-angina pectoris, anti-platelet aggregation and other operations or drugs. According to the whole concept and the characteristics of syndrome differentiation, traditional Chinese medicine (TCM) treats CHD according to different syndromes and points out that qi deficiency and blood stasis are the basic pathogenesis of CHD. Xuefu Zhuyu Decoction (XFZYD), as a classic prescription of TCM, has certain value in the treatment of CHD, with the effects of promoting qi, activating blood circulation, dredging collaterals and relieving pain. In addition, it also exhibits advantages in high efficiency, low toxicity, high cost performance, few side effects, and high patient acceptance.

Objective: The therapeutic effect and mechanism of XFZYD in the treatment of CHD were searched by literature search, and the components and targets of XFZYD in the treatment of CHD were analyzed by computer simulation technology for molecular docking, providing theoretical basis for clinical treatment of CHD.

Method: This study comprehensively searched CNKI, Wanfang, VIP, CBM, Pubmed, Embase, Web of science and other databases, included clinical studies with efficacy evaluation indicators in hospitals according to randomization, and excluded literatures with low quality and no efficacy evaluation indicators. Clinical cases and studies, molecular mechanisms and pharmacological effects of XFZYD in the treatment of CHD were searched, and the effective ingredients and core targets of XFZYD in the treatment of CHD were docked through molecular docking, providing theoretical support for clinical treatment of CHD.

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Results and Conclusion: Through this study, we found that XFZYD has a significant therapeutic effect in the clinical treatment of coronary heart disease, which can play a role in the treatment of CHD by inhibiting atherosclerosis, inhibiting cardiovascular remodeling, improving oxidative stress damage, improving hemorheology, improving myocardial fibrosis and other mechanisms. Through computer simulation, it was found that the main effective components of XFZYD treatment for CHD were quercetin, kaempferol and luteolin, and the key core targets were IL6, VEGFA and P53, and each component had a high VEGFA libdock score. It is speculated that VEGFA is the key target of XFZYD in the treatment of CHD. Kaempferol and VEGFA had the highest libdock score. kaempferol and IL6 have the highest number of hydrogen bonds, kaempferol and IL6 have the highest number of hydrogen bonds, which indicates that they are most stable, indicating that kaempferol is the key component of XFZYD in the treatment of CHD, which provides a theoretical basis for follow-up experimental research.

1. Introduction

Coronary atherosclerotic heart disease (CHD) is caused by narrowing or obstruction of the vascular lumen due to atherosclerotic (AS) lesions in the coronary vessels, resulting in myocardial ischemia, hypoxia, or necrosis. CHD is the leading cause of human death worldwide [1–3]. Various factors such as lipid metabolism disorders, chronic inflammation, endothelial cell dysfunction, and immune dysfunction can promote atherosclerosis and lead to CHD [4]. CHD belongs to the category of chest obstruction in TCM, and its main pathogenesis is heart vein obstruction, which belongs to the diseases of deficiency of vital energy. The basic pathogenesis of CHD is qi deficiency and blood stasis, and its pathological factors are mainly associated with blood stasis, blood, and phlegm [5–8]. The movement and balance of qi are crucial to maintaining the health of the body. In traditional Chinese medicine treatment, restoring the health of the body by adjusting the movement and balance of qi is an important therapeutic principle. Blood is rich in nutrition, can fill the viscera, and plays a role in nourishing and nourishing the tissues and organs. Only with sufficient qi and blood can the heart perform its normal function.

XFZYD was first found in “Medicine Forest Correction”, a modified prescription of Sini Powder and Taohong Siwu Decoction written by Wang Qingren, a famous doctor in the Qin dynasty. XFZYD is one of the most widely used prescriptions for promoting blood circulation and removing blood stasis in TCM clinical practice, and its efficacy has been confirmed by clinical studies. XFZYD is composed of 12 g of Persicae Semen, 9 g of Flos Carthami, 9 g of Radix Angelicae Sinensis, 9 g of Radix Rehmanniae Preparata, 6 g of Paeoniae Radix Rubra, 9 g of Radix Achyranthis Bidentatae, 3 g of Radix Bupleuri, 4.5 g of Rhizoma Chuanxiong, 4.5 g of Radix Platycodonis, 6 g of Fructus Aurantll Immaturus and 6 g of Radix Glycyrrhizae [9] (Fig. 1, Table 1). It has the effects of promoting qi, activating blood circulation, dredging collaterals and relieving pain, and is a classic prescription for the treatment of CHD. Persicae

Fig. 1. Composition of XFZYD.

Table 1
Composition of XFZYD.

Drug Names	Botanical Name	Family name	dosage (g)	Part Used
Persicae Semen	*Prunus persica*	*Rosaceae*	12	Seed
Flos Carthami	*Carthamus tinctorius*	*Compositae*	9	flower
Radix Angelicae Sinensis	*Angelica sinensis*	*Umbelliferae*	9	Root
Radix Rehmanniae Preparata	*Rehmannia glutinosa*	*Scrophulariaceae*	9	Root
Paeoniae Radix Rubra	*Paeonia lactiflora*	*Buttercup*	6	Root
Radix Achyranthis Bidentatae	*Achyranthes bidentata*	*Amaranthaceae*	9	Root
Radix Bupleuri	*Bupleurum chinense*	*Umbelliferae*	3	Root
Rhizoma Chuanxiong	*Ligusticum chuanxiong*	*Umbelliferae*	4.5	Rhizome
Radix Platycodonis	*Platycodon grandiflorum*	*Campanulaceae*	4.5	Root
Fructus Aurantll Immaturus	*Citrus aurantium*	*Rutaceae*	6	Fruit
Radix Glycyrrhizae	*Glycyrrhiza uralensis*	*Leguminosae*	6	Root and rhizome

Semen, Flos Carthami, Radix Angelicae Sinensis, Rhizoma Chuanxiong and Paeoniae Radix Rubra activeblood circulation and remove blood stasis. Radix Angelicae Sinensis and Radix Rehmanniae Preparata show the function of nourishing blood and removing blood stasis. Radix Bupleuri and Fructus Aurantll Immaturus could soothe the liver and regulate qi. Radix Achyranthis Bidentatae breaks the stasis through the channel, causing the stasis blood downward; Radix Platycodonis opens lung qi and draws medicine up; Radix Glycyrrhizae is slow and urgent, harmonizing various medicines, and playing the work of activating blood and regulating qi. It was judged as strong recommendation level evidence in the newly issued "Guideline for Diagnosis and Treatment of Coronary Heart Disease with Stable Angina Pectoris" [10].

The therapeutic effect of XFZYD on CHD has also been confirmed by clinical studies. To further study the effect mechanism of XFZYD on CHD and explore the effective chemical components in each component of XFZYD, this paper summarizes and analyzses the clinical study, pharmacological effects, molecular mechanism, chemical components and core targets of XFZYD in the treatment of CHD. This study may provide a theoretical basis for the clinical application of XFZYD in the treatment of CHD.

2. Clinical study of XFZYD in the treatment of CHD

2.1. Clinical experimental study of XFZYD in treating CHD

Clinical studies have shown that XFZYD is effective in the treatment of CHD, whether used alone, XFZYD plus or minus formula, or in combination with other drugs (Table 2).

A total of 118 patients with stable angina pectoris of the heart-blood stasis type were randomly divided into a treatment group (Xuefu Zhuyu Pills + Nicorandil) and a control group (nicorandil). After 3 courses of treatment, the total effective rate of the treatment group was 91.52% (54/59), which was higher than the 76.27% (45/59) of the control group. After treatment, the whole blood viscosity (high shear), plasma viscosity, erythrocyte deformation index, fibrinogen level and vascular endothelin-1 (ET-1), vascular endothelin-1 (Hcy), and cardiac troponin T (cTnT) levels in the two groups were lower than those before treatment, and the incidence of adverse reactions was 13.56% (8/59) in the treatment group and 10.17% (6/59) in the control group. The results showed that Xuefu Zhuyu Pills were effective in treating stable angina pectoris of CHD with heart-blood stasis, which could improve hemorheology and reduce ET-1, Hcy and cTnT levels, with good therapeutic safety [11].

In addition, Lai et al. found that modified XFZYD could reduce the time and frequency of angina pectoris, down-regulate the levels of serum soluble intercellular adhesion molecule-1 (sICAM-1), ET-1 and interleukin-6 (IL-6), up-regulate the levels of serum superoxide dismutase (SOD) and interleukin-10 (IL-10), reduce hemorheological parameters such as plasma hematocrit, high whole blood viscosity, and plasma viscosity in patients with stable angina pectoris of phlegm-blood stasis type CHD, and its total effective rate in the treatment of CHD was as high as 95.24% (60/63), indicating that modified XFZYD treatment helps to promote Th1/Th2 balance, reduce the inflammatory response, regulate hemorheology, improve angina pectoris attack, and improve the clinical efficacy of CHD [12].

Another study randomly divided 94 patients with CHD into a control group (conventional western medicine treatment) and an observation group (conventional western medicine treatment + XFZYD). After 1 month of treatment, the angina pectoris efficacy and electrocardiogram (ECG) efficacy in the observation group were 93.62% and 91.49%, respectively, which were higher than the 78.72% and 74.47% in the control group. After treatment, the frequency and duration of angina pectoris, TCM syndrome score, left ventricular ejection fraction (LVEF), stroke volume (SV), cardiac index (CI) and the baseline of hemorheology in the two groups were better than those before treatment, and the change range in the observation group was better than that in the control group, indicating that XFZYD has a significant effect in the treatment of CHD, can effectively reduce the TCM syndrome score, improve cardiac function and reduce blood viscosity [13].

Clinical researchers who used XFZYD in patients with CHD found that TCM syndrome scores decreased, high density lipoprotein cholesterol (HDL-C) levels increased, and total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), MCP-1, TXB2, and hs-CRP levels decreased, indicating that XFZYD can improve blood lipid levels, reduce the expression of MCP-1, TXB2, and hs-CRP, improve the therapeutic effect, and reduce nitroglycerin dosage in patients with CHD [14]. Li Shu et al. found that the effective rate of XFZYD in treating CHD was as high as 81.4%, which could enhance left ventricular ejection fraction (LVEF), stroke volume (SV)

Table 2
Clinical experimental studies of XFZYD in treating CHD.

	Group	Medication (Dosage of drug)	Number of people	Age (average age)	Treatment effect	The medication time	Inclusion time	Site	Reference
1	Observation group	On the basis of the control group Xuefuzhuyu Pill 0.2 g (1 pill) was added	59	50–75	The total effective rate was 91.52% (54/59), whole blood viscosity (high cut), plasma viscosity, erythrocyte deformation index, fibrinogen level and ET-1, Hcy and cTnT levels were all lower than those before treatment in this group, and the incidence of adverse reactions was 10.17% (6/59).	Oral treatment twice a day, 4 weeks for 1 course, a total of 3 courses of treatment	July 2019 to July 2021	Fifth Hospital of Zhangjiakou	[11]
	Control group	Nicordil tablets 5 mg	59	50–75	The total effective rate was 76.27% (45/59), whole blood viscosity (high cut), plasma viscosity, red blood cell deformation index, fibrinogen level, ET-1, Hcy and cTnT levels were all lower than those before treatment, and the incidence of adverse reactions was 13.56%	Oral treatment 3 times a day, 4 weeks for 1 course, a total of 3 courses of treatment			
2	Observation group	On the basis of control group combined with XFZYD treatment (Radix Bupleuri 10 g, Fructus Aurantll Immaturus 10 g, Radix Angelicae Sinensis 10 g, SAlvia Miltiorrhiza 10 g, PInellia Ternata 10 g, Persicae Semen 10 g, Flos Carthami 10 g)	63	18–75	The total effective rate was 95.24% (60/63), the duration of angina pectoris, the weekly frequency of angina pectoris and the total score of TCM symptoms were improved compared with those before treatment, and better than the control group. Serum sICAM-1, ET-1 and IL-6 levels were lower than those before treatment ($P < 0.05$), serum SOD and IL-10 levels were higher than those before treatment, and the effect was better than that of control group. The hemorheological indexes, such as plasma hematocrit, whole blood viscosity and plasma viscosity, were all lower than those before treatment, and the effect was better than that of control group	One dose a day, decocted twice, 200 mL each time, divided into 2 times for 8 weeks	September 2019 to January 2022	Hainan Hospital of Traditional Chinese Medicine	[12]
	Control group	Atorvastatin calcium tablet 20 mg, isosorbide mononitrate 20 mg, aspirin enteric-coated tablet 100 mg	63	18–75	The total effective rate was 77.78% (49/63), the duration of angina pectoris, the weekly frequency of angina pectoris and the total score of TCM symptoms were improved compared with those before treatment. Serum sICAM-1, ET-1 and IL-6 levels were decreased compared with those before treatment ($P < 0.05$), serum SOD and IL-10 levels were increased compared with those before treatment. The hemorheological indexes, such as plasma hematocrit, whole blood viscosity and plasma viscosity, were all lower than those before treatment	The patients were treated with Atorvastatin calcium tablet once a day, isosorbide mononitrate twice a day and aspirin enteric-coated tablet once a day for 8 weeks			

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Table 2 (*continued*)

	Group	Medication (Dosage of drug)	Number of people	Age (average age)	Treatment effect	The medication time	Inclusion time	Site	Reference
3	Observation group	On the basis of control group combined with XFZYD treatment (Radix Angelicae Sinensis 10 g, Flos Carthami 10 g, Radix Achyranthis Bidentatae 10 g, Radix Rehmanniae Preparata 10 g, Fructus Aurantll Immaturus 10 g, Paeoniae Radix Rubra 10 g, SAlvia Miltiorrhiza 10 g, Persicae Semen 15 g, Rhizoma Chuanxiong6g, Radix Platycodonis6g, Radix Bupleuri 6 g, Radix Glycyrrhizae 6 g)	47	45–74	The efficacy of angina pectoris and electrocardiogram were 93.62% and 91.49%, respectively. After treatment, the baseline values of angina pectoris attack frequency and duration, TCM syndrome score, LVEF, SV, CI and hemorheology in the observation group were better than those in the control group	The dosage was divided into 2 times, one dose a day and the course of treatment was 4 weeks	June 2019 to June 2022	Jinjiang Hospital of Traditional Chinese Medicine	[13]
	Control group	Isosorbide mononitrate sustained release capsule 50 mg; Aspirin enteric-coated tablet 100 mg; Atorvastat tablet 20 mg	47	45–74	The curative effect of angina pectoris and electrocardiogram were 78.72% and 74.47%, respectively. The baseline values of angina pectoris attack frequency and duration, TCM syndrome score, LVEF, SV, CI and hemorheology were better than those before treatment	Treatment was performed once a day for 4 weeks			
4	Observation group	On the basis of control group combined with XFZYD treatment (Persicae Semen 10 g, Flos Carthami 10 g, Radix Achyranthis Bidentatae 10 g, Rhizoma Chuanxiong 10 g, Radix Platycodonis 10 g, Fructus Aurantll Immaturus 10 g, Radix Angelicae Sinensis 15 g, Radix Rehmanniae Preparata 15 g, Radix Bupleuri 15 g, Paeoniae Radix Rubra 15 g, Radix Glycyrrhizae 6 g)	55	24–75	TCM syndrome score decreased, HDL-C level increased, TC, TG, LDL-C, MCP-1, TXB2, hs-CRP levels decreased	The dosage was divided into 2 times, one dose a day, and the course was 8 weeks	February 2018 to July 2021	Hainan Hospital of Traditional Chinese Medicine	[14]
	Control group	Aspirin enteric-coated tablet 100 mg, Clopidogrel bisulfate 75 mg, β-blocker metoprolol tartrate 25–50 mg, atorvastatin calcium tablet 20 mg	55	25–75	N	The patients were treated once a day for 8 weeks			
5	Observation group	On the basis of control group combined with XFZYD treatment (Persicae Semen12 g, Flos Carthami 9 g, Radix Angelicae Sinensis 9 g, Radix Rehmanniae Preparata 9 g, Radix Achyranthis Bidentatae 9 g, Rhizoma Chuanxiongs4.5 g, Radix Platycodonis 4.5 g, Paeoniae Radix Rubra 6 g, Fructus Aurantll Immaturus 6 g, Radix Glycyrrhizae 6 g, Radix Bupleuri 3 g)	43	45–70	The effective rate was 81.40%, the levels of LVEF, SV and CI were increased, and higher than the control group, and the indexes of MMP-9, TNF-α, IL-6 and hs-CRP were decreased, and lower than the control group	Decoction with water, one dose a day, twice in the morning and evening, continuous treatment for 28 days	January 2019 to January 2021		[15]
	Control group	Isosorbide mononitrate 20 mg, metoprolol 25 mg, simvastatin 10 mg	43	41–72	The effective rate was 60.47%, the levels of LVEF, SV and CI were increased, and the indexes of MMP-9, TNF-α, IL-6 and hs-CRP were decreased	The patients were treated with Isosorbide mononitrate twice a day, metoprolol twice a day, and simvastatin once a day for 28 days			

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Table 2 (*continued*)

	Group	Medication (Dosage of drug)	Number of people	Age (average age)	Treatment effect	The medication time	Inclusion time	Site	Reference
6	Observation group	On the basis of control group combined with XFZYD treatment (Persicae Semen 12 g, Flos Carthami 9 g, Radix Angelicae Sinensis 9 g, Radix Rehmanniae Preparata 9 g, Radix Achyranthis Bidentatae 9 g, Rhizoma Chuanxiongs 4.5 g, Radix Platycodonis 4.5 g, Paeoniae Radix Rubra 6 g, Fructus Aurantll Immaturus 6 g, Radix Glycyrrhizae 6 g, Radix Bupleuri 3 g)	50	N	TCM syndrome score, cardiac function index and serum LDL-C, sICAM-1 and LDH levels were significantly better than control group	The treatment was taken orally twice a day for 4 weeks	January 2020 to January 2021	Dengta central Hospital	[16]
	Control group	Aspirin 100 mg; Clopidogrel bisulfate 75 mg; Atorvastatin 20 mg orally	50	N	TCM syndrome score, cardiac function index and serum LDL-C, sICAM-1 and LDH levels were significantly better than those before treatment	The patients were treated with Aspirin once a day, Clopidogrel bisulfate once a day and Atorvastatin once a day for 4 weeks			

N: Unclear.

and cardiac index (CI), and down-regulate the expression levels of inflammatory factors such as MMP-9, tumor necrosis factor-α (TNF-α), IL-6 and hs-CRP [15]. XFZYD could also improve TCM syndrome scores and vascular endothelial function, cardiac function parameters and LDL-C, sICAM-1 and lactate dehydrogenase (LDH) levels in the serum of patients with CHD [16].

Many clinical reports have shown that XFZYD has a certain therapeutic effect on CHD, which can improve the effectiveness of treatment, accelerate blood flow, reduce blood lipids, improve the levels of plasma homocysteine, regulate blood flow and inflammatory factor-related indicators, improve patients TCM syndromes and quality of life [17–28].

2.2. Clinical case study of XFZYD in treating CHD

TCM researchers have enriched the connotation of XFZYD in clinical practice, accumulated a lot of valuable experiences. They flexibly combined them with the methods of regulating qi, reducing phlegm, removing dampness, supplementing qi, nourishing yin, warming yang, and tonifying kidney to improve the clinical efficacy of XFZYD. Professor Wang Hai is good at using XFZYD to treat CHD. On the basis of XFZYD, XFZYD was added or subtracted according to the syndrome differentiation type of patients with CHD. After treatment, the chest pain symptoms of patients with CHD are basically recovered, and other accompanying symptoms are also relieved [29]. Zhan et al. also added or subtracted drugs to treat CHD according to syndrome types on the basis of XFZYD [30].

After patients with CHD took 4 doses of modified, chest pain was significantly reduced, more than 20 doses were taken continuously, the symptoms disappeared, and ECG showed ST-T improvement [31]. Wang suffered from CHD for 13 years. Due to angina pectoris attack, XFZYD was used for addition and subtraction, decoction, twice a day, once in the morning and once in the evening. After 5 doses, the frequency of angina pectoris attacks was significantly reduced, the duration and pain were alleviated,and shortness of breath, and sleep were improved. After 7 doses, all symptoms disappeared, and did not recur after 1 year of follow-up [32].

3. Mechanism of XFZYD in treating CHD

Modern pharmacological studies have shown that XFZYD can increase the level of antiatherosclerotic factor synthesis and secretion, interfere with vascular smooth muscle proliferation and migration, promote angiogenic factor production, inhibit atherosclerosis, reduce blood viscosity, improve circulation, prolong myocardial cell life span, and protect damaged myocardium [33]. XFZYD treatsCHD through many different mechanisms (Fig. 2).

3.1. Inhibition of atherosclerosis

Studies have found that XFZYD can increase the collagen fiber area/total plaque area, reduce the total plaque area/vascular lumen area, down-regulate the LDL and TC levels in serum, up-regulate the HDL level in serum, and reduce the HIF-1α and VEGFR2 positive area/total plaque area in aortic tissue of mice with CHD, indicating that XFZYD can reduce the atherosclerotic plaque area and maintain the stability of plaques by lowering blood lipids and inhibiting the HIF-1α signaling pathway, effectively treating CHD [34].

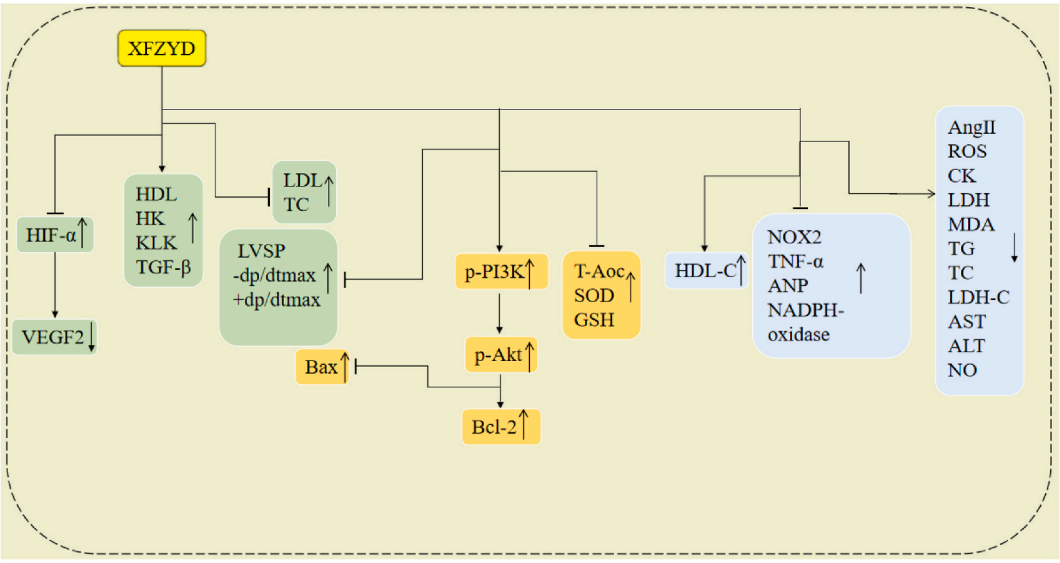


Fig. 2. Mechanism chart of XFZYD in treating CHD.

3.2. Inhibition of cardiovascular remodeling

It has been reported that XFZYD can increase the absolute values of left ventricular systolic peak pressure (LVSP), -dp/dtmax and +dp/dtmax, improve the degree of myocardial damage, reduce the ratio of arterial intima-media thickness, up-regulate the phosphorylation of PI3K and AKT, increase the expression of Bcl-2 and inhibit the level of Bax in rats with CHD. These results suggest that XFZYD can inhibit vascular remodeling and protect the heart in rats with CHD, and the mechanism may be related to the mediation of the PI3K-AKT signaling pathway [35].

3.3. Improving oxidative stress injury

The results of Tang et al. [36] showed that XFZYD could down-regulate the levels of angiotensin II (Ang II), reactive oxygen species (ROS), creatine kinase (CK), LDH, and malondialdehyde (MDA), increase the levels of T-AOC, SOD, and glutathione (GSH), and decrease the expression of NOX2, suggesting that XFZYD had the effect of alleviating myocardial oxidative damage and may be part of its onset link in the treatment of CHD. Another study showed that XFZYD could down-regulate Ang II, ROS, triacylglycerol (TG), serum TC, LDL-C, aspartate aminotransferase (AST), alanine aminotransferase (ALT), CK, and LDH levels and NOX2 protein expression, and up-regulate HDL-C levels in CHD model rats. indicatinng that XFZYD not only reduced oxidative stress damage but also reduced blood lipid levels, partially reflecting its effects of promoting blood circulation and removing blood stasis [37].

XFZYD can decrease the levels of Ang II, ET and ROS in plasma and increase the level of nitric oxide (NO) in the serum of rabbits with CHD and blood stasis, indicating that XFZYD can restore the secretion level of vasoactive substances in rabbits with CHD and blood stasis syndrome, and it is speculated that some mechanisms of its onset may be achieved by reducing oxidative stress and improving endothelial function [38].

3.4. Improving hemorheology

In addition, the study also found that XFZYD can reduce the whole blood specific viscosity, whole blood reduction specific viscosity and hematocrit of patients with CHD, prolong the formation time of thrombi *in vivo*, and reduce the weight of thrombus formation *in vitro*, the rate of platelet aggregation and the red blood cell filtration index, indicating that XFZYD can improve the abnormal hemorheology of rabbits with blood stasis and restore normal blood flow [39].

3.5. Improving myocardial fibrosis

Jiang et al. [40] found that XFZYD could enhance the ejection fraction, increase the contents of hexokinase (HK) and kallikrein (KLK), key proteins in the contact system, reduce the myocardial infarct size, and improve cardiac function and myocardial fibrosis in rats with CHD and blood stasis syndrome. XFZYD can also improve cardiac function, inhibit myocardial pathological changes, restore vasoactive factors Ang II, TNF-α, ROS, NO levels and vascular morphology, indicating that Xuefu Zhuyu Decoction can reduce coronary vascular oxidative damage, improve myocardial blood supply and lesions, and thus restore cardiac function [41].

XFZYD can down-regulate the activities of atrial natriuretic polypeptide (ANP), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase AngIIand improve the cardiac function indexes of left ventricular end diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular mass index (LVWI), right ventricular mass index (RVWI), left ventricular end-systolic diameter (LVDS), stroke volume(SV) and left ventricular ejection fraction (LVEF) in rabbits with CHD and blood stasis, indicating that XFZYD can restore the secretion of Ang II water/flat in CHD and blood stasis syndrome. It is speculated that its effect on improving cardiac function and ventricular remodeling may be partially mediated by Ang II to regulate the levels of NADPH oxidase activity, ANP

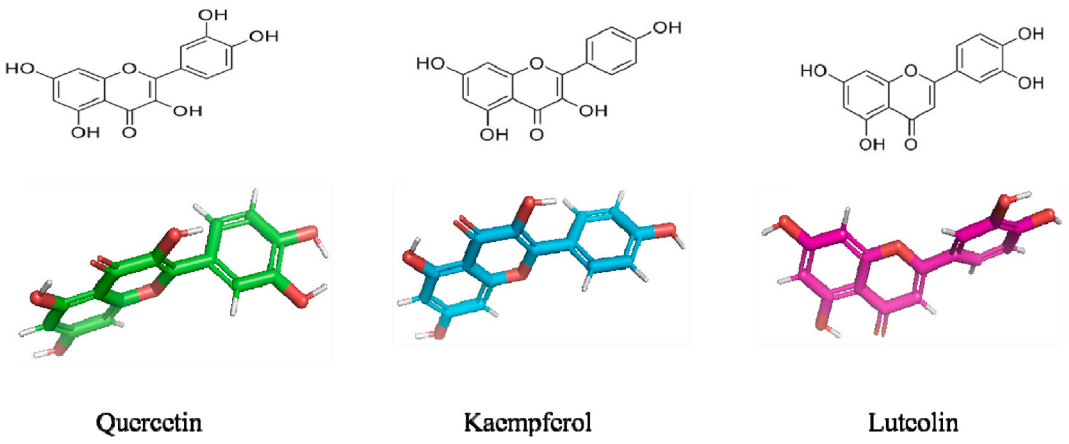


Fig. 3. Main active components of XFZYD in treating CHD.

and α-MHC/β-MHC [42]. In addition, XFZYD can improve aortic vessel wall thickness, stabilize atheromatous plaques and regulate HMGB-1 and TGF-β-related inflammatory factor expression in CHD model rats [43].

4. Molecular docking study of XFZYD in treating CHD

Network pharmacological studies have found that the main active components of XFZYD in treating CHD are quercetin, kaempferol, and luteolin (Fig. 3), and the key core targets are IL-6, VEGFA, and P53 [44]. Quercetin and kaempferol are derived from Radix Bupleuri, Radix Glycyrrhizae and Flos Carthami, while luteolin is derived from Flos Carthami and Radix Platycodonis (**Table 3**). Therefore, we performed molecular docking to further analyze the active ingredients and core targets of XFZYD in treating CHD and provide a theoretical basis for XFZYD in treating CHD (Fig. 4(A-I), Table 4).

Through Pubchem (https://pubchem.ncbi.nlm.nih.gov/) software search quercetin, kaempferol, and luteolin and download the structure data files(sdf) 3D structure of ligand, Search the PDB ids of IL-6, VEGFA, and P53 using Uniprot (https://www.uniprot.org/) database. Paste PDB ID into PDB (https://www.rcsb.org/) database for search to obtain 3D structure of receptor sdf, import small molecule receptor into Pymol software to remove water, and export it into pdb format by hydrogenation. The prepared ligands and receptors were imported into the Discovery Studio 2.5 software for docking.

According to the molecular docking results (Fig. 4, Table 4), each component and target bind through multiple binding modes and different sites. The LibDock score was higher when VEGFA bound to each component, that VEGFA is a key target of XFZYD in the treatment of CHD. At the same time, kaempferol has the highest LibDock score with VEGFA and hydrogen bonding at TYRA: 45, what's more, Kaempferol and IL6 have the highest number of hydrogen bonds, which indicates that they are most stable. so we can experimentally verify this result in subsequent studies to provide a theoretical basis for the clinical treatment of CHD.

5. Summary and outlook

CHD is a chronic cardiovascular disease caused by many factors such as arterial endothelial cells, extracellular matrix, local hemodynamics and environment, which cause coronary artery stenosis and insufficient blood supply, followed by myocardial dysfunction or organic disease [45]. CHD is the disease with the highest mortality among cardiovascular and cerebrovascular diseases, and the incidence and mortality of CHD are increasing annually [46]. TCM theory emphasizes syndrome differentiation and treatment from the overall macroscopic perspective, and points out that qi deficiency and blood stasis are the basic pathogenesis of CHD [6]. Based on this, XFZYD is a good choice for the treatment of CHD, and XFZYD has been widely used in clinical practice for the treatment of CHD. The mechanism of action of XFZYD in the treatment of CHD involves multiple targets, and its molecular mechanism in CHD is difficult to elucidate. Therefore, this study comprehensively searched the literature, summarized the mechanism of XFZYD in the treatment of CHD, and elucidated that XFZYD could play a role in the treatment of CHD by inhibiting atherosclerosis, inhibiting cardiovascular remodeling, improving oxidative stress injury, improving hemorheology and improving myocardial fibrosis.

In addition, the active ingredients and core targets of XFZYD in the treatment of CHD were analyzed with a computer simulation technique, and the results showed that VEGFA had a higher LibDock score with each component, and it was speculated that VEGFA was the key target of XFZYD in the treatment of CHD. Meanwhile, kaempferol had the highest LibDock score of VEGFA and bound at TYRA: 45. This result provides an important theoretical basis for the clinical treatment of CHD with XFZYD. Scientific researchers could conduct in-depth studies and provide a reference for the treatment of CHD with XFZYD in the future.

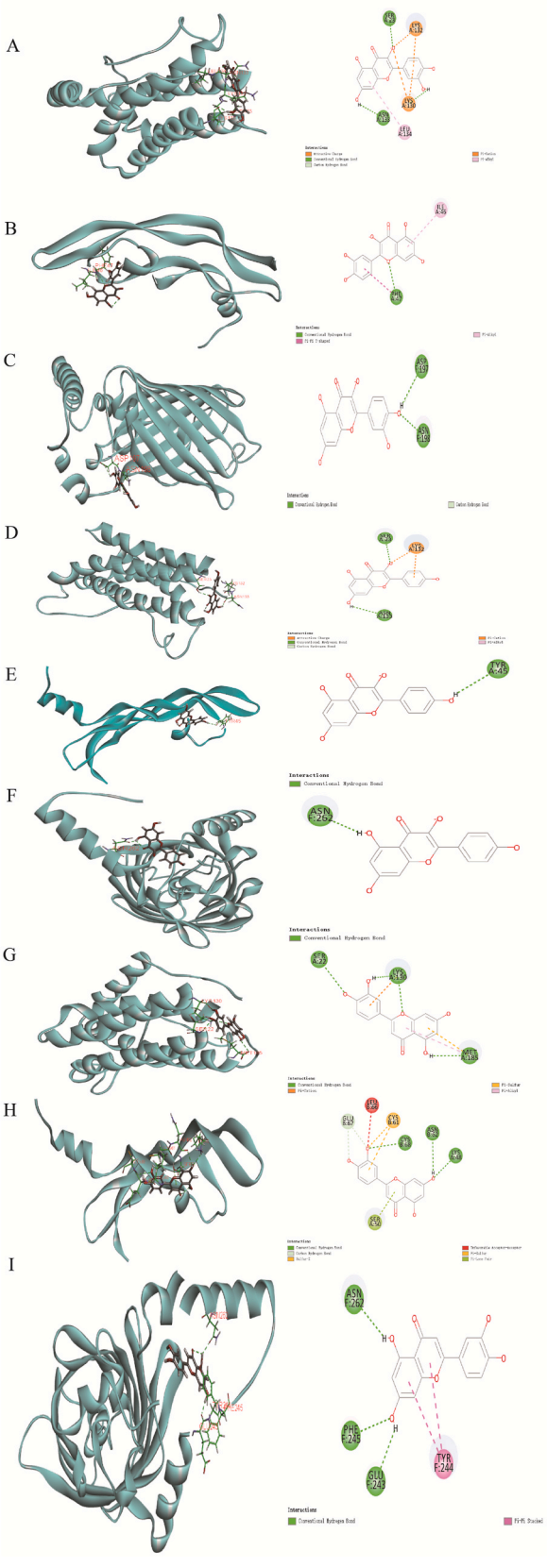
VEGFA has multiple biological effects such as promoting vascular proliferation and increasing vascular permeability [47]. Studies have found that VEGF expression levels in the serum of patients with CHD are significantly higher than those in healthy individuals [48]. Therefore, VEGFA has important clinical significance for the diagnosis of CHD, disease evaluation and efficacy determination.

The results showed that Kaempferol could decrease left ventricular end-systolic diameter, left ventricular end-diastolic diameter, left ventricular fractional shortening, left ventricular ejection fraction, and serum CK-MB and cTnI levels, significantly reduce myocardial histopathological damage, significantly decrease apoptosis rate and inflammatory factor(TNF-α, IL-6 and IL-1β) levels, and significantly down-regulate myocardial inflammation-related protein and PARP-1 protein expression in rats with myocardial infarction, indicating that Kaempferol may inhibit the myocardial inflammatory response and myocardial apoptosis by down-regulating PARP-1 expression and then improving cardiac dysfunction in rats with myocardial infarction [49]. Kaempferol protects against myocardial ischemia/reperfusion injury (MI/RI) by activating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/-glycogen synthase kinase 3β (GSK-3β) pathway [50]. Moreover, Kaempferol regulates nuclear factor E2-related factor 2, nuclear factor κ and PI3K/Akt/GSK-3β signaling pathways to ameliorate heart failure in diabetic rats [51]. Kaempferol relievesisoproterenol-induced myocardial injury in rats by anti-inflammatory, antioxidant and anti-apoptotic effects [52].

Quercetin has outstanding medicinal value in cardiovascular diseases and plays an important role in the prevention and treatment of CHD [53]. Some scholars have found that the cause of CHD is often gradual deterioration on the basis of coronary atherosclerosis,

Table 3
Basic information of main active components of XFZYD in treating CHD.

Mol ID	Active ingredients	OB(%)	DL	Source of Chinese medicine
MOL000098	quercetin	46.43	0.28	Radix Bupleuri, Glycyrrhizae radix et rhizome, Flos Carthami
MOL000422	kaempferol	41.88	0.24	Radix Bupleuri, Glycyrrhizae radix et rhizome, Flos Carthami
MOL000006	luteolin	36.16	0.25	Flos Carthami, Radix Platycodonis



(caption on next page)

Fig. 4. Schematic diagram of the docking of active components to core proteins. A, quercetin-IL6; B, quercetin-VEGFA; C, quercetin-P53; D, kaempferol-IL6; E, kaempferol-VEGFA; F, kaempferol-P53; G, luteolin-IL6; H, luteolin–VEGFA; I, luteolin–P53.

and the promotion of this process is more common in the increase of blood lipids, and quercetin can reduce the generation of triglycerides and play a certain preventive role in the pathogenesis of CHD [54]. Clinical trials have found that IL-1b, TNF-a, and IL-10 levels are increased in the serum of patients with chronic coronary artery disease (CAD), and quercetin intervention reduces the expression of the IkBa gene, resulting in decreased IL-1b, IL-10, and TNF-α levels. In the pathogenesis of coronary heart disease, acute coronary thrombosis plays a crucial role, while quercetin plays a role in the treatment of CHD by being able to resist platelet aggregation [55]. Quercetin activated the silent information regulator 1(SIRT1)/p53/(solute carrier family 7 member 11) SLC7A11 signaling pathway, reduced the levels of creatine kinase-MB (CK-MB), Cardiac troponin I (cTnI), inflammatory cell infiltration, MDA, nicotinamide adenine dinucleotide phosphate(NADPH), cytoplasmic cytochrome C, cellular Fe^{2+}, and PTGS2 but upregulated the levels of GSH, TOM 20, GPX4, and ferritin to alleviate Sepsis-induced cardiomyopathy (SIC) [56]. In addition, quercetin can reduce the transcriptional activity of NF-kB to play a role in the treatment of stable coronary heart disease [57].

Luteolin is also of outstanding value in cardiovascular disease [58], significant effect especially in MI/RI [59]. Luteolin prevented MI/RI by inhibiting TFPI2 expression through downregulation of miRNA-23a [60]. Luteolin treatment of I/R rats downregulates SHP-9 expression in heart tissue and H1c3 cells, subsequently up-regulates p-STAT2, protects the heart, and reduces myocardial infarct size, apoptosis rate, and inflammatory levels in I/R models [61]. In addition, luteolin can prevent and treat vascular restenosis by inhibiting the activation of transforming growth factor β receptor 1(TGFBR1) signaling pathway, inhibiting VSMC proliferation, migration and proliferation of vascular endothelial membrane [62]. By activating the AMP-activated protein kinase (AMPK)/Sirtuin 3(SIRT3) pathway, it up-regulates mimics of manganese superoxi dedismutase (MnSOD) antioxidant protein expression, inhibits NF-κB nuclear activation, reduces myocardial oxidative stress and inflammation, reduces myocardial fibrosis, and improves cardiac function in CHF rats [63]. Quercetin, kaempferol, and luteolin have significant therapeutic effects in cardiovascular diseases, but they are rarely used in clinical experimental studies, and for this reason, researchers need to further work to further explore the application of Quercetin, kaempferol, and luteolin in the clinical treatment of cardiovascular diseases in order to develop more therapeutic drugs for the clinical treatment of cardiovascular diseases.

Although the components of XFZYD are very complex, not all components produce efficacy, and it is generally believed that the components absorbed into the blood after oral administration are direct pharmacodynamic component. LC-ESI/MSn technique was used to analyze the components in XFZYD. The total ion current map obtained in the negative ion mode was very characteristic, and 10 chemical components, catalpol, hydroxypaeoniflorin, amygdalin, paeoniflorin, liquiritin, hydroxysaffyellow A (HSYA), 5-Hydroxy-2-(4-hydroxyphenyl)-4-oxo-3,4-dihydro-2H-chromen-7-yl 6 -O-(6-deoxyhexopyranosyl)hexopyranoside, naringin, New Zealand vitexin II, and neohesperidin, were identified [64]. LC-MS analysis of plasma samples from rabbits after oral administration of XFZYD extract revealed ferulic acid, hydroxypaeoniflorin, amygdalin, paeoniflorin, niringin, and neohesperidin as prototypes, naringgenin and neohesperidin may be prototypes, or phase I metabolites formed by intestinal metabolic hydrolysis of naringin and neohesperidin. Urine analysis revealed paeoniflorin, kaempferol 3-rutin, naringin, naringin, and neohesperidin as prototypes, naringin and neohesperidin may be prototypes, or phase I metabolites hydrolyzed by intestinal metabolism [65]. Eight components (amygdalin, hydroxysafflor yellow A, liquiritin, rutin, narirutin, niringin, neohesperidin and saikosapA) in 8 batches of XFZYD were quantitatively studied by IT-TOF-MS with high mass accuracy. The results showed that the contents of the other 6 components fluctuated except neohesperidin and saikosaponin A, which HSYA fluctuated greatly [66].

Regarding XFZYD in the clinical treatment of CHD,the drug composition of the dose is different, and exploring the drug dose of XFZYD in the treatment of CHD is also one of the problems worth paying attention. Moreover, in addition to the use of a decoction in clinical practice, XFZYD is also made into pills for the treatment of CHD. The effects of decoction and pill treatment are also worthy for researchers to continue to explore the medical problems.

In summary, in the study of XFZYD in treating CHD, we should continue to strengthen experimental and clinical studies, solve the existing problems. It is necessary to continuously develop more effective components and targets to provide scientific theoretical basis and reference for the clinical treatment of CHD.

Table 4
Molecular docking of active components and core targets.

Component	Target	libdock score	Site	Hydrogen bond number
Quercetin	IL6	80.299	SERA:23, ASNA:133, LYSA:130	3
	VEGFA	102.053	PHEA:47	1
	P53	94.1593	ASPF:197, ASNF:198	2
Kaempferol	IL6	79.4247	SERA:23, ASNA:133	2
	VEGFA	106.766	TYRA:45	1
	P53	87.7026	ASNF:262	1
Luteolin	IL6	77.4575	SERA:22, LYSA:130, META:185	4
	VEGFA	102.538	CYSB:68, ASNB:62, LYSA:48	3
	P53	90.8697	ASNF:262, PHEF:245, GLUF:243	3

Data availability statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

CRediT authorship contribution statement

Xuezhen Wang: Writing – review & editing, Writing – original draft. **Xunyan Xing:** Writing – original draft. **Peifeng Huang:** Writing – original draft. **Zhibin Zhang:** Supervision. **Zehua Zhou:** Writing – review & editing. **Leiqin Liang:** Writing – review & editing. **Rongmei Yao:** Writing – original draft. **Xuerun Wu:** Writing – review & editing. **Long Yang:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Meirong Yao reports financial support was provided by Scientific Research Project of Tianjin Municipal Education Commission. If there are other authors, they 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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