To explore the active constituents of *Sedum aizoon L* in the treatment of coronary heart disease based on network pharmacology and molecular docking methodology

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Background: There is a lack of effective drugs for the treatment of coronary heart disease (CHD). *Sedum aizoon L* (SL) has multiple effects, and there is no report on CHD in SL at present. The aim of this study is to explore the mechanisms of action of SL in the treatment of CHD based on network pharmacology and molecular docking technology.

Methods: The targets and active ingredients of SL were screened using the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database, and CHD-related targets were obtained by searching GeneCards and DisGeNet databases. The intersection of LS active ingredient targets and CHD targets was used to construct a "drug-ingredient-disease-target" network using the Cytoscape software. The STRING database was used to construct a protein-protein interaction (PPI) network, and Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed. Key targets and core active ingredients were selected and molecular docking was performed using the AutoDock software.

Results: According to the predicted results, a total of 134 corresponding target genes for LS, 12 active components, 1,704 CHD-related targets, and 52 intersecting targets were obtained. GO function and KEGG pathway analysis showed that the key targets were involved with signal transducer and activator of transcription 3 (*STAT3*), tumor protein p53 (*TP53*), and vascular endothelial growth factor A (*VEGFA*). The molecular docking results showed that the key targets bound to the important active ingredients in a stable conformation. The core active ingredients of LS in the treatment of CHD were determined to be ursolic acid, myricetin, and beta-sitosterol.

Conclusions: SL may act on targets such as *STAT3*, *TP53*, and *VEGFA* through tumor necrosis factor (TNF) signaling pathway, interleukin 17A (*IL-17A*) signaling pathway, AGE-RAGE signaling pathway in diabetic complications, and other related pathways, thereby playing a role in preventing and treating CHD.

Keywords: *Sedum aizoon L* (SL); coronary heart disease (CHD); network pharmacology; molecular docking

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Introduction

Cardiovascular disease (CVD) is currently one of the leading causes of human mortality, and the residual risk of CVD patients remains high through lifestyle interventions and pharmacological treatment (1). Although mortality from coronary heart disease (CHD) has declined in recent years, CHD remains the leading cause of death worldwide and carries a significant economic burden (2,3). The search for drugs that can prevent and treat CHD is important to further reduce the incidence of major adverse cardiovascular events in patients with CHD. Currently, most drugs used in clinical practice are chemically synthesized and are prone to drug resistance and certain adverse events. In contrast, Chinese herbal medicines have achieved promising clinical efficacy by treating the disease from a multi-pathway and multi-target perspective (4).

Studies have shown that herbal medicines can prevent CHD by regulating oxidative stress and promoting angiogenesis to protect against myocardial ischemic injury and other pathways (5,6). *Sedum aizoon L* (SL), an herb of the *Sedum* family, contains a large number of active substances that are considered to have medicinal and food-related effects. Numerous reports have indicated that SL mainly exerts antibacterial and blood pressure-lowering activity (7-9). Recent study has shown that components of SL can effectively improve glucolipid metabolism, organ coefficients and antioxidant stress enzymes, reduce liver tissue damage, and regulate redox imbalance in type 1 diabetes mellitus (T1DM) mice by modulating the Nrf2/Keap1/ARE signaling pathway (10). However, there is a paucity of examining the role of SL in the treatment of CHD and this warrants further investigation.

Cyberpharmacology is an interdisciplinary field based on bioinformatics, molecular biology, and major databases to study the relationship between "drug-gene target and disease" (11,12). Cyberpharmacology can elucidate the mechanisms of action of multi-component and multi-target herbal medicines, while screening the main active ingredients. There is currently a lack information regarding the potential effects and mechanisms of SL in the treatment of CHD. Therefore, this study conducted an in-depth analysis of the effective active ingredients of SL in the treatment of CHD, and the related action targets and signaling pathways through a network pharmacology approach. This information will provide novel insights into potential clinical treatments for CHD. We present the following article in accordance with the STREGA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5391/rc).

Methods

Acquisition of active ingredients and targets of SL

The active ingredients and corresponding targets of *SL* were identified by searching with the keyword *SL* in the Systematic Pharmacology Database and Analysis Platform for Traditional Chinese Medicine (https://old.tcmsp-e.com/tcmsp.php; TCMSP), as well as the Uniprot database (https://www.uniprot.org/). i.e., the targets on which the active ingredients of King's panax ginseng act. We used cytoscape to visualize and analyze the active ingredients of *SL* and their corresponding targets.

Acquisition of CHD targets

Using "coronary heart disease" as a keyword, the DisGeNet (https://www.disgenet.org/) and GENECARDS (https://www.genecards.org/) databases were searched to obtain datasets of CHD targets. The CHD dataset was retrieved using the Gene Expression Omnibus data base (GEO) database to obtain the GSE20680 and GSE20681 datasets, which were normalized using the "limma" package in R software. In the above datasets, P<0.05 was set as the criteria for differential genes, which were considered key genes for CHD. The "VennDiagram" package in R software was used to obtain the intersection as a potential target for improving CHD. There were at least two datasets intersecting as potential targets for improving CHD. Finally, the Venn diagram of the therapeutic targets of SL and the disease targets of CHD was drawn as the potential targets of SL for

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Key findings
• SL may be a potential therapeutic agent for CHD.

What is known and what is new?
• SL have been variously used to treating several diseases.
• SL role of CHD did not have researched. In presents study,it act as on targets such as STAT3, TP53, and VEGFA through tumor necrosis factor (TNF) signaling pathway, thereby playing a role in preventing and treating CHD.

What is the implication, and what should change now?
• SL may contribute to the treatment and prevention of CHD.

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improving CHD. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Functional enrichment analysis of potential action targets

Gene Ontology (GO) functional enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed using the Cluster Profiler package in the R software to determine the potential targets of the Chinese medicine SL to improve CHD.

Protein-protein interaction (PPI) network construction

The intersection targets obtained above were uploaded to the STRING 11. 0 database (https://string-db.org/), the species was set as "Homo sapiens", and the minimum interaction threshold was set to 0.4. The free nodes were removed to obtain the PPI network, and the cytohubba plug-in in Cytoscape software was used to obtain the top 10 key targets for improving CHD based on the MCC algorithm, from the highest to the lowest MCC score.

The main components of SL in the treatment of CHD

To determine the main active ingredients of SL in improving CHD, the active ingredients of SL and the potential targets of improving CHD were used to construct an intersection gene Venn diagram using the "VennDiagram" package in R software. The active ingredients with the potential to improve CHD were considered the main active ingredients of SL in improving CHD. Based on these intersecting genes, the Cluster Profiler package was used to construct the GO functional analysis and KEGG enrichment analysis to elucidate the potential mechanisms of action.

Molecular docking

The network pharmacology analysis identified 10 key genes that play important roles in the ability of SL to improve CHD. Using the RSCB PDB (http://www.rcsb.org/) database, we downloaded the optimal pdb format files of the above 10 key protein receptors, performed dehydration and hydrogenation operations with PyMOL. The Auto Dock software was used to merge non-polar hydrogen, determine the atom type and other characteristics, and the results were saved in pdbqt format. The coordinates and sizes of the binding sites of the key protein receptors

were determined and saved in the relevant format as txt files. Finally, vina diagram was run separately for molecular docking to virtually screen the active ingredients of Chinese medicine SL for improving CHD. The docking results of each important protein receptor with the screened active ingredients of SL with lower binding energy and better conformation were selected and visualized using the PyMOL software.

Statistical analysis

Data were obtained from public database downloads. For the identification of differentially expressed genes (DEGs), |log2 (foldchange)| >1 and P value <0.05 were set as the statistically significant criteria. For GO and KEGG analyses, a q value <0.05 was considered statistically significant.

## Results

Active components and targets of SL

According to the screening conditions, a total of 12 active ingredients and 134 therapeutic targets of SL were obtained from the TCMSP database, and the regulatory network of active ingredients and targets of SL was constructed using Cytoscape software. As shown in *Figure 1A*, the center circle is the active ingredient of SL, and the surrounding circles are the targets, the color shades and the size of the diagram are determined by the connectivity between the active ingredient and the targets. The results identified the top three active ingredients as ursolic acid, myricetin, and beta-sitosterol (*Table 1*).

CHD target screening

A total of 221 DEGs were identified in the GSE20680 dataset, of which, 150 were upregulated and 71 were downregulated. In the GSE2681 dataset, a total of 297 DEGs were identified, including, 212 upregulated genes and 85 downregulated genes (*Figure 1B,1C*).

Potential therapeutic targets of SL

Based on the DEGs screened in the GEO dataset and the CHD-related genes identified in the DisGeNet and GENECARDs databases, the targets that intersected at least 2 or 3 times were identified and defined as CHD-

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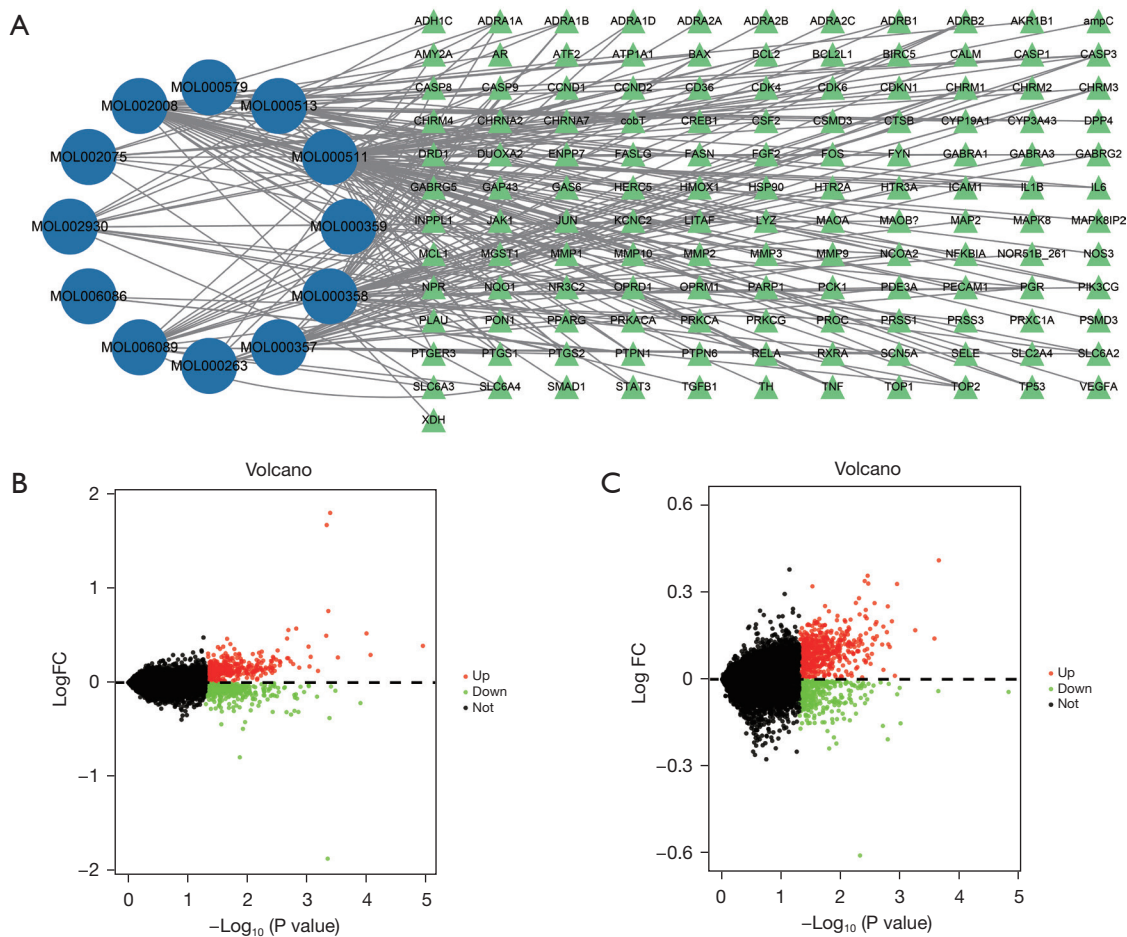
Figure 1 The differential expression of genes for the target and active ingredients of SL in coronary heart disease. (A) Active ingredients and targets of SL. (B,C) Volcano plots for the GSE20680 and GSE20681 datasets. SL, Sedum aizoon L; FC, fold change.

Table 1 The active ingredient of *Sedum aizoon L*

| MOL ID	Active ingredients
MOL002008	Myricetin
MOL002075	1-[(2S)-1-methyl-2-piperidyl]acetone
MOL000263	Oleanolic acid
MOL002930	Tyrosol
MOL000357	Sitogluside
MOL000358	Beta-sitosterol
MOL000359	Sitosterol
MOL000511	Ursolic acid
MOL000513	3,4,5-trihydroxybenzoic acid
MOL000579	Hydroquinone
MOL006086	Isomyricitrin
MOL006089	(1R)-2-[(2S)-1-methyl-2-piperidyl]-1-phenyl-ethanol

MOL, molecular.

related therapeutic targets. Finally, a total of 52 potential targets were identified for SL in the treatment of CHD (*Figure 2A,2B*).

GO and KEGG analyses, and the PPI network

To further explore the mechanisms of action of *SL* in the treatment of CHD, we performed enrichment analysis and PPI network construction on the above screened targets. The genes that intersected in the two databases were examined. The targets were mainly enriched in the biological processes (BP) including response to lipopolysaccharide, response to molecule of bacterial origin, and response to oxidative stress; cell components (CCs) including membrane raft, membrane microdomain, and membrane region; and molecular functions (MFs) including endopeptidase activity, RNA polymerase II transcription
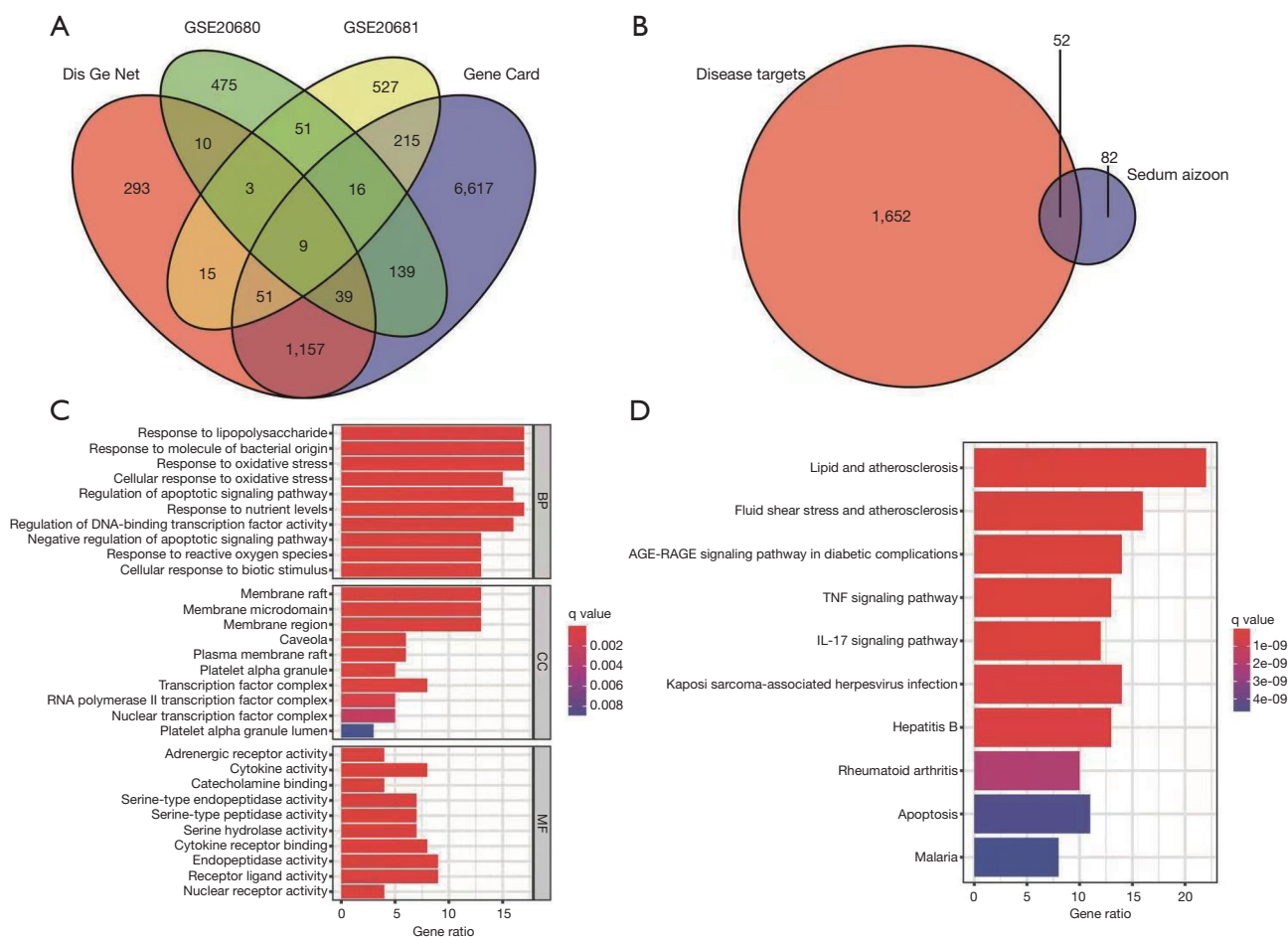
Figure 2 The targets and enrichment analysis related to coronary heart disease treatment. (A) The therapeutic targets of CHD in two disease databases and GEO datasets. (B) The targets in at least 2 databases in (A) and the SL therapeutic targets. (C) GO enrichment analysis. (D) KEGG enrichment analysis. BP, biological process; CC, cell component; MF, molecular function; TNF, tumor necrosis factor; IL, interleukin; CHD, coronary heart disease; GEO, Gene Expression Omnibus; SL, Sedum aizoon L; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

factor binding, and activating transcription factor binding. KEGG enrichment analysis showed that the targets were mainly enriched in lipid and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, TNF signaling pathway, and *IL-17* signaling pathway (*Figure 2C,2D*). The PPI network was then constructed for potential therapeutic targets, and the results showed that *STAT3*, *TP53*, *VEGFA*, intercellular adhesion molecule 1 (*ICAM1*), interleukin 1B (*IL1B*), interleukin 6 (*IL-6*), matrix metallopeptidase 2 (*MMP2*), matrix metallopeptidase 9 (*MMP9*), *TNF*, and prostaglandin-endoperoxide synthase 2 (*PTGS2*) were the top 10 core genes (*Figure 3*).

Identification of core active ingredients and their mechanisms of action

The identified active ingredients of SL were intersected with the disease targets of CHD. A total of 28 target genes were identified, and ursolic acid was determined to be the main core ingredient of SL. Further enrichment analysis showed a high degree of overlap with GO and KEGG of SL target genes (*Figure 4*).

Molecular docking

The top 10 identified targets, including *TP53*, *TNF*,

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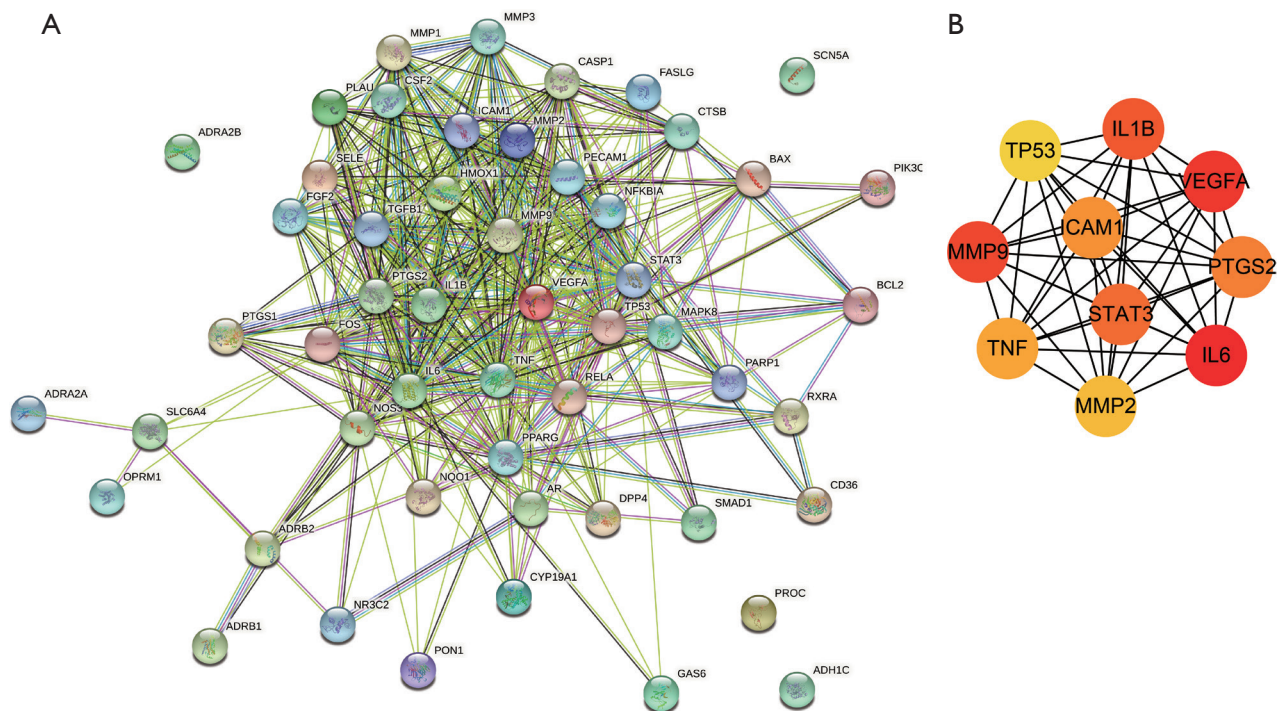
Figure 3 The protein-protein interaction network involved in the treatment of coronary heart disease using SL. (A) The PPI network analysis of intersection targets of at least two databases. (B) The PPI network analysis of the intersection targets of three databases. TP53, tumor protein p53; IL1B, interleukin 1, beta; VEGFA, vascular endothelial growth factor A; ICAM1, intercellular adhesion molecule 1; MMP9, matrix metallopeptidase 9; PTGS2, prostaglandin-endoperoxide synthase 2; STAT3, signal transducer and activator of transcription 3; TNF, tumor necrosis factor; IL-6, interleukin 6; MMP2, matrix metallopeptidase 2; SL, Sedum aizoon L; PPI, protein-protein interaction network.

and *IL-6*, were identified by PPI network analysis, and the corresponding active ingredients were identified by molecular docking (*Figure 5*).

Discussion

Medications are one of the main treatment modalities for CHD, but the need for patients to take multiple medications at the same time due to underlying comorbidities is a great burden for both patients and society. Despite the multiple drugs available for the treatment of CHD, they have limited mechanisms of action and long-term use can lead to complications. Network pharmacology is of great significance and high research value in revealing the treatment mechanism and pharmacology laws of complex traditional Chinese medicine. The practical application of network pharmacology also proves that the combination of traditional Chinese medicine and modern medical technology is a powerful way and can play an important role

in the field of traditional Chinese medicine. This current study used network pharmacology to identify the potential targets and active ingredients of SL in the treatment of CHD, and preliminarily elucidated the possible mechanisms of action.

The PPI core network and molecular docking analysis revealed that the major components of SL may be involved in the regulation of CHD through genes such as *STAT3*, *TP53*, *VEGFA*, *IL-6*, *MMP2*, *MMP9*, and *PTGS2*. CHD is a chronic, progressive, and inflammatory lesion of the coronary arteries. *STAT3* and *TP53*, as transcription factors of the classical cellular pathway, may play a key role in the inflammatory and immune response (13,14). Study has shown that the IL-6/JAK/STAT3 signaling pathway plays an vital role in endothelial cell dysfunction and immune cell differentiation in atherosclerosis (15). *VEGFA* has been demonstrated to be associated with pathological angiogenesis, and its genetic polymorphisms may have a significant impact on susceptibility to CHD in the Han
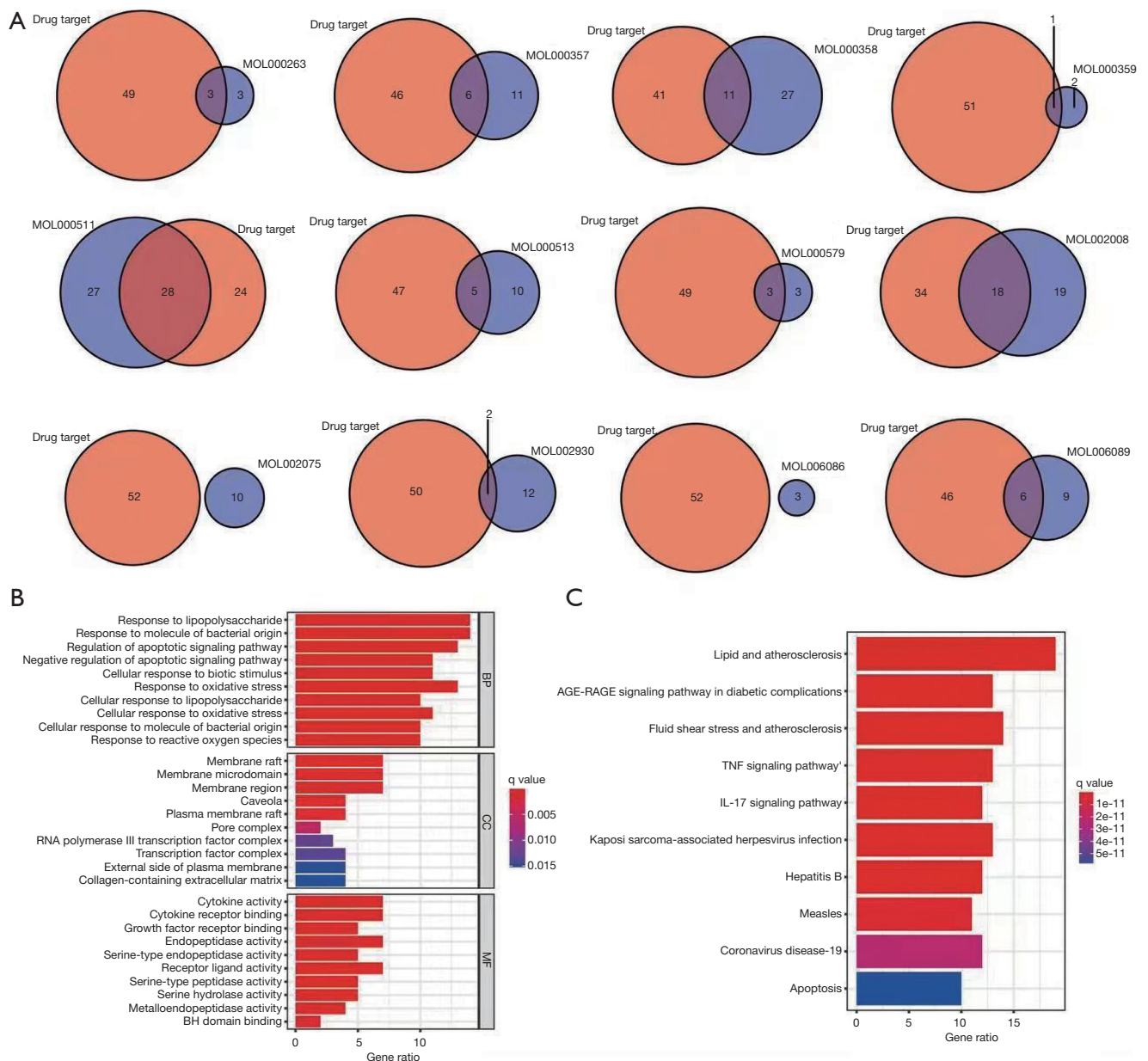
Figure 4 Enrichment analysis of the action and active components of SL in the treatment of coronary heart disease. (A) Target genes of SL and CHD. (B) GO enrichment analysis. (C) KEGG enrichment analysis. BP, biological process; CC, cell component; MF, molecular function; TNF, tumor necrosis factor; IL, interleukin; SL, Sedum aizoon L; CHD, coronary heart disease; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Chinese population (16). The *VEGF* family has shown extraordinary potential in the treatment of CHD by regulating angiogenesis, inflammation, and apoptosis (17). *IL-6* is independently associated with the risk of major adverse cardiovascular events, as well as cardiovascular and all-cause mortality in patients with stable CHD, possibly

reflecting the pathophysiological involvement of *IL-6* in the development of these events (18). *MMP2* and *MMP9* play important roles in extracellular matrix and collagen metabolism, and studies have shown that atheromatous plaques in patients with acute coronary syndrome have a large number of macrophages and smooth muscle cells

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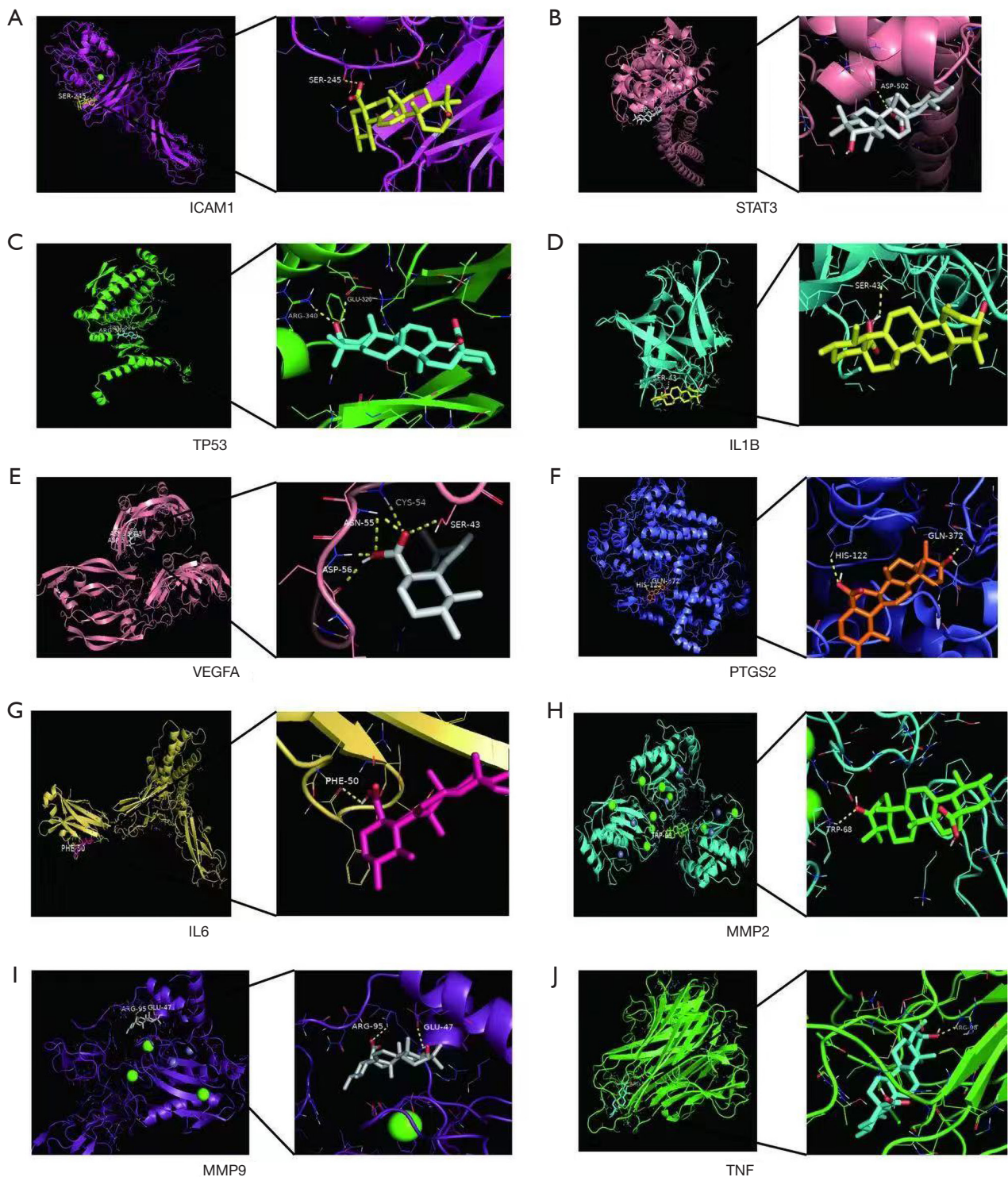
Figure 5 Molecular docking of the top 10 core genes. (A) *ICAM1*. (B) *STAT3*. (C) *TP53*. (D) *IL1B*. (E) *VEGFA*. (F) *PTGS2*. (G) *IL-6*. (H) *MMP2*. (I) *MMP9*. (J) *TNF*. ICAM1, intercellular adhesion molecule 1; STAT3, signal transducer and activator of transcription 3; TP53, tumor protein p53; IL1B, interleukin 1, beta; VEGFA, vascular endothelial growth factor A; PTGS2, prostaglandin-endoperoxide synthase 2; IL-6, interleukin 6; MMP2, matrix metallopeptidase 2; MMP9, matrix metallopeptidase 9; TNF, tumor necrosis factor.

with a significant increase in MMP2/MMP9 expression, suggesting a significant role of MMP2/MMP9 in the pathogenesis of atherosclerosis (19-21). *PTGS2* is a key enzyme in the synthesis of prostaglandins and has a critical role in the inflammatory response, and previous reports have suggested that *PTGS2* may be a potential therapeutic target in CHD (22,23).

KEGG enrichment analysis revealed that *SL* treatment of CHD was mainly enriched in signaling pathways such as AGE-RAGE signaling pathway in diabetic complications, *TNF* signaling pathway, and *IL-17* signaling pathway. AGE/RAGE signaling pathway in diabetic complications can regulate the production and expression of *TNF-α* in type 2 diabetes and promote endothelial dysfunction, which leads to cardiovascular disease (24). *VEGF* enhances vascular endothelial cell proliferation, migration, and survival, and is an important mediator of angiogenesis (25). *TNF-α* promotes *VEGF* expression and angiogenesis, mediates endothelial chemerin expression under hypoxic conditions, and promotes early angiogenesis (26,27). *IL-17* acts mainly on vascular and cardiac myocytes and exacerbates inflammation, coagulation, and thrombosis, in addition to activating downstream pathways such as NF-KB and promoting the secretion of related cytokines (28,29). In addition, it was found that hyperglycemia may exacerbate the complexity of coronary atherosclerosis through IL-17/IL-10 signaling (30). It is thus hypothesized that the active ingredients of SL may act on the core targets of the above-mentioned signaling pathways to treat CHD.

The results of this study showed that ursolic acid, myricetin, and beta-sitosterol are the main active ingredients of SL for the treatment of CHD. Ursolic acid belongs to a group of pentacyclic triterpenoids with C-3 hydroxyl and C-28 carboxylic acid groups and is widely found in the wax layer of coffee, lavender, and fruits (31,32). Studies have shown that ursolic acid can be used as an alternative drug in the treatment of diseases such as swelling, diabetes, and liver disease (33). In addition, it has been reported that the use of ursolic acid reduces oxidative effects in rats with diabetic cardiomyopathy, decreases the expression of *TNF-α*, *MCP-1*, and *TGF-β1* in the heart, and lowers blood glucose levels, in addition to improving the function of the heart (34,35). Myricetin is a natural flavonoid that inhibits the proliferation and migration of vascular smooth muscle cells through inhibition of the TGFBR1 signaling pathway, thereby inhibiting neoplastic endothelial proliferation (36). Myricetin can reduce myocardial injury and heat stroke mortality through upregulation of heat shock protein

(HSP)-72, which is expected to be a novel therapeutic agent for heat stroke prevention (37). In addition, myricetin has a protective effect on myocardial injury caused by acute ischemia-reperfusion in isolated rat hearts (38). Taken together, these findings are consistent with our findings that myricetin has cardioprotective effects. Beta-sitosterol is a polyphenolic hydroxamic acid compound widely found in plants and also one of the main components of eukaryotic cell membranes. It has a high concentration in plant oils, seeds, and fruits and vegetables, with antioxidant, cholesterol-lowering, anti-inflammatory, and anti-diabetic effects (39). It has been shown that beta-sitosterol-mediated silver nanoparticles appear cytotoxic in human colon cancer and promote apoptosis in colon cancer cells (40). The advantage of network pharmacology is that it can effectively predict the target of drug and disease interaction, but the difficulty is that molecular docking requires corresponding computer simulation technology. The lack of basic experimental verification is our limitation.

Conclusions

In summary, SL may act on the above targets and pathways to achieve hypoglycemic and anti-inflammatory effects to prevent and treat CHD. However, since the information in the online database does not completely cover all potential targets, this may have limited the study somewhat. Further cellular and animal experiments are warranted to verify the results herein, and to provide further support and theoretical basis for the clinical use of SL in the treatment of CHD.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STREGA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5391/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5391/coif).

The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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