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Exploring the mechanism of *Crocus sativus* and *Rosa rugosa* for the treatment of coronary heart disease based on network pharmacology and molecular docking

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Abstract Coronary atherosclerotic heart disease (CHD) is the main type of cardiovascular disease. The efficacy of Uyghur drug compound Saffron formula in CHD has been clinically proven. However, the underlying mechanism remains unclear. In this study, researchers investigated the active ingredients and mechanism of action of *Crocus sativus* and *Rosa rugosa* in the treatment of CHD by network pharmacology and molecular docking techniques, collected target information with the help of TCMSP, GEO, GeneCards, and other databases, constructed protein-protein interaction (PPI) network diagrams by STRING database, performed GO and KEGG pathway enrichment analysis on common targets, and finally molecularly docked the active ingredients with core targets. *C. sativus-R. rugosa* have a variety of polyphenol compounds, a total of 12 active ingredients, including quercetin and kaempferol, were screened. The first three targets intersected with the core targets of CHD as AKT1, TNF, and IL-1B. Enrichment results of KEGG pathway showed that *C. sativus-R. rugosa* against CHD involved atherosclerosis pathways. The molecular docking results showed that quercetin and kaempferol were well bound to the core targets, and it was speculated that these components might be the main active ingredients for the treatment of CHD. The potential mechanism of action of *C. sativus-R. rugosa* for the treatment of coronary heart disease was initially revealed.

Keywords: coronary heart disease; *Crocus sativus*; molecular docking; network pharmacology; polyphenol; *Rosa rugosa*

1 Introduction

Coronary atherosclerotic heart disease, also known as coronary heart disease (CHD), refers to localized myocardial ischemia, hypoxia, and even necrosis caused by atherosclerosis [1]. With the change of people's lifestyles, the morbidity and mortality of CHD are increasing year by year, and the incidence of the population tends to be younger, which threatens human life and health [2, 3]. In clinical treatment, western drugs are mainly used to treat CHD, but the clinical practice has found that the effect of western drugs alone is not ideal, such as recurrent angina symptoms, low overall efficacy, and high incidence of adverse drug reactions [4]. Therefore, it is important to seek safe and effective drugs for the treatment of CHD.

Traditional Chinese medicine (TCM) has multi-component and multi-target characteristics. With the application in clinical treatment, more and more studies have confirmed that TCMs can significantly improve the effect of CHD and reduce the incidence of adverse reactions. Uyghur medicine is a major

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component of Chinese medicine, and the Compound Saffron Formula is one of the drugs that have achieved remarkable results in the prevention and treatment of cardiovascular diseases. The formula is effective in promoting blood circulation, benefiting the kidney and strengthening the heart, and relieving depression and waking up the brain [5]. The compound saffron formula contains a total of 13 herbs: *Crocus sativus* L., *Moschus berezovskii* Flerov, *Rosa rugosa* Thunb., *Lavandula angustifolia* Mill., and *Anchusa italica* Retz., among others. The heart-protecting pill made with *M. berezovskii* can inhibit oxidative damage and inflammatory processes caused by myocardial infarction [6, 7], and *L. angustifolia* can improve coronary blood flow velocity and exert cardioprotective effects against myocardial infarction by targeting inflammation and oxidative stress [8, 9]. *C. sativus* and *R. rugosa* in the compound are two flowers that are both medicines and foods, both with cardiovascular benefits.

The theory of homology of medicine and food is rooted in TCM theory, medicine and food homologous flowers contain a variety of active ingredients and nutrients [10], which are now used in many fields such as medicine, food, and cosmetics. *C. sativus* contain flavonoids under polyphenol compounds such as saffron glycosides, and terpenoids, including saffron acid and saffron aldehyde [11, 12]. Modern pharmacological studies have shown that it has antitumor [13-15], antidepressant [16], antioxidant [17], anti-inflammatory [18] and cardioprotective [19] effects. *R. rugosa* has volatile oils, flavonoids, polysaccharides, phenolic acids, and other types of polyphenol compounds [20]. It has different uses and targets, which together form its unique medicinal and edible value [21]. However, Uyghur medicine regional nature has led to a relative lack of relevant research and few studies on its potential pharmacological mechanisms for the treatment of cardiovascular diseases.

With the rapid development of systems biology, multifaceted pharmacology, and bioinformatics, network pharmacology based on large databases have provided new ways and ideas for pharmaceutical research [22]. This approach comprehensively investigates the interactions of bioactive components, targets, and diseases, and visualizes this relationship through interaction networks [23]. Use of network pharmacology allows a clearer visualization of the complex synergistic relationships between the drug itself and the compounds [24].

The aim of this study is to identify bioactive compounds and potential target genes through modern network pharmacology technology and the technical system of drug molecular information docking (Fig. 1), to reveal the potential mechanism of *C. sativus-R. rugosa* on CHD, and to provide a basis for further research on the experimental study and clinical application of *C. sativus-R. rugosa*.

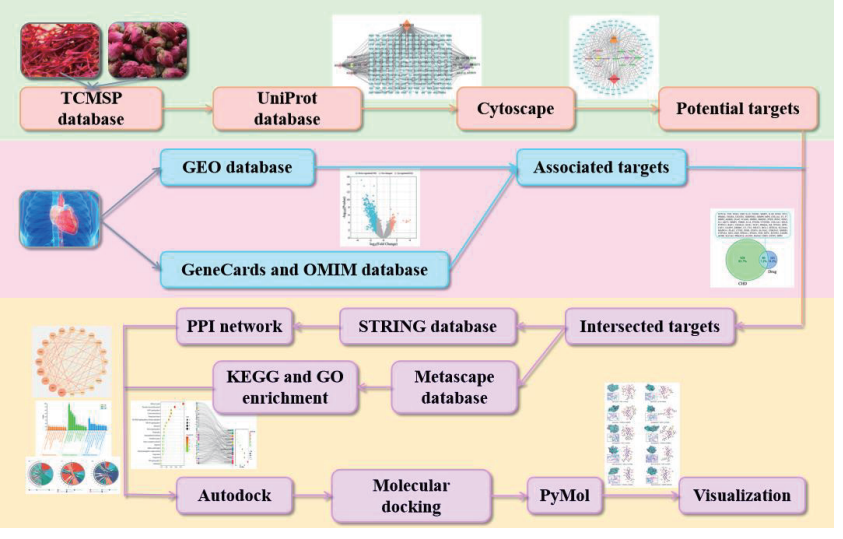


Fig. 1 Network pharmacology and molecular docking flow chart of *C. sativus-R. rugosa* in CHD

2 Material and methods

2.1 Acquisition of main active components and targets

The main chemical constituents of *C. sativus* and *R. rugosa* were searched by TCMSP Pharmacologic database and analysis platform (https://old.tcmsp-e.com/) [25, 26]. The target information was standardized by UniProt database (https://www.uniprot.org/) to obtain the predicted target of drug [27].

2.2 Acquisition of CHD-related target genes

Datasets of differentially expressed mRNA expression profiles in normal and disease groups (GSE66360 and GSE98583) were obtained using the gene expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/).

2.3 Construction of disease target library

Through GeneCards (https://www.genecards.org/) and OMIM (https://omim.org/) to "coronary heart disease" as the keyword search, including GEO database, to exclude repeat the corresponding disease targets. Venn diagram was drawn by mapping disease-related genes to target genes of *C. sativus-R. rugosa*.

2.4 Construction and analysis of "Drug-Component-Target" and "Component-Target-Disease" interaction network

Using Cytoscape 3.6.1 bioinformatics analysis software, the "Drug-Component-Target" interaction network of *C. sativus-R. rugosa* was plotted. The circle represents the drug, the quadrilateral represents the active ingredient of drug, the red quadrilateral represents the common component, and the blue quadrilateral represents the target. In the "Component-Target-Disease" interaction network, the orange color represents the disease.

2.5 Construction and analysis of protein-protein interaction (PPI) network

The protein target was imported into String database (https://cn.string-db.org/). Using Cytoscape 3.6.1 software, information is imported and drawn into PPI network for visual analysis.

2.6 Gene Ontology and Kyoto Encyclopedia of Genesand Genomes enrichment analysis

Metascape database (https://metascape.org/) was used to enrich the Gene Ontology (GO) and Kyoto Encyclopedia of Genesand Genomes (KEGG) biological signaling pathways of the core targets, and the corresponding functional analysis and signal pathway analysis data were obtained.

2.7 Molecular docking

Use molecular docking to validate the binding of core targets to compounds. The protein crystal structure of the CHD-related target was obtained from the RCSB Protein Data Bank database (https://www.rcsb.org/). The structure and chemical formula of the target and drug, respectively, were obtained from the RCSB Protein Data Bank structured and PubChem (https://pubchem.ncbi.nlm.nih.gov/).

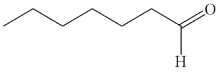
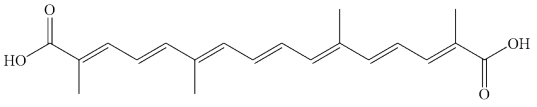
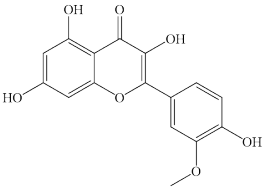
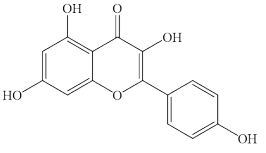
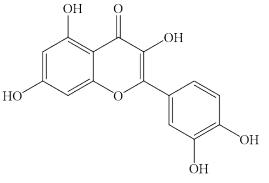
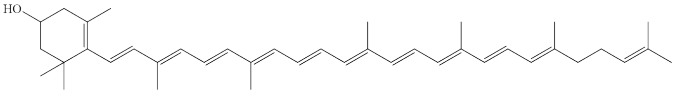
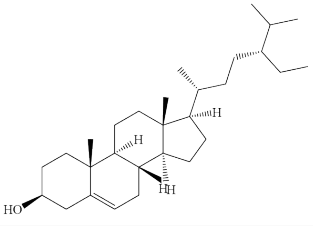
3 Results

3.1 Network of components and targets

A total of 12 main active components (Table 1) and 181 action targets were obtained through screening and weight reduction. As shown in Fig. 2A, red dots represent significantly up-regulated expressed genes, blue dots represent significantly up-regulated expressed genes, and gray plots represent insignificant genes, of which there are 222 up-regulated genes and 769 down-regulated genes, which are considered as potential therapeutic targets for CHD. The intersection of the action targets of drug with CHD was compared,

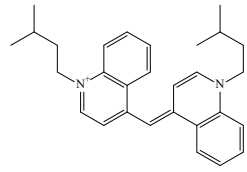
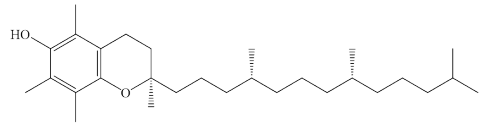
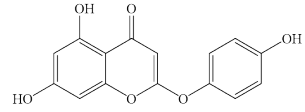
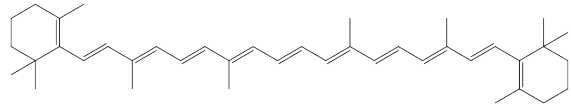
as shown in Fig. 2B, and 80 common targets were obtained, which were identified as target genes of drug in the treatment of CHD. The "Drug-Component-Target" interaction network of *C. sativus* and *R. rugosa* (Fig. 3A) showed a total of 194 nodes and 349 edges. The larger the color area is, the more the target is, and the number of edges represents the interaction between the active components and the target in the treatment of CHD by drug. The figure shows that there are relationships between multiple targets and multiple active ingredients, which indicates the characteristics of multiple components and multiple targets of TCM. According to the analysis by Network Analyzer, the degree value of quercetin is 147. There are 247 edges in the "Component-Target-Disease" interaction network (Fig. 3B), and the target degree value of the inner circle is higher than that of the outer circle.

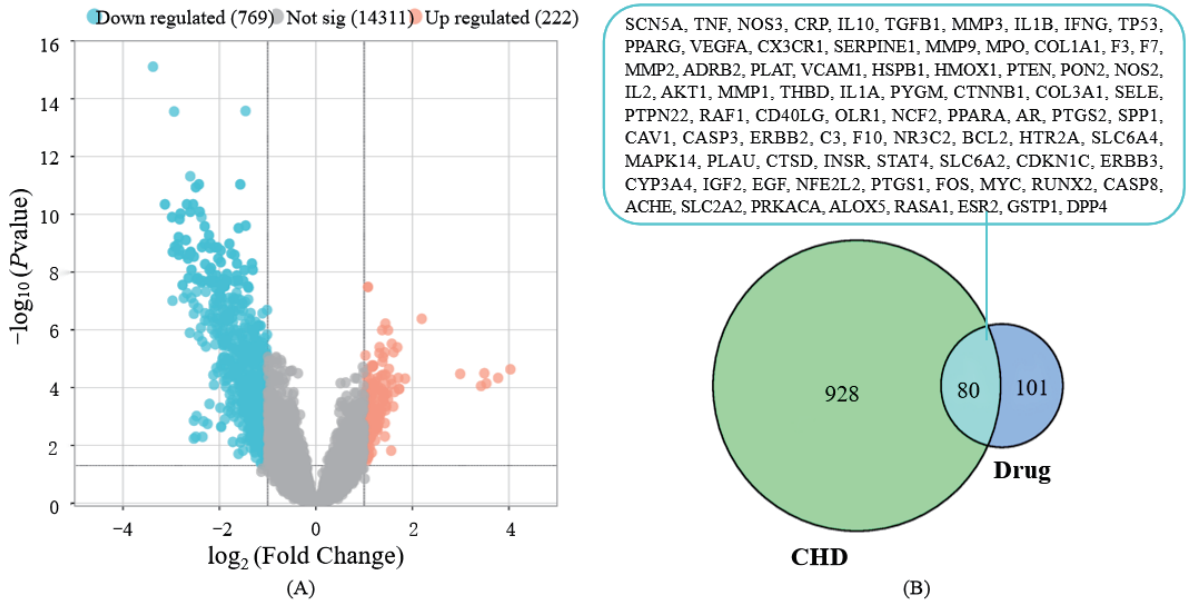
Table 1 Information for the candidate bioactive compounds of *C. sativus* and *R. rugosa*

MOL ID	Compound	MF	OB (%)	DL	Structure
MOL001389	n-Heptanal	$C_7H_{14}O$	79.74	0.59	
MOL001406	Crocetin	$C_{20}H_{24}O_4$	35.30	0.26	
MOL000354	Isorhamnetin	$C_{16}H_{12}O_7$	49.60	0.31	
MOL000422	Kaempferol	$C_{15}H_{10}O_6$	41.88	0.24	
MOL000098	Quercetin	$C_{15}H_{10}O_7$	46.43	0.28	
MOL010736	Rubixanthin	$C_{40}H_{56}O$	47.26	0.53	
MOL000358	Beta-sitosterol	$C_{29}H_{50}O$	36.91	0.75	

(to be continued)

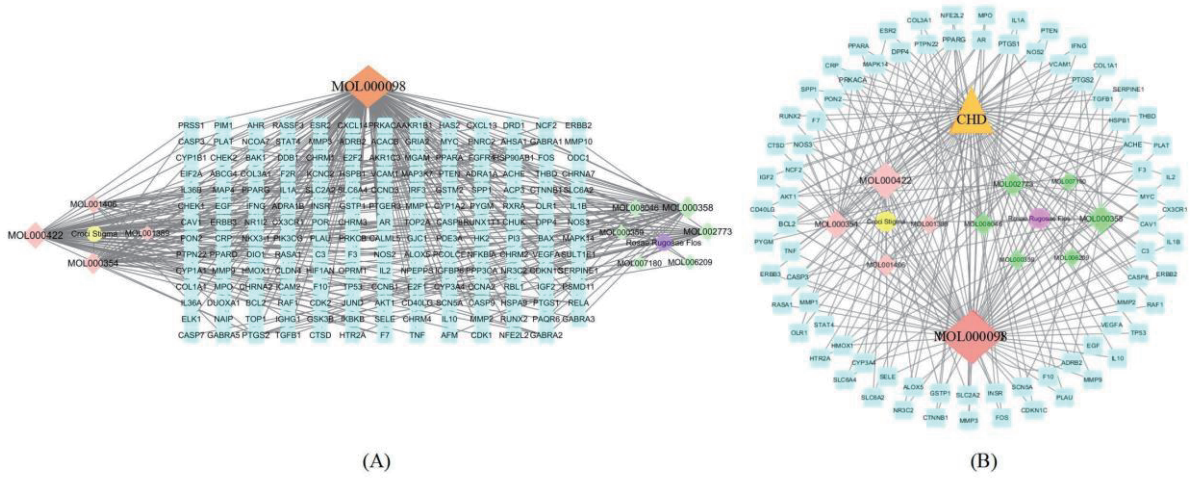
Continued Table 1

MOL ID	Compound	MF	OB (%)	DL	Structure
MOL006209	Cyanin	$C_{29}H_{35}IN_2$	47.42	0.76	
MOL007180	Vitamin E	$C_{33}H_{54}CaO_6$	32.29	0.70	
MOL008046	Demethoxycap-illarisin	$C_{15}H_{10}O_6$	52.33	0.25	
MOL002773	Beta-carotene	$C_{40}H_{56}$	37.18	0.58	



A − Volcano map of disease gene distribution; B − Venn diagrams of cross targets between drug and coronary heart disease (CHD).

Fig. 2 Gene relationship map



A – "Drug-Component-Target" interaction network; B – "Component-Target-Disease" interaction network.

Fig. 3 Interaction network diagram

3.2 PPI network

In this study, 20 core targets of PPI protein interactions were screened, with 183 edges and circles representing the targets. The size and color of the circle were proportional to the degree of the node, among which AKT1 had the highest degree value (Fig. 4).

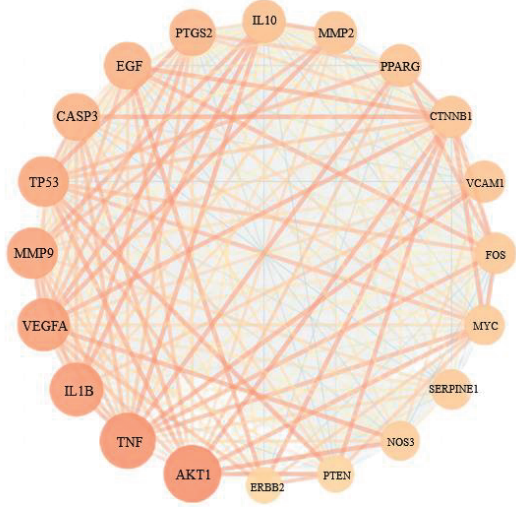
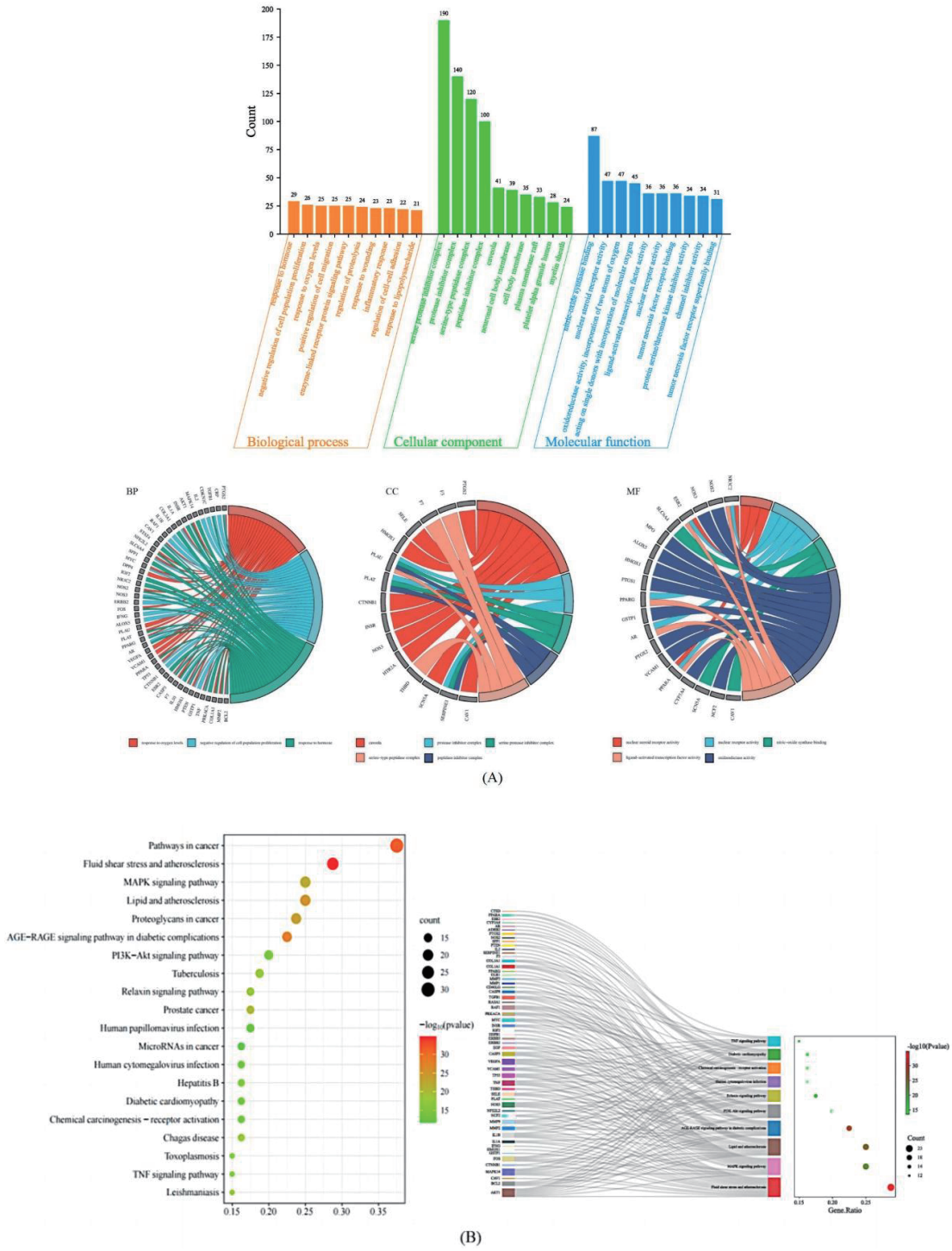


Fig. 4 PPI network of identified major targets

3.3 GO and KEGG pathway enrichment

GO enrichment analysis was conducted on potential targets of drug in the intervention of CHD, including BP (biological process), MF (molecular function), and CC (cellular component). The top 10 BP, MF, CC terms are displayed in three-in-one bar chart as shown in Fig. 5A, respectively. In BP, it acts on cellular response to hormone, negative regulation of cell population proliferation and oxygen levels, etc. At the level of MF, it acts on nitric-oxide synthase binding, nuclear steroid receptor activity, oxidoreductase activity, incorporation of two atoms of oxygen, etc. In terms of CC, action on serine protease

inhibitor complex, protease inhibitor complex, serine-type peptidase complex, etc. KEGG pathway analysis of 20 core targets (Fig. 5B) showed that related pathways include fluid shear stress and atherosclerosis, MAPK signaling pathway, lipid and atherosclerosis, etc.



A − GO enrichment analysis of intersected targets between drug and disease; B − KEGG enrichment analysis of intersected targets between drug and disease.

Fig. 5 GO and KEGG enrichment analysis

3.4 Molecular docking

In this study, the binding of the core target to the compound was verified using AutoDock Tools 1.5.6 and the lowest energy docking model was chosen. When the binding energy is < 0 kcal/mol, the small molecule ligand can spontaneously bind to the protein receptor. If the binding energy is < −5.0 kcal/mol or lower, it indicates that both have good binding ability. The heat map of the docking results is shown in Fig. 6, the results showed that the core target bound well to the compound and exhibited a strong ability to bind to the core target. Researchers show the targets with the highest affinity (Fig. 7) and demonstrate the interactions between compounds and residues at the protein binding sites. Quercetin had the lowest score with TNF, −7.58 kcal/mol. This further suggests that the compounds may play an important role in the treatment of coronary artery disease.

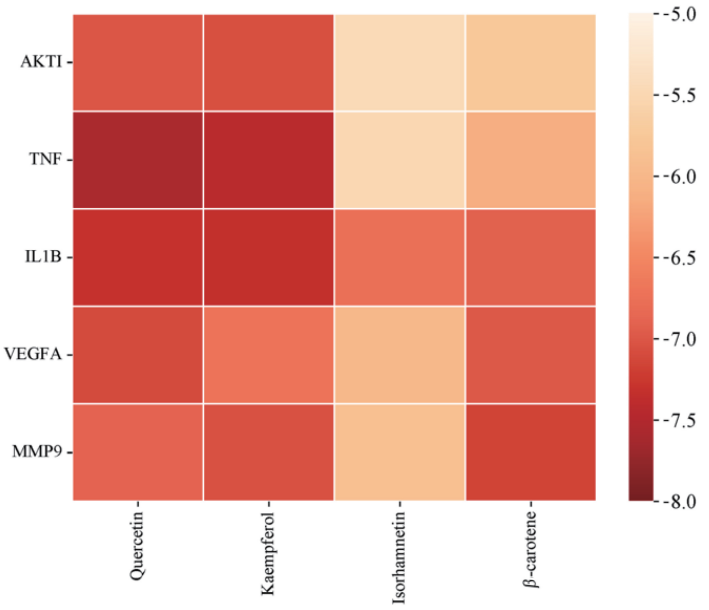


Fig. 6 Heat map of docking results

4 Discussion

CHD is a common cardiovascular disease, mostly in middle-aged and elderly people, but nowadays the incidence trend is younger, causing a huge burden to families and society. TCM formulations have been used for thousands of years to achieve therapeutic effects through the action of the active ingredients of multiple drugs in biological networks, using their multiple targets and pathways to interfere with the onset and progression of disease [28].

In this study, 11 active ingredients and several core common targets were initially screened. Among them, quercetin has the highest degree value in the network and belongs to the class of flavonoids, which are also polyphenols characterized by compounds containing a large number of phenolic structural units. It can play a cardiovascular protective role through multiple pathways such as inhibition of inflammation and protection of endothelial function [29]. It has been observed that quercetin can reduce the transcriptional activity of NF-κB in stable coronary artery disease and play a therapeutic role in stable coronary artery disease [30]. Clinical trials have revealed that the use of quercetin reduced serum levels of IL-1B, IL-10 and TNF-α in patients with chronic coronary artery disease, thus playing a therapeutic role in coronary artery disease. In the pathogenesis of coronary artery disease, quercetin in ability to antiplatelet aggregation and play a therapeutic role in coronary artery disease [31]. The pathogenesis of CHD is often based on the progressive deterioration of coronary atherosclerosis,

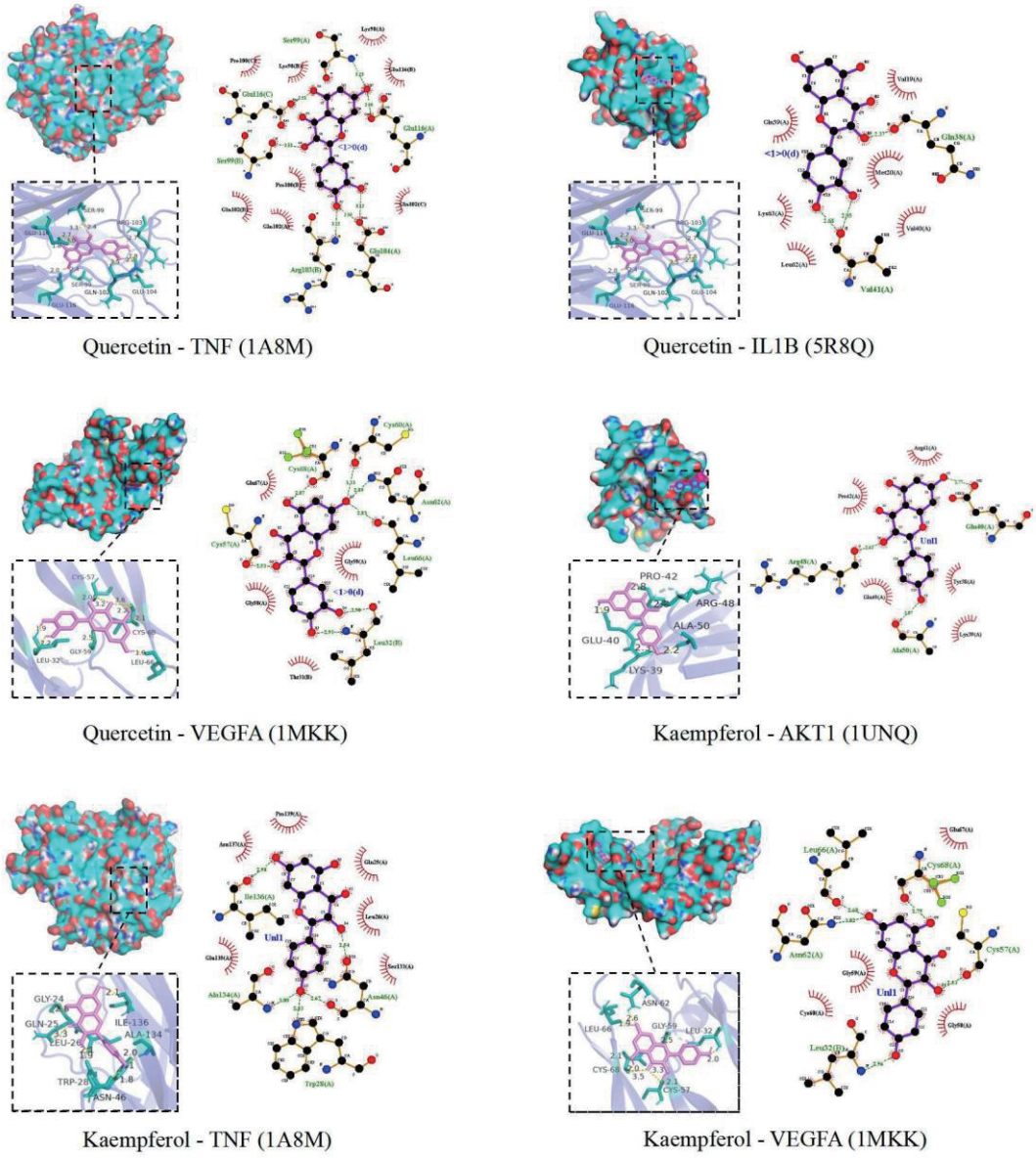


Fig. 7 Molecular docking and visualization of docking results

and the promoters of this process are mostly seen in the increase of blood lipids, and quercetin can reduce the production of triglycerides [32]. Kaempferol is a plant-derived polyphenolic compound, a type of flavonoid that has a positive impact on the prevention and treatment of diabetes and cardiovascular disease [33], with antioxidant, anti-inflammatory, and anti-apoptotic effects, and its intake is linearly associated with lower cardiovascular risk [34]. Kaempferol attenuates myocardial hypertrophy induced by aortic striation and improves myocardial function by inhibiting ASK1/MAPK signaling pathway and regulating oxidative stress [35], and also reduces oxidative stress and inflammation via AGE-RAGE/MAPK pathway thereby alleviating myocardial ischemia-reperfusion injury in diabetic rats [36].

AKT1 is one of three closely related serine/threonine protein kinases (AKT1, AKT2, AKT3) involved in the regulation of various processes including metabolism, value addition, cell survival, growth and angiogenesis, and is an important intermediate molecule in the PI3K-AKT signaling

pathway, which is associated with atherosclerotic plaque formation and is a key player in cardiovascular disease [37]. AKT1 is the only AKT isoform that is enriched in both heart and brain, and it is essential in the proliferation and migration of vascular smooth muscle cells to protect cardiomyocytes and reduce oxidative stress-induced cellular regulation. Deletion of Akt1 reduces the proliferation and migration of vascular smooth muscle cells and induces plaque vulnerability and cardiac dysfunction [38]. It was noted that AKT1 may improve cardiac contraction through the upregulation of phosphoprotein phosphorylation [39] and play a role in mediating positive muscle force [40]. In addition, studies in male mice expressing only AKT1 hematopoietic cells revealed a significant decrease in the expression levels of B cells, leukocytes, and monocytes in mice, which impaired the viability of macrophages and reduced the development of early atherosclerosis [41]. TNF (Tumor Necrosis Factor), as an upstream signaling molecule of the NF-κB pathway, is mainly expressed by activated macrophages and also promotes the production of other cytokines and chemokines that exacerbate the chronic inflammatory process in coronary artery disease, and has an important role in initiating the inflammatory-immune response and mobilizing the cascade response [42]. In general, the inflammatory response is driven by a sustained elevation of TNF-α, which is associated with a variety of myocardial diseases such as myocardial hypertrophy, myocardial ischemia, myocardial reperfusion injury, and myocardial infarction [43]. TNF-α actively participates in the inflammatory response of atherosclerotic plaques, on the one hand, promoting plaque formation and rupture, leading to the development of CHD and even acute myocardial infarction; on the other hand, it directly damages vascular endothelial cells and increases vascular permeability, leading to *in vivo* cholesterol penetration of the intima and deposition in the vessel wall, ultimately aggravating the process of atherosclerotic plaques [44]. Kumari, et al. [45] showed that TNF-α may be an independent predictor of coronary artery disease in the North Indian population. VEGFA (vascular endothelial growth factor A) is mainly involved in the regulation of vascular endothelial growth and is an important factor affecting angiogenesis [46].

Shear stress is the frictional force of blood flow acting on the inner surface of the vascular wall, and endothelial cells covering the inner surface of the vessel are constantly exposed to shear, and endothelial cells respond to changes in local shear stress to modulate intracellular signals, which regulate the structure and function of the vascular endothelium [47]. In addition, shear forces play an important role in a variety of cardiovascular diseases by altering endothelial functions such as proliferation, inflammation and hydrogen monoxide inhibition, and ultimately atherosclerosis [48]. MAPK signaling pathway is an important pathway for signaling from the cell surface to the interior of the nucleus and plays an important role in a variety of cardiovascular diseases by mediating cell proliferation, differentiation, and apoptosis [49]. Logatkina, et al. [50] found that increased MAPK signaling pathway components can lead to sustained inflammatory activation of whole blood cells in patients with CHD. MAPK pathway plays an important role in the pathogenesis of CHD. As an important member of the MAPK family, p38 MAPK plays a major role in important signaling pathways mediating cardiomyocyte regulation and is involved in ischemia, reperfusion, and regulation of cardiomyocytes [51-53].

All these results suggest that *C. sativus*-*R. rugosa* shows effectiveness in various biological processes of CHD, and the interaction of different components can be achieved by different modes of action of each component. This study reasonably confirms the new drug, provides potential pharmacological pathways, and successfully fills a gap in the use of medicine and food homologous flowers combinations in the treatment of diseases.

5 Conclusion

In this study, researchers investigated the core components and targets of *C. sativus*-*R. rugosa* for the treatment of CHD by means of network pharmacology

and GEO data mining and verified their reliability by molecular docking technology, which laid a theoretical foundation for the clinical application of *C. sativus-R. rugosa* and provided a direction for the study of the therapeutic mechanism of CHD.

Acknowledgments

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