1. Introduction

Coronary heart disease (CHD) is a cardiac disease caused by the interruption of blood and oxygen supply to myocardial cells due to narrowing and occlusion of the coronary artery lumen, which eventually leads to necrosis of myocardial cells. With the accelerated rate of population aging in China, CHD has become one of the important causes of cardiovascular disease mortality. The exact pathogenesis of CHD is complex, in terms of lifestyle, such as obesity, type 2 diabetes, hypertension, sedentary lifestyle, and genetic factors, are all critical factors in its development. The routine clinical use of drugs or surgery to treat CHD often disadvantages higher costs to patients, extensive physical trauma, and inconsistent treatment outcomes. In recent years, the advantages of Chinese medicine in the treatment of CHD have been widely appreciated because of its effective improvement of clinical symptoms, low rate of adverse reactions, and higher safety profile.

Methods: The GLXBGZD effective components were searched on the pharmacological database platform of the Traditional Chinese Medicine Systems Pharmacol, and its potential target was predicted. The Online Mendelian Inheritance obtained CHD disease target in Man and GeneCards database. The Venn map of the intersection target for GLXBGZD and CHD was constructed by using Venn online website. The “drug-component-target-disease” network map was constructed by Cytoscape 3.7.2 software. The DAVID online platform was used to analyze the function of Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) at the intersection of targets of drugs and diseases.

Results: A total of 27 articles were searched for GLXBGZD, including 111 potential targets, 5521 disease targets, 100 drug and disease intersection targets. The core target network maps that Interleukin (IL)-6, TNF, vascular endothelial growth factor (VEGFA), TP53, EGF, JUN, MAPK1, Catalase (CAT), and prostaglandin-endoperoxide synthase 2 (PTGS2) may be the key targets in CHD therapy. GO functional enrichment analysis revealed that the biological functions of GLXBGZD involved biological processes such as response to drugs, positive regulation of nitric oxide biosynthesis process, and response to hypoxia. KEGG pathway enrichment analysis showed that GLXBGZD might participate in CHD treatment through Hypoxia-inducible factor-1 (HIF-1), Tumor necrosis factor (TNF), Phospholipid-3 Kinase--Threonine protein kinase (PI3K-Akt), and the calcium signal pathway.

Conclusions: This study reveals that the GLXBGZD mechanism in CHD treatment has the characteristics of multi-components, multi-targets, and multi-pathways, which provides a theoretical basis for its clinical application and subsequent experimental verification.

Abbreviations: CHD = coronary heart disease, DL = drug-like properties, GLXBGZD = Gualou Xiebai Guizhi decoction, OB = oral bioavailability, OMIM = Online Mendelian Inheritance in Man, TCM = Traditional Chinese medicine, TCMSP = TCM Systems Pharmacol, VEGFA = vascular endothelial growth factor A.

Keywords: coronary heart disease, Gualou Xiebai Guizhi decoction, mechanism of action, network pharmacology
Traditional Chinese medicine (TCM) formulations are challenging to elucidate the mechanism of action due to their complex compound composition and inadequate research methods. In recent years, with the development of bioinformatics, the emerging network pharmacology is based on large databases, and the traditional "one drug, one target" model has been upgraded to a "multi-component, multi-target" model by constructing the network relationship between active drug components and targets. This is also in line with the theory of TCM that the human body itself can act as a complete system, with each system influencing the other. Network pharmacology is a novel therapeutic approach in drug research and effectively identifies new active ingredients and mechanisms of action for TCM, which is expected to provide new strategies for TCM study.

Modern pharmacological studies have shown the effectiveness of GLXBGZD in CHD treatment. Guai (Trichosanthes kirilowii Maxim) is the dried ripe fruit of Trichosanthes kirilowii Maxim or Tr. rosthornii Harm, family Cucurbitaceae. The chemical components of Guaiuoli mainly include triterpenoids, flavonoids, phytosterols, fatty acids, amino acids and proteins, alkaloids, polysaccharides, and so on. The extract of Guai has the effects of dilating coronary arteries, increasing coronary blood flow, enhancing ischemia-reperfusion, and reducing the viscosity of α-tocatechuic aldehyde, -copane, etc. The cinnamaldehyde in -cymene, pro-aldehyde, phenylpropyl aldehyde, 1, 8-cineole-β-methoxycinnamaldehyde, benzenepropanal, 3-hydroxy-benzaldehydes, organic acids, which include cinnamaldehyde, cinnamic alcohol, Cinnamomum cassia Presl, mainly containing volatile oils and Teng et al. • Medicine (2022) 101:29

Table 1

| Drugs   | MOL_ID | Molecule_name | OB   | DL   |
|---------|--------|---------------|------|------|
| Gualou  | MOL001494 | Mandenol      | 41.99 | 0.19 |
|         | MOL002881 | Diosmetin     | 31.13 | 0.27 |
|         | MOL004355 | Spinasterol   | 42.97 | 0.75 |
|         | MOL005530 | Hydroxyeugenin| 36.46 | 0.27 |
|         | MOL006756 | Schottorol    | 37.42 | 0.75 |
|         | MOL007165 | 10α-acucurbita-5,24-diene-3β-ol | 44.01 | 0.74 |
|         | MOL007171 | 5-dehydrokarounidiol | 30.22 | 0.77 |
|         | MOL007172 | 7-oxo-dihydrokarounidiol | 36.85 | 0.75 |
|         | MOL007175 | Karounidiol 3-o-benzoate | 43.99 | 0.49 |
|         | MOL007179 | Lindolic acid methyl ester | 46.10 | 0.19 |
|         | MOL007180 | Vitamin-e | 32.28 | 0.69 |
| Xiebai   | MOL000998 | Quercetin | 46.43 | 0.27 |
|         | MOL000332 | n-coumaroyltyramine | 85.62 | 0.20 |
|         | MOL000358 | Beta-sitosterol | 36.91 | 0.75 |
|         | MOL000482 | (Z)-3-(4-hydroxy-3-methoxy-phenyl)-N-[2-(4-hydroxyphenyl)ethyl]acrylamide | 118.34 | 0.26 |
|         | MOL000332 | n-coumaroyltyramine | 85.62 | 0.20 |
|         | MOL000358 | Beta-sitosterol | 36.91 | 0.75 |
|         | MOL000482 | (Z)-3-(4-hydroxy-3-methoxy-phenyl)-N-[2-(4-hydroxyphenyl)ethyl]acrylamide | 118.34 | 0.26 |

2.2. Collection of CHD disease targets

The keyword "coronary heart disease" was used to search the database, and the selected databases were the Online Mendelian Inheritance in Man (OMIM) database and GeneCards database to obtain the relevant targets of CHD disease. The values of the 2 databases were merged, and the duplicate values were removed to obtain the disease targets of CHD.

2.3. Construction of intersection targets

The targets of GLXBGZD and the disease targets of CHD were imported into Venn (https://bioinfogp.cnb.csic.es/tools/venny/) online platform to construct drug-disease intersection targets.
and the obtained intersection targets may be the potential action targets of GLXBZGD for the treatment of CHD.

### 2.4. Construction of drug-component-target-disease network diagram

The active ingredients and targets of GLXBZGD have been imported into Cytoscape 3.7.2 software, and the network diagram of “GLXBZGD-ingredient-target-CHD” was constructed based on Cytoscape software. The nodes in the diagram represent the active ingredients and targets; the edges represent the interactions between the drug and active ingredients, active ingredients and targets, and disease and target\(^{[15]}\); the Degree value of the nodes represents the number of edges connected to the nodes. A higher degree value means a more significant role in treating CHD with GLXBZGD.\(^{[16]}\)

### 2.5. PPI network graph construction and core target screening

The drug-disease intersection targets obtained in 1.3 were imported into STING (HTTP://string-db.org online database).

![Figure 2. The Drug-component-target-disease network diagram.](image-url)
platform, selected “Multiple-Proteins”, limited the species to “human” (*Homo sapiens*), and constructed a PPI network between proteins. The obtained data were imported into Cytoscape 3.7.2 software in TSV format, and the mean value more significant than the degree was used as the screening criterion to obtain the core targets for CHD treatment with GLXBGZD.

### 2.6. Gene Ontology function and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis

The intersecting genes of drugs and diseases obtained in 1.3 were imported into the DAVID (https://david.ncifcrf.gov/) database, and the species was restricted to “human” (*Homo sapiens*). The genes were corrected to official genes, and the top 10 Gene Ontology (GO) biological functions were selected with $P < .05$ and False discovery rate (FDR) $< 0.05$ as screening criteria and visualized in a bar chart; the top 20 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were selected.

### 3. Results

#### 3.1. Acquisition of active ingredients and targets of GLXBGZD

Using OB $\geq 30\%$ and DL $\geq 0.18$ as the screening criteria, a total of 11 active ingredients of GuaLou, 11 active ingredients of XieBai, and 5 active ingredients of Guizhi were retrieved from the TCMSP database. A total of 111 potential action targets were predicted after deleting duplicate values. The primary active ingredient information is shown in Table 1.

#### 3.2. Venn diagram construction of intersecting targets

A total of 5521 CHD-related disease targets were retrieved from OMIM and GeneCards databases, and 100 mapping targets were obtained by intersecting CHD disease targets with the drug targets of GLXBGZD and making Venn diagrams for visualization and analysis (Fig. 1).

![The Protein protein interaction (PPI) network diagram and core target network diagram.](image3)

Figure 3. The Protein protein interaction (PPI) network diagram and core target network diagram.

![Degree values of the core target network graph for GLXBGZD. GLXBGZD = Gualou Xiebai Guizhi decoction, NOS = nitric oxide synthase, VEGFA = vascular endothelial growth factor. For abbreviations not defined here, please refer to Fig. 2.](image4)

Figure 4. Degree values of the core target network graph for GLXBGZD. GLXBGZD = Gualou Xiebai Guizhi decoction, NOS = nitric oxide synthase, VEGFA = vascular endothelial growth factor. For abbreviations not defined here, please refer to Fig. 2.
3.3. Drug-component-target-disease network diagram

The above obtained active ingredients and targets of GLXBGZD and the intersection targets of drugs and diseases were imported into Cytoscape 3.7.2 software to construct the “drug-ingredient-target-disease” network diagram, which has 147 nodes (one disease, 26 active ingredients, 3 drugs, 117 targets) and 590 edges. This suggests that the above nodes may be the key active ingredients of GLXBGZD for CHD treatment (Fig. 2).

3.4. PPI network diagram and core target network diagram construction

The intersection targets obtained in 2.3 were imported into the STING database, the species was selected as human, and the PPI network graph between the proteins was constructed. The graph includes 100 nodes, 1002 edges, and the average node value is 20, and the detailed results are shown in Figure 3. The obtained data were imported into Cytoscape 3.7.2 software in Tab separated values File (TSV) format, and the core targets of drug treatment diseases were obtained with Degree > 25 as the screening criterion, and the histogram was made to display, see Figure 4.

3.5. GO functional enrichment analysis

The intersecting targets obtained in 2.3 were imported into the DAVID database. When \( P < .05 \) and FDR < 0.05 were used as screening criteria. The screening yielded 102 biological processes, 22 cell compositions, and 29 molecular functions. The top 10 items were selected separately and made into histograms for visual analysis, and the detailed results are shown in Figure 5.

3.6. Results of KEGG pathway enrichment analysis

Eighty-four KEGG pathways were screened by the same method as in 2.5, and the top pathways were mainly involved in the HIF-1 signaling pathway, TNF signaling pathway, pathways in cancer, PI3K-Akt signaling pathway, calcium signaling pathway, and estrogen signaling pathway (Fig. 6 and Table 2). PI3K-Akt signaling pathway, calcium signaling pathway, estrogen signaling pathway, etc. The present results suggest that GLXBGZD may be involved in the therapeutic process of CHD through several of these pathways.

4. Discussion

Chinese medical theory classifies CHD under the categories of “thoracic obstruction” and “heartache,” and believes that its primary pathogenic mechanism is related to irregular diet and emotional disorders. According to TCN theory, the occurrence of CHD is primarily due to the rich diet of modern people coupled with high life stress leading to the patient’s body with dampness endogenous and emotional and mental disorders, and Qi-blood deficiency in the patient’s body. In Chinese medicine, clinical treatment for CHD mainly uses GLXBGZD, which can move Qi and dispel phlegm, open the veins and relieve pain. By observing 80 CHD patients with phlegm and blood stasis, found that the GLXBGZD could significantly improve the myocardial metabolic function of patients. In the treatment of 88 patients with acute myocardial infarction combined with left heart failure, Wang found that the addition of GLXBGZD to conventional treatment could significantly improve the cardiac function of patients. All of the above studies suggest that GLXBGZD can be used to treat patients with CHD. However, the detailed mechanism of how the drug works is not well understood. Therefore, this study investigated the molecular mechanism of GLXBGZD in the treatment of CHD by using the network pharmacology method to provide methods and strategies for the clinical application of this drug in patients with CHD.

Our analysis by Cytoscape software yielded high values of active ingredients such as \( \beta \)-sitosterol, quercetin, naringenin, and hesperidin in GLXBGZD. Studies have shown that quercetin, as a flavonoid, has been widely reported in preventing and treating coronary atherosclerosis. Quercetin can limit the formation of atherosclerotic plaques in the aorta by upregulating the expression of nitric oxide synthase; quercetin can also...
stabilize atherosclerotic endothelial plaques by downregulating the expression of MMP1. Therefore, understanding the relationship between quercetin metabolic activity and coronary atherosclerosis can provide new ideas for this drug in treating CHD. β-sitosterol has beneficial effects on the treatment of cardiovascular diseases. Studies have shown that β-sitosterol can effectively enhance the cellular glutathione redox cycle, thereby reducing oxidative damage in rat cardiomyocytes and thus slowing the progression of coronary heart disease. In addition, β-sitosterol could protect hypoxia/reoxygenation-injured cardiomyocytes and ischemia/reperfusion injury of cardiomyocytes by regulating the expression of PPARγ protein levels.

This study further indicates that GLXBGZD may be involved in the therapeutic process of patients with CHD through a complex mechanism of action.

The core target network map shows high IL-6, TNF, vascular endothelial growth factor (VEGFA), Tumor Protein 53 (TP53), Endothelial growth factor (EGF), v-jun sarcoma virus 17 oncogene homolog (JUN), and Mitogen-activated protein kinase (MAPK1), which may be the key targets of GLXBGZD in the treatment of CHD. There is increasing evidence that inflammation has an essential role in the development and progression of coronary atherosclerosis. Active inflammatory processes may trigger plaque rupture, thereby increasing the incidence of coronary atherosclerotic events. Activating proinflammatory factors, such as IL-6 and TNF, can disrupt the endothelial function of blood vessels and accelerate the rupture of plaques, thus accelerating the onset of coronary atherosclerosis. Therefore, inhibition of inflammatory factor activation can reduce the adverse incidence of cardiovascular events in CHD. VEGFA has been shown to promote microvessel formation and development by binding to vascular endothelial cell receptors to induce their differentiation, proliferation, and migration. VEGFA promotes revascularization and the establishment of collateral circulation and enhances endothelium-dependent vasodilation, which is closely associated with CHD. VEGFA may play a

Figure 6. The key pathway-target map of GLXBGZD for the treatment of CHD. CHD = coronary heart disease, GLXBGZD = Gualou Xiebai Guizhi decoction.
crucial role in regulating endocardial formation through epithelial-mesenchymal transition. Therefore, precise regulation of VEGFA expression may reduce the occurrence of cardiovascular diseases, including CHD.\(^\text{[27]}\) This further confirms the characteristics of GLXBGZD to treat CHD through multiple components and targets.

The GO biological process of GLXBGZD in the treatment of CHD involves the reaction of the drug, positive regulation of nitric oxide biosynthesis process, response to hypoxia, extracellular space, plasma membrane, enzyme binding, protein homopolymerization activity, steroid binding, and other biological processes. This indicates that all of the above biological processes are essential in treating CHD by GLXBGZD. The enrichment analysis of the KEGG pathway revealed that GLXBGZD was mainly involved in the treatment of CHD through the HIF-1, TNF, cancer, PI3K-Akt, calcium, and estrogen signaling pathway, etc. HIF-1 can regulate the occurrence and development of atherosclerosis. Under hypoxic conditions, factors in the HIF-1 signaling pathway induce VEGF gene expression and can promote neovascularization.\(^\text{[3]}\) Activation of the PI3K-Akt signaling pathway promotes atherosclerotic vascularization and the expression of inflammatory factors, and the PI3K/Akt signaling pathway enables Nuclear Factor kappa-B (NF-kB) transcription factors to enhance the activity of inflammatory mediator genes, thus promoting the production of many cytokines.\(^\text{[29]}\) Thus, inhibition of the PI3K/Akt signaling pathway allows inhibiting the progression of coronary atherosclerosis. Coronary artery calcification is closely related to the diagnosis and treatment of CHD. Factors related to the estrogen signaling pathway can regulate the expression of proteins related to bone-associated protein Bone morphogenetic protein 2 (BMP-2) and Phosphorylated drosophila mothers against decapentaplegic protein gene 1/5/8 (p-Smad1/5/8) signaling pathway to inhibit vascular calcification and thus the progression of CHD.\(^\text{[10]}\) All of the above studies suggest that GLXBGZD can be involved in the treatment of CHD through multi-component, multi-target, and multi-pathway.

5. Conclusions

In summary, this study used network pharmacology to analyze that the treatment of CHD by GLXBGZD is associated with 27 active ingredients, which are involved in the therapeutic process of CHD through 100 intersecting targets. By constructing a “drug-component-target-disease” network diagram, this article also illustrates the treatment of CHD by GLXBGZD at the molecular level and indirectly proves the rationality of the drug formulation. This study provides a new basis for the promotion and use in the clinical treatment of CHD and provides a new method and strategy for the scientific research of Chinese medicine.\(^\text{[3]}\) Due to the limited number of database articles, the data collection process has limitations. Therefore, the conclusions obtained in this article still need to be validated by subsequent clinical trials.

Author contributions

TC and LXZ conceived and designed this study; WY, PS, and WX performed the acquisition and analysis of data, and all authors reviewed the article.

Reference

[1] Zheng J, Li J. Clinical research progress of salvianolic acids for injection in treating angina pectoris of coronary heart disease. Drug Eval Res. 2020;43:1919–22.
[2] Dong Y, Chen H, Gao J, et al. Molecular machinery and interplay of apoptosis and autophagy in coronary heart disease. J Mol Cell Cardiol. 2019;136:27–41.
[3] Zhuang Q, Shen C, Chen Y, et al. Association of high sensitive C-reactive protein with coronary heart disease: a mendelian randomization study. BMC Med Genet. 2019;20:170.
[4] Zhang HX, Li HL, Liu X. Effects of gualou xiebai guizhi decoction on elderly patients with coronary heart disease. World Chin Med. 2020;15:1157–61.
[5] Chen Y, Kern TS, Kiser PD, et al. Eyes on systems pharmacology. Pharmacol Res. 2016;114:39–41.
Teng et al. • Medicine (2022) 101:29

Ke ZP, Zhang XZ, Geng T, et al. Research on the molecular mechanism of giiwei tongbil oral liquid in treatment of rheumatoid arthritis via network pharmacology. Chin Tradit Herb Drugs. 2020;51:4489–97.

Li L, Zhang L, Yang CC. Multi-target strategy and experimental studies of traditional chinese medicine for alzheimer's disease therapy. Curr Top Med Chem. 2016;16:537–48.

Wei-dong L. Sixty-eight cases of angina pectoris due to acute myocardial infarction treated with gualou xiebai guizhi decoction. Henan Tradit Chin Med. 2015;35:1262–3.

Zhang H, Lei P, Zhang S. Research progress of gualou xiebai in the treatment of coronary heart disease. Proc Anticancer Res. 2021;5:86–90.

Gao J, Pan Y, Zhao Y, et al. Network pharmacology study on molecular mechanisms of zhishi xiebai guizhi decoction in the treatment of coronary heart disease. Evid-Based Complement Alternat Med. 2021;20:3574321.

Yu YD, Hou W-J, Zhang J, et al. Network pharmacology and molecular docking-based analysis on bioactive anticoronary heart disease compounds in trichosanthes kirilowii maxim and bulbus allii macrostemi. Evid-Based Complement Alternat Med. 2021;16:6704798.

Yao F. Clinical study on the treatment of stable angina pectoris in coronary artery disease (chest Yang type) with gualou xiebai guizhi decoction. master. Shandong Univ Tradit Chin Med. 2014.

Yang XX, Duanmu LJ. Effectiveness of gualou xiebai guizhi decoction in treating 160 cases of acute myocardial infarction combined with left heart failure. J Clin Med Lit. 2017;4:6289–90.

Li L, Chu YF. Effect of gualou xiebai guizhi decoction in treating senile chronic congestive heart failure with syndrome of qi deficiency, blood stasis and phlegm-damp. J Changchun Univ Tradit Chin Med. 2015;35:1262–3.

Pei C, Shao LL, Liu J, et al. Study on the mechanism of carthami Flos in treating retinal vein occlusion based on network pharmacology and molecular docking technology. Nat Prod Res Dev. 2020;32:1844.

Li JY, Zhang ZP, Ye JF, et al. Study on the mechanism of couplet medicine of cuscutae semen-lycii fructus in the treatment of premature ovarian failure based on network pharmacology. Chin Pharm. 2020;31:2202–9.

Yang XY. Clinical observation of gualou xiebai guizhi decoction combined with western medicine in the treatment of phlegm-stasis interconnection type of coronary heart disease in the elderly. Chin Naturpathy. 2020;28:77–9.

Wang H. The effect of using gii gua guai bei gii zhi tang plus and minus discriminatory treatment on cardiac function in patients with acute myocardial infarction combined with left heart failure. Prevent Treat Cardiovasc Dis. 2020;10:35–6.

Wu DN, Guan L, Jiang YX, et al. Microbiome and metabonomics study of quercetin for the treatment of atherosclerosis. Cardiovasc Diagn Ther. 2019;9:545–60.

Al-Taweel AM, Raish M, Perveen S, et al. Nepeta deflersiana attenuates isoproterenol-induced myocardial injuries in rats: Possible involvement of oxidative stress, apoptosis, inflammation through nuclear factor (NF)-kappaB downregulation. Phytomedicine. 2017;34:67–75.

Wong HS, Chen N, Leong PK, et al. beta-Sitosterol enhances cellular glutathione redox cycling by reactive oxygen species generated from mitochondrial respiration: protection against oxidant injury in H9c2 cells and rat hearts. Phytother Res. 2014;28:999–1006.

Lin F, Xu L, Huang M, et al. Beta-sitosterol protects against myocardial ischemia/reperfusion injury via targeting PPARgamma/NF-kappaB signalling, Evid Based Complement Alternat Med. 2020;2020:2679409.

Dai W, Li Y, Lv YN, et al. The roles of a novel anti-inflammatory factor, milk fat globule-epidermal growth factor 8, in patients with coronary atherosclerotic heart disease. Atherosclerosis. 2014;233:661–5.

Han W, Wei Z, Zhang H, et al. The association between sortolin and inflammation in patients with coronary heart disease. J Inflamm Res. 2020;13:71–9.

Tettamanti G, Malagoli D, Benelli R, et al. Growth factors and chemo kines: a comparative functional approach between invertebrates and vertebrates. Curr Med Chem. 2006;13:2737–50.

Griffin HR, Hall DH, Topf A, et al. Genetic variation in VEGF does not contribute significantly to the risk of congenital cardiovascular malformation. PLoS One. 2009;4:e4978.

Sun G, Li Y, Ji Z. Up-regulation of MIAT aggravates the atherosclerotic heart disease. Atherosclerosis. 2014;233:661–5.

Wu DN, Guan L, Jiang YX, et al. Microbiome and metabonomics study of quercetin for the treatment of atherosclerosis. Cardiovasc Diagn Ther. 2019;9:545–60.

Al-Taweel AM, Raish M, Perveen S, et al. Nepeta deflersiana attenuates isoproterenol-induced myocardial injuries in rats: Possible involvement of oxidative stress, apoptosis, inflammation through nuclear factor (NF)-kappaB downregulation. Phytomedicine. 2017;34:67–75.

Wong HS, Chen N, Leong PK, et al. beta-Sitosterol enhances cellular glutathione redox cycling by reactive oxygen species generated from mitochondrial respiration: protection against oxidant injury in H9c2 cells and rat hearts. Phytother Res. 2014;28:999–1006.

Lin F, Xu L, Huang M, et al. Beta-sitosterol protects against myocardial ischemia/reperfusion injury via targeting PPARgamma/NF-kappaB signalling, Evid Based Complement Alternat Med. 2020;2020:2679409.

Dai W, Li Y, Lv YN, et al. The roles of a novel anti-inflammatory factor, milk fat globule-epidermal growth factor 8, in patients with coronary atherosclerotic heart disease. Atherosclerosis. 2014;233:661–5.

Han W, Wei Z, Zhang H, et al. The association between sortolin and inflammation in patients with coronary heart disease. J Inflamm Res. 2020;13:71–9.

Tettamanti G, Malagoli D, Benelli R, et al. Growth factors and chemo kines: a comparative functional approach between invertebrates and vertebrates. Curr Med Chem. 2006;13:2737–50.

Griffin HR, Hall DH, Topf A, et al. Genetic variation in VEGF does not contribute significantly to the risk of congenital cardiovascular malformation. PLoS One. 2009;4:e4978.

Sun G, Li Y, Ji Z. Up-regulation of MIAT aggravates the atherosclerotic heart disease. Atherosclerosis. 2014;233:661–5.