Exploring the Active Compounds of Traditional Mongolian Medicine Baolier Capsule (BLEC) in Patients with CAD Based on Network Pharmacology Analysis and Molecular Docking Method

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Research Article

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Abstract

Baolier Capsule (BLEC) is a Traditional Mongolian Medicine comprising of fifteen herbs. In China, this medicine has been used to treat CAD for many years. However, the molecular mechanism of BLEC in the treatment of CAD is not yet fully understood. Hence, this study aims to illustrate the synergistic mechanism of BLEC in the treatment of CAD by using network pharmacology method and molecular docking. Searching and screening the active ingredients of different herbs in BLEC and target genes related to CAD in multiple databases. Subsequently, STRING and Cytoscape were used to analyze and construct the PPI network. In addition, clustering and topological analysis are used to analyze the PPI network. Then, using R project for GO and KEGG enrichment analysis. Finally, AutoDock was used to verify the binding ability between the active ingredient and the key target through molecular docking. There are 144 active components and 80 CAD-related targets that are identified in BLEC in the treatment of CAD. What is more, 8 core genes (AKT1, EGFR, FOS, etc.) were obtained by clustering and topological analysis. Further, GO and KEGG analysis showed that fluid shear stress and atherosclerosis is the key pathways for RWW to treat CAD. These results were validated by molecular docking method. Our research firstly revealed the basic pharmacological effects and relevant mechanisms of the BLEC in the treatment of CAD. The prediction results might facilitate the development of BLEC or its active compounds as alternative therapy for CAD. Our research first revealed the basic pharmacological effects and related mechanisms of BLEC in the treatment of CAD. The predicted results provide some theoretical support for BLEC or its important active ingredients to treat CAD.

Introduction

At present, major progress has been made to prevent and treat cardiovascular disease (CVD) through lifestyle changes and drugs, but CVD is still the main cause of death in humans, especially in developed country and developing country[1]. It is worth noting that the residual risk of CVD in patients is still high, even though on the basis of the best lifestyle intervention and high-dose statin therapy, new lipid-lowering drugs such as ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and (cholesterol ester transfer protein) CETP inhibitors, and even kanazumab are used[2–6]. Therefore, looking for drugs that can prevent and treat coronary artery disease (CAD) is of great significance to further decrease the incidence of major adverse cardiovascular events (MACEs) in patients who suffer from CAD.

Traditional Chinese medicine has opened up a new path for the treatment of CAD. Among them, Mongolian medicine, as one of the outstanding cultural heritage of the Mongolian nationality, is a summary of the Mongolian experience in fighting against diseases for a long time, and gradually formed by absorbing the experience of traditional Chinese medicine and Tibetan medicine. The curative effect is remarkable and it is increasingly accepted by people. Yogurt, which is a popular Mongolian dairy products, contributed to prevent and manage hyperlipidemia, blood glucose and inflammatory marker[7]. *Syringa pinnatifolia Hemsl.* ,which is a Mongolian folk medicine in China, may protect against myocardial ischemia[8]. Eerdun Wurile (EW) is a well established traditional Mongolian medicine with proven clinical application for treatment of stroke recovery[9, 10]. Qingganjiuwei powder (QGJWS) is a commonly used

Mongolian drug to treat patients with chronic hepatic disease through protecting liver fibrosis[11]. The use of Mongolian drugs to treat CAD has certain application prospect.

Baolier capsule (BLEC), one of the Mongolian drugs, comes from the classic Mongolian medicine book “Coral Experience Prescription”, “ The Set of Mongolian medicine prescription” and “Zhigao prescription”[12]. BLEC consists of fifteen herbs[12]. BLEC can protect vascular endothelial function, inhibit inflammation and significantly improve the symptoms of patients with CAD, including number and duration of episodes of angina and number of using for Nitroglycerin[13, 14]. However, BLEC is formed of dozens of compounds from Chinese patent medicine and Chinese herbal compound formula, which leads to the difficulties in exploring BLEC mechanism. It is importance clinically to discover the target genes and compounds of BLEC in discovering new drugs. Our study innovatively applies network pharmacology method and molecular docking to analyze key targets, and signal pathways of BLEC in treating CAD, to guide future researches of this formula. The detailed workflow is showed in Fig. 1.

Materials And Methods

Collection and Screening of Candidate Compounds in Baolier Capsule

The herbs in BLEC decoction include Guangzao (*Choerospondiatis Fructus*), Danshen (*Radix Salviae*), Roudoukou (*Myristicae Semen*), Zhizi (*Gardeniae Fructus*), Qiancao (*Rubia Cordifolia*), Honghua (*Carthami Flos*), Sanqi (*Panax Notoginseng (Burk.) F. H. Chen Ex C. Chow*), Muxiang (*Aucklandiae Radix*), Tanxiang (*Santalum Album L.*), Niuhuang (*Bovis Calculus*), Dahuang (*Radix Rhei Et Rhizome*), Mutong (*Caulis Akebiae*), Huangqi (*Hedysarum Multijugum Maxim.*), Biba (*Piperis Longi Fructus*) and Hezi (*Chebulae Fructus*).The active ingredients in BLEC are gained from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) Database and Analysis Platform (http://tcmspw.com/tcmsp.php), with the keywords Guangzao, Danshen, Roudoukou, Zhizi, Qiancao, Honghua, Sanqi, Muxiang, Tanxiang, Niuhuang, Dahuang, Mutong, Huangqi, Biba and Hezi respectively. TCMSP is a Chinese herbal medicine system pharmacology platform that includes 449 herbs, can catch the relations between diseases, targets and drugs. The database comprises targets, chemicals and corresponding drug-target networks. Oral Bioavailability (OB) is an important parameter in pharmacokinetics, which is directly related to bioavailability. Drug-like (DL) indicates active ingredient’s similarities to present drugs. We selected active ingredients with OB > 30% and DL > 0.18 for later research[15].

Identification of potential targets of active ingredients and CAD

We obtain potential targets of active ingredients in BLEC from the database, retrieve related targets of CAD from Gene cards (https://www.genecards.org), Online Mendelian Inheritance in Man (OMIM, https://www.omim.org/), PharmGKB (http://www.pharmgkb.org), Therapeutic Target Database (TTD, http://db.idrblab.net/ttd/) and DrugBank (https://go.drugbank.com/). In addition, genes related to CAD,

which are obtained from Gene cards, were selected according to relevance score greater or equal to 30. UniProt (https://www.uniprot.org) can help people find full name, ID and symbols of related gene.

Construction of ingredient-target-disease network

To further explore the relations between potential targets and active ingredients, we loaded the them into Cytoscape 3.8.0 to form an ingredient-target-disease network.

Construction of protein-protein interaction network

STRING (http://string-db.org) is an convenient online database to build protein-protein interaction (PPI) network[16]. Every interaction between target proteins will be scored. Then, following steps will be performed: selecting “multiple proteins”, inputting target genes that may interact with active ingredients in BLEC and related genes of CAD, searching in “Homo sapiens”, setting minimum required interaction score to high confidence (0.9) and hiding disconnected nodes in the network. Finally, target proteins will be put into Cytoscape to build the interaction network.

Analysis of gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG)

Target genes which are potential ones of active ingredients in BLEC and related ones in CAD are put into the R project for GO and KEGG analysis, in order to discover what role the selected targets plays in signal pathways.

Molecular docking

Construction of receptor structure

The ID of core target proteins of PPI network was obtained from Uniprot. According to the ID, receptor structure file was downloaded from RCSB PDB (http://www1.rcsb.org/) as pdb format. We import the receptor structure file into pyMOL software and save it in pdb format after removing molecules and small molecule ligands.

Construction of ligand structure

The 2D structure of the ligand was downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/) as SDF format. The ligand structure file is imported into Chem3D software and converted into 3D structure then saved as mol2 format file after using the MM2 position to optimize the energy of all small molecules.

Molecular docking

Calculation method of molecular docking Autodock vina ADT auto dock tool MGL tools Use ADT 1.5.6 (Auto Dock Tool) to convert the format of receptor and ligand structure files. Import The receptor structure pdb format file was imported into ADT 1.5.6 (Auto Dock Tool) and was saved as pdbqt format after adding hydrogens. The ligand structure pdb format file was converted to pdbqt format. The receptor structure was converted to 2D structure through ADT 1.5.6. set. The number of points in X-dimension, Y-dimension and Z-dimension are set as 40, respectively. Spacing (angstrom) was set as 1. Active pocket parameters is exported to GPF format file. modify The input file is modified according to active pocket parameters. The maximum energy difference is 5. The number of models is 20. The outputting the pdbqt file has been imported the pyMOL software together with the receptor file to save the optimal model.

Results

Active ingredients in BLEC

1331 bioactive ingredients are selected from TCMSP database consisting of 43 types in Guangzao, 202 types in Danshen, 64 types in Roudoukou, 98 types in Zhizi, 54 types in Qiancao, 189 types in Honghua, 119 types in Sanqi, 106 types in Muxiang, 70 types in Tanxiang, 19 types in Niuhuang, 92 types in Dahuang, 43 types in Mutong, 87 types in Huangqi, 104 types in Biba and 41 types in Hezi. According to the standards OB and DL, 228 active ingredients are selected for further study, including 9 types in Guangzao, 65 types in Danshen, 9 types in Roudoukou, 15 types in Zhizi, 19 types in Qiancao, 22 types in Honghua, 8 types in Sanqi, 6 types in Muxiang, 3 types in Tanxiang, 5 types in Niuhuang, 16 types in Dahuang, 8 types in Mutong, 20 types in Huangqi, 15 types in Biba and 8 types in Hezi (**Supplementary Table 1**).

Potential target genes of active ingredients in BLEC

After removal of duplicates, 280 target genes of BLEC are acquired from TCMSP database and stored for further study (**Supplementary Table 2**).

Related genes of CAD

As Fig. 2 shown, 618 target genes of CAD are attained from Gene cards, OMIM, PharmGKB, TTD and DrugBank. As Fig. 3 shown, there are a total of 80 target genes, which are potential ones of BLEC's active ingredients and CAD's related genes.

Construction of ingredient-target-disease interactive network

To thoroughly reveal the potential ingredients and targets of BLEC against CAD, the "component-target-disease" interactive network is constructed. Moreover, this research applies network pharmacological analysis to conduct visual analysis with relevant parameters of each target. 192 nodes and 543 edges with 144 ingredients and 80 targets was displayed in this network. The network shows that the nodes possessing more edges and greater degree value play a more important role in the regulation (Fig. 4).

Accordingly, this research also establishes the network of ingredients with common targets of drugs and the disease, to directly display the interactions between potential targets and active ingredients. Degree refers to the number of routes that connect to one node and other in the network. The higher the value is, the more significant the corresponding ingredient or target is. After the Network Analyzer plugin in Cytoscape software done its analysis, ten essential active ingredients were listed in Tables 1. The result tells us that active ingredients of BLEC mainly achieved its effect on CAD through acting on the essential targets above.

Table 1
Active ingredients of BLEC in the treatment of CAD

Molecular ID	Ingredient	Degree	Source
MOL000098	quercetin	51	Zhizi/Sanqi/Guangzao/Huangqi/Honghua
MOL000006	luteolin	18	Tanxiang/Danshen/Honghua
MOL000422	kaempferol	18	Zhizi/Guangzao/Huangqi/Honghua
MOL004328	naringenin	16	Guangzao
MOL007154	tanshinone IIA	13	Danshen
MOL002773	beta-carotene	13	Honghua
MOL000378	7-O-methylisomucronulatol	13	Huangqi
MOL001592	piperine	11	Biba
MOL000354	isorhamnetin	10	Tanxiang/Huangqi
MOL006174	Xyloidone	10	Qiancao

Outcomes of PPI network

We use STRING to construct PPI network to study the mechanism of target genes of BLEC in treating CAD in accordance with protein-level high confidence (0.9). There are541 edges and 73 nodes in this network (Fig. 5). In order to obtain core target proteins, PPI network was filtered using Cytoscape software. If the Betweenness (BC), Closeness (CC), Degree (DC), Eigenvector (EC), LAC and Network (NC) of the protein is greater than the median, the protein is retained. After two filtration (Filter 1: BC = 21.71263724, CC = 0.1518718315, DC = 4.5, EC = 0.0574660525, LAC = 1.6, NC = 2.7083333335. Filter 2: BC = 8.3583916085, CC = 0.605263158, DC = 8, EC = 0.189531028, LAC = 3.25, NC = 4.3714285715), a total of 8 core target proteins were retained (Fig. 6).

Results of GO and KEGG enrichment analysis

This research uses DAVID database for GO analysis of BLEC with potential targets for CAD. 2195 GO entries are selected based on P value ($P < 0.05$). It includes 128 cellular components, 73 molecular function, and 1994 biological processes. In these biological processes, potential targets mainly focus on

responding nutrient levels, oxidative stress, oxygen levels and so on. And the targets mainly relate to membrane raft, membrane microdomain, membrane region and so on in the cellular components. For molecular function, potential targets mainly work for phosphatase binding, protein phosphatase binding, cytokine receptor binding and so on (Fig. 7 and **Supplementary Table 3**).

When we use DAVID to do the KEGG enrichment analysis of BLEC for CAD ($P < 0.05$), 162 pathways are acquired. According to P value, the top 20 pathways are selected (Fig. 8A). The pathway map of the fluid shear stress and atherosclerosis was illustrated in Fig. 8B.

Molecular docking of active compounds and core target proteins

This research use the 8 core target proteins from PPI network to perform molecular docking. Then, we get active compounds targeting core target proteins from the compound-target interaction network respectively. Subsequently, as it shows in molecular docking, all active compounds can enter and bind the active pocket of the protein easily (Fig. 9A-H). The scores of docking are displayed in Table 2.

Table 2
Molecular docking score

Protein name	Molecule name	Docking score (kcal/mol)
AKT1	baicalein	−7.8
	β-carotene	−8.0
	kaempferol	−7.7
	luteolin	−8.0
	naringenin	−8.0
	quercetin	−8.1
EGFR	luteolin	−6.0
	quercetin	−5.6
FOS	baicalein	−9.5
	piperine	−8.6
	quercetin	−10.2
	tanshinone IIA	−9.4
MAPK1	luteolin	−9.0
	naringenin	−8.7
	quercetin	−8.7
MAPK14	3_Methylkempferol	−7.7
	7-O-methylisomucronulatol	−7.5
	Calycosin	−7.4
	formononetin	−7.5
	Isoguaiacin	−7.5
	isorhamnetin	−7.5
	Sudan III	−7.4
	Xyloidone	−7.5
STAT3	cryptotanshinone	−7.4
TP53	aloe-emodin	−7.8
	baicalein	−8.1
	ellipticine	−8.8

Protein name	Molecule name	Docking score (kcal/mol)
	luteolin	−8.6
	quercetin	−8.3
	tanshinone IIA	−9.0
VEGFA	baicalein	−7.5
	β-carotene	−7.8
	ellagic acid	−7.5
	luteolin	−7.5
	quercetin	−7.3

AKT1: AKT Serine/Threonine Kinase 1, EGFR: Epidermal Growth Factor Receptor, FOS: Proto-oncogene c-Fos, MAPK1: Mitogen-activated protein kinase 1, MAPK14: Mitogen-activated protein kinase 14, STAT3: Signal transducer and activator of transcription 3, TP53: Cellular tumor antigen p53 and VEGFA: Vascular endothelial growth factor A.

Discussion

CAD is called "heart tingling" in Mongolian medicine. It is due to the dysfunction of the "three roots" and "seven elements", which hinders the movement of Heyi and the blood. The three roots refer to Heyi Xila and Badagan. Seven elements refer to dietary essence, blood, muscle, fat, bone, bone marrow and semen. Combining modern Western medicine theories, Mongolian medicine currently divides CAD into Heyi heart tingling, bloody heart tingling, adhesive heart tingling and Huyang heart tingling. Mongolian medicine mainly treats CAD by promoting the differentiation of turbidity and improving Heyi and blood circulation[17]. BLEC is a prescription confirmed by famous Mongolian medicine experts repeatedly based on the above-mentioned etiology and pathogenesis and combined with Mongolian medicine theory and clinical practice experience[12]. It can treat CAD by adjusting functions of the body's three root and seven element[12] .

To the best of our knowledge, this is the first study integrating network pharmacology and molecular docking analyses to reveal the pharmacological mechanisms of BLEC for treating CAD. We identified a total of 228 active compounds in BLEC. Furthermore, a total of 80 potential target genes related to the action of BLEC on CAD were identified. PPI analysis revealed that the top-ranking genes, AKT Serine/Threonine Kinase 1 (AKT1), Epidermal Growth Factor Receptor (EGFR), Proto-oncogene c-Fos (FOS), Mitogen-activated protein kinase 1 (MAPK1), Mitogen-activated protein kinase 14 (MAPK14), Signal transducer and activator of transcription 3 (STAT3), Cellular tumor antigen p53 (TP53) and Vascular endothelial growth factor A (VEGFA), may be the crucial targets for BLEC treating CAD. Functional enrichment analysis revealed the over-represented GO terms and their functional domains. KEGG pathway enrichment analysis revealed that the 80 target proteins were significantly enriched in 162 related signal pathways. Among them, fluid shear stress and atherosclerosis appeared to be the most

critical pathways involved in the treatment of CAD. Furthermore, molecular docking analysis demonstrated that the representative compounds could bind to the target protein binding site.

In this study, systematic pharmacological method is applied to forecast and explain the molecular mechanisms of BLEC on CAD. In BLEC's active components-targets network, we get 81 targets affected by 144 bioactive compounds. The 10 top-ranking compounds including quercetin, luteolin, kaempferol, naringin, tanshinone IIA, beta-carotene, 7-O-methylisomucronulatol, piperine, isorhamnetin, Xyloidone are identified as BLEC's active ingredients. Their biological activities against CAD were mentioned above. Quercetin is a natural bioflavonoid found in vegetables and fruits including onions, grapes, tea, apples, and red wine. It can improve endothelial cell function[18–20], inhibit dendritic cell activation[21], inhibit foam cell formation by inhibiting oxidized low-density lipoprotein-induced apoptosis of macrophages[22] and regulates cholesterol metabolism and lipoprotein metabolism by regulating cholesterol metabolism-related gene expression[23–25]. Luteolin, is a natural flavone which is abundant in edible plants, including green chilies, broccoli, French beans, onion leaf, white radish, carrots, ragweed pollen and clover blossom[26]. Studies have shown that it can inhibit the occurrence of atherosclerosis by inhibiting macrophage inflammation[27, 28]. Kaempferol, is a common natural yellow flavonoid with a low molecular weight, which exists in a number of traditional Chinese medicine and plant derived foods. Kaempferol and its glycosides have many pharmacological functions, for example, they can serve as anti-inflammatory, antioxidant, and anticancer, antidiabetic, neuroprotective, analgesic, antimicrobial, and anti-allergic drugs[29]. Studies have shown that kaempferol conducts anti-atherosclerotic effect by regulating the expression of gene and protein in inflammatory molecules[30]. Naringin is the bitter component in a kind of grapefruit which is often found in its flowering parts, peels, juice and vegetative parts[31]. Naringin can improve blood lipid levels[32], metabolic imbalances[33], and inhibit inflammatory reactions[34], and inhibit atherosclerosis[35]. Tanshinone IIA is a main bioactive component isolated from the roots of the Chinese herb *Salviae miltiorrhiza Bunge* (Danshen)[36], can regulate the autophagy and polarization of macrophages[37], and even the expression of non-coding RNA related to atherosclerosis and inflammation[38], antioxidant[39], improve endothelial cell function[40], and regulate cholesterol metabolism-related pathways affect cholesterol metabolism[41, 42]. Epidemiological evidence suggests that beta-carotene helps decrease the risk for atherosclerosis by protecting LDL from oxidation[43, 44]. Isorhamnetin, a bioactive compound, exists in herbal plants, and possesses multiple biological properties. It can inhibit macrophage apoptosis and inhibit atherosclerosis[45].

According to PPI core network analysis and molecular docking results, it is shown that the main components of BLEC can prevent and treat CAD by affecting CAD-related top-ranking genes AKT1, EGFR, FOS, MAPK1, MAPK14, STAT3, TP53 and VEGFA. A large number of studies have confirmed that intervention of the above key genes can achieve the effect of preventing and treating atherosclerosis. The lack of AKT1 can promote the release of pro-inflammatory factors, and enhance the apoptosis of endothelial cells and macrophages, leading to the development of atherosclerosis[46]. The expression of FOS in monocytes in the blood of patients with CAD is significantly increased, and its expression level is related to the severity of atherosclerosis[47]. Inhibiting the expression of FOS of THP-1 cells can reduce the release of inflammatory factors[47]. The activation of STAT3 can promote the occurrence of

atherosclerosis by affecting endothelial cell dysfunction, macrophage polarization, inflammation, and immunity. Inhibition of STAT3 can achieve the effect of inhibiting atherosclerosis[48]. P53 is a classic tumor suppressor gene. Inhibition of P53 can significantly increase the proportion of cell proliferation and apoptosis, and promote the occurrence of atherosclerosis[49]. The MAPK pathway is a classic inflammatory pathway. Inhibiting MAPK can reduce the release of macrophages MCP-1, inhibit the infiltration of macrophages into the plaque, and inhibit the occurrence and development of atherosclerosis[50]. The expression of EGFR and its ligands on arterial plaques of patients with CAD is significantly increased. By inhibiting EGFR, the uptake and inflammatory release of lipids by macrophages can be restricted, thereby inhibiting the occurrence and development of atherosclerosis[51]. VEGFA plays an important role in the formation of blood vessels, and can induce apolipoprotein to change in the direction of pro-inflammatory, and its expression increases in atherosclerosis model mice. Inhibiting the expression of VEGFA in vascular smooth muscle can reduce the size of atherosclerotic plaques[52].

However, the study also has its limitations. On the one hand, we ignored the actual dosage and performance of traditional Mongolian medicine, which can be significant in research. Besides, network pharmacology is based on the data in the existing literature. The prediction is limited.

In this pharmacology network–based study, active ingredients, core targets, and key signal pathways of BLEC in treating CAD are systematically investigated. It also provides potential therapeutic mechanisms for further researches. However, intensive explorations are required to explain the in-depth mechanisms of the active compounds, which may give guidance to the development of novel broad-spectrum antiviral agents.

Declarations

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in this article, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

Kai Guo and Zebing Ye designed the study. Mengqiu Wei, Jun Liu and Kai Guo performed the experiments and analyzed the data. Kai Guo supervised the study. Mengqiu Wei drafted the text. Jun Lai and Meifang Leng corrected the manuscript.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest

The authors have declared that no confict of interest exists.

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Figures

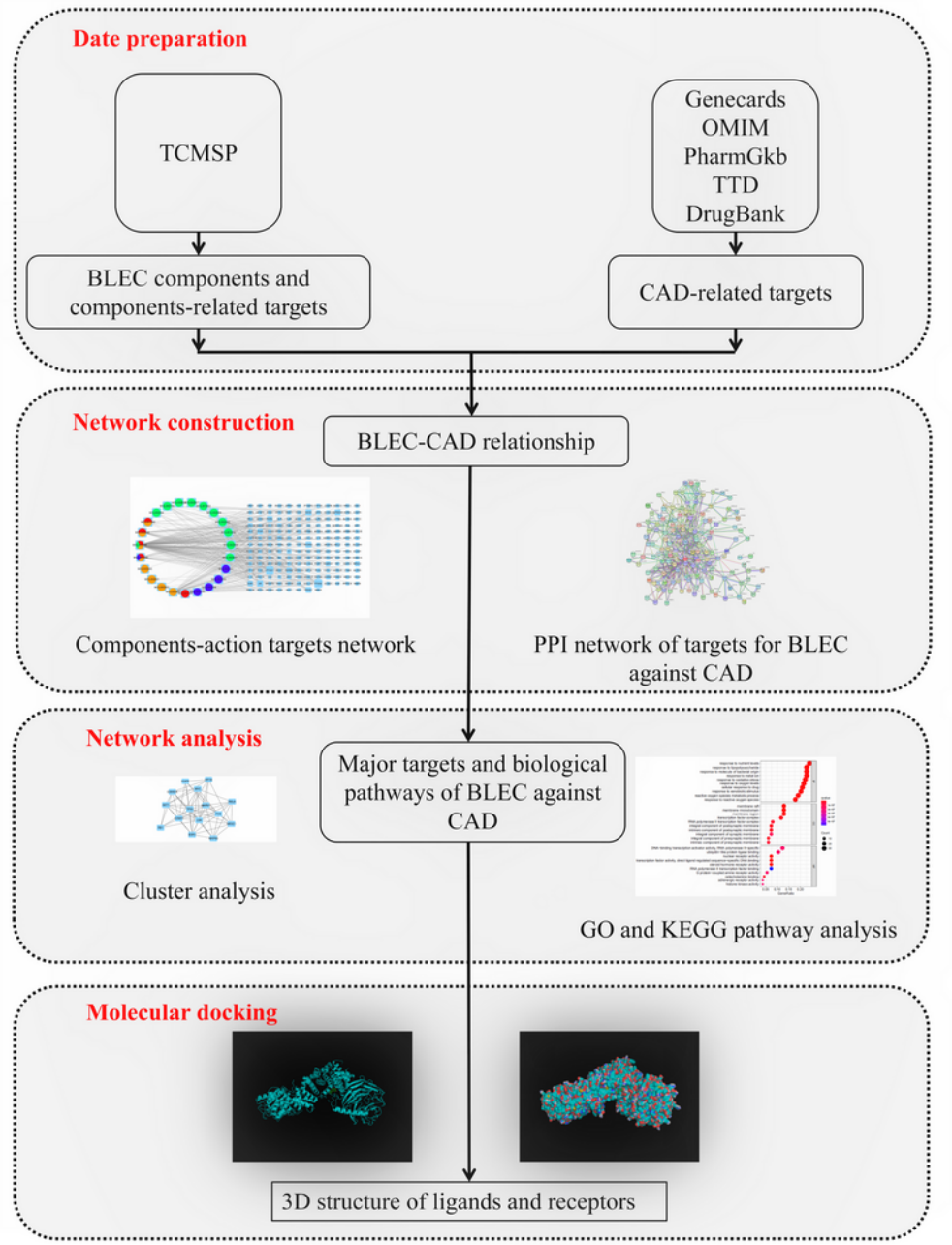

Figure 1

Schematic of the network pharmacological analysis used to identify the potential mechanism of BLEC action on CAD. BLEC: Baolier capsule, CAD: Coronary artery disease.

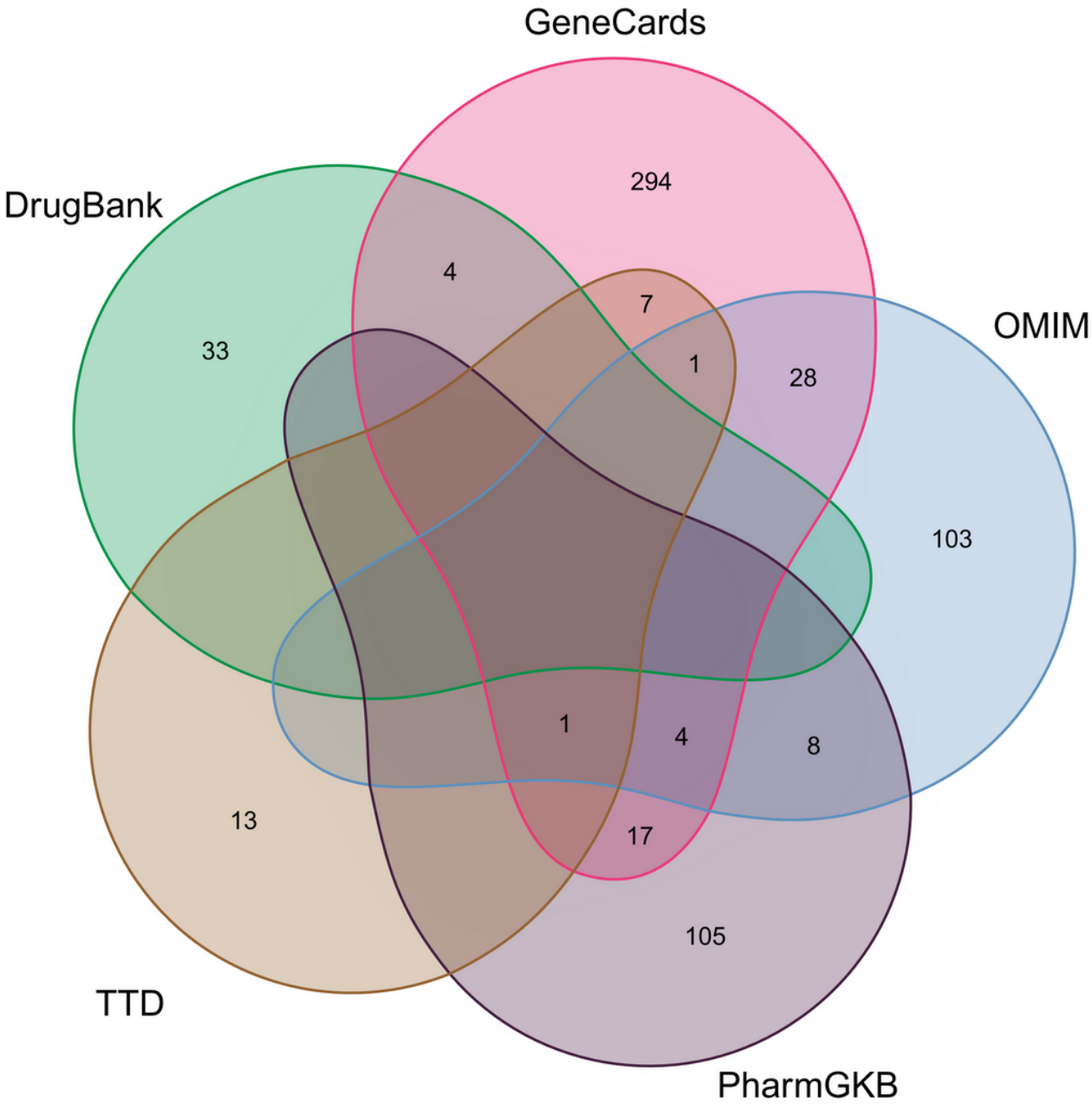

Figure 2

Identification of the CAD–related genes by taking a union of all the results from 5 database. CAD: Coronary artery disease.

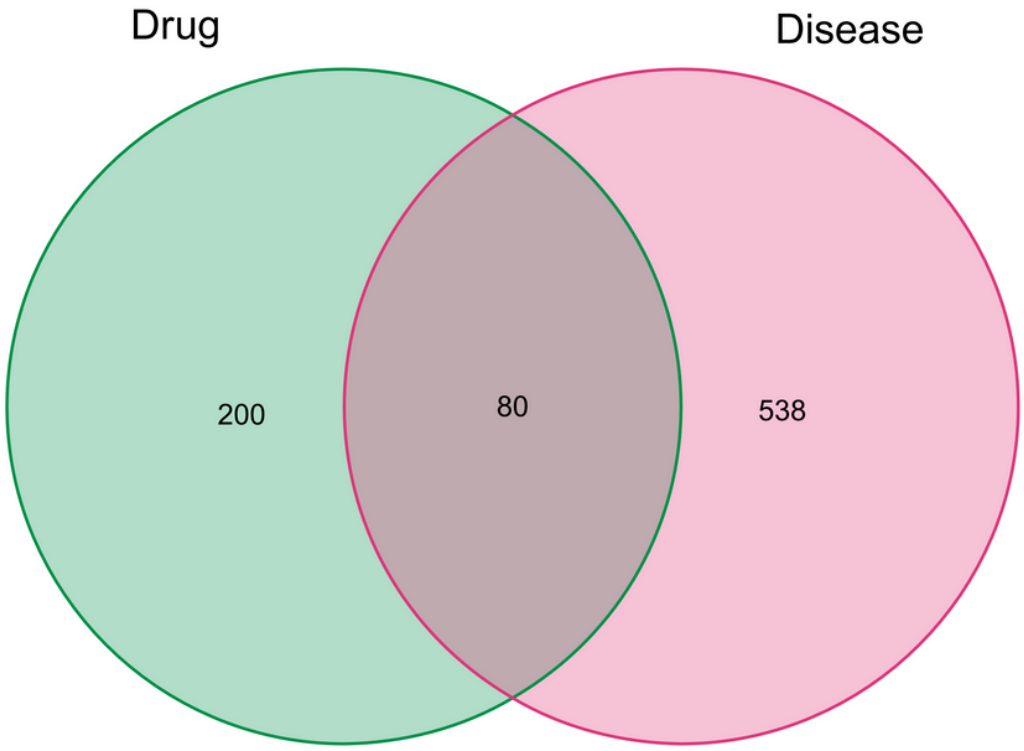

Figure 3

Identification of the drug-target disease-related genes by taking an intersection of drug target genes and CAD–related genes. CAD: Coronary artery disease.

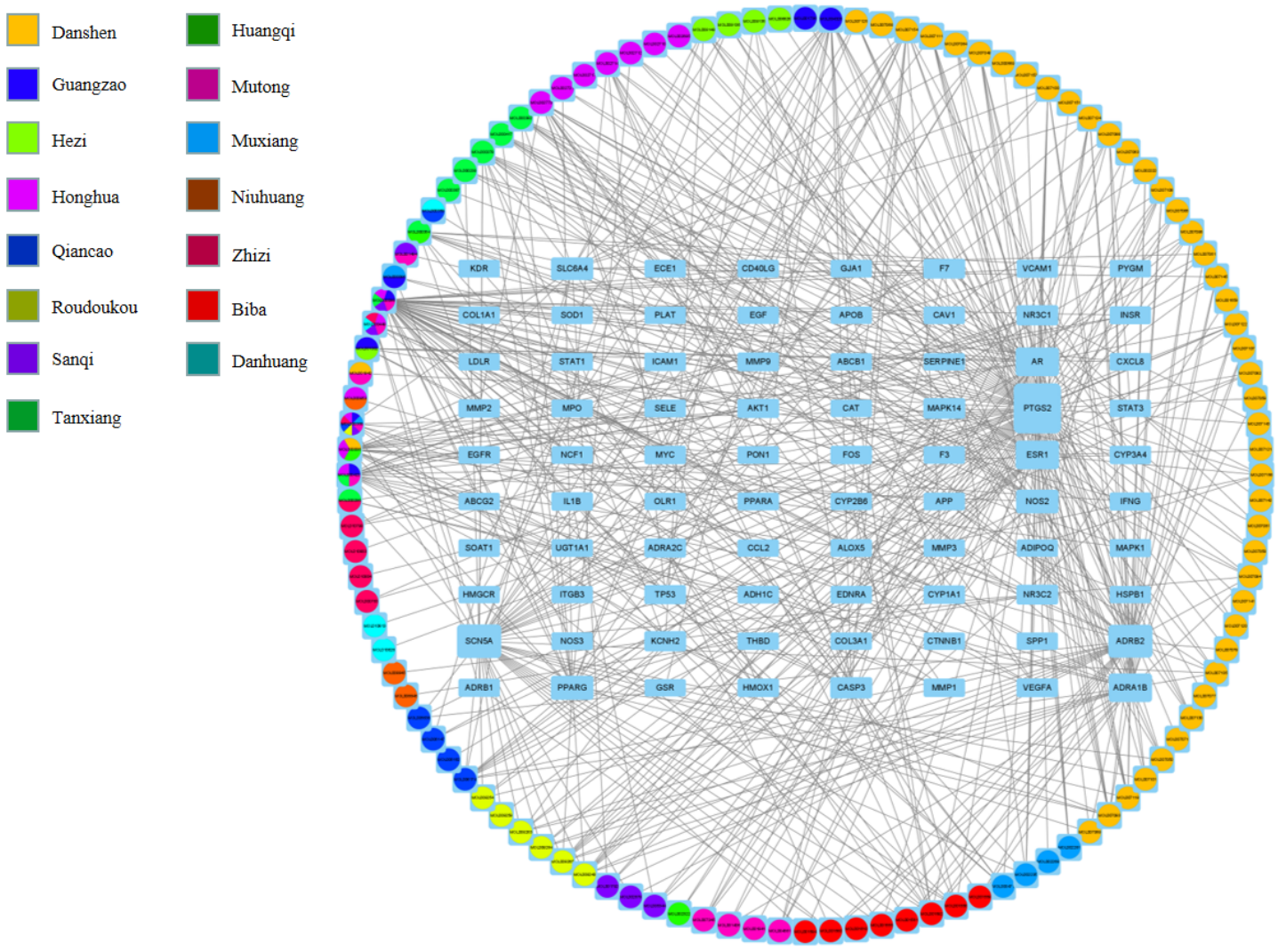

Figure 4

Construction of the drug-target pharmacology network. A, The drug-targets interaction pharmacology network. Circles represent the small molecule active compounds in BLEC. Each colour represents a traditional Chinese medicine ingredient. Rectangle represents the CAD–related target genes, and edges represent the interaction between the small molecule compounds and the target genes. CAD: Coronary artery disease.

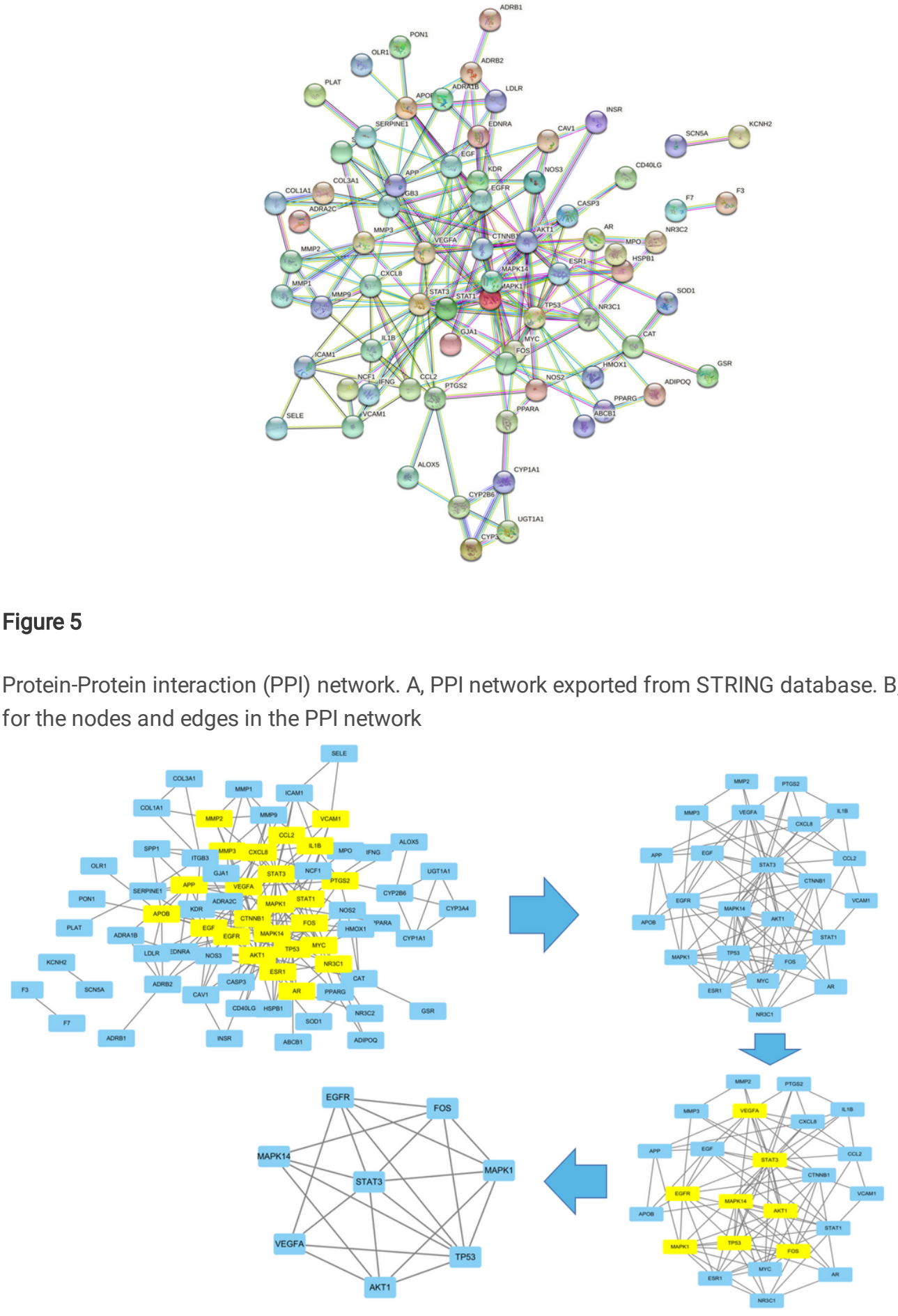

Figure 5

Protein-Protein interaction (PPI) network. A, PPI network exported from STRING database. B, Annotations for the nodes and edges in the PPI network

Figure 6

Identification of key subnetwork using Cytoscape. A, PPI network and the first filtration by CytoNca, the yellow nodes were screened with each score higher than median. B, Subnetwork constructed by a second filtration via CytoNca. The yellow nodes were screened with a score higher than the median. C, Final key subnetwork screened after two filtrations using CytoNca. D, Key subnetwork of top 9 nodes analysed by CytoHubba

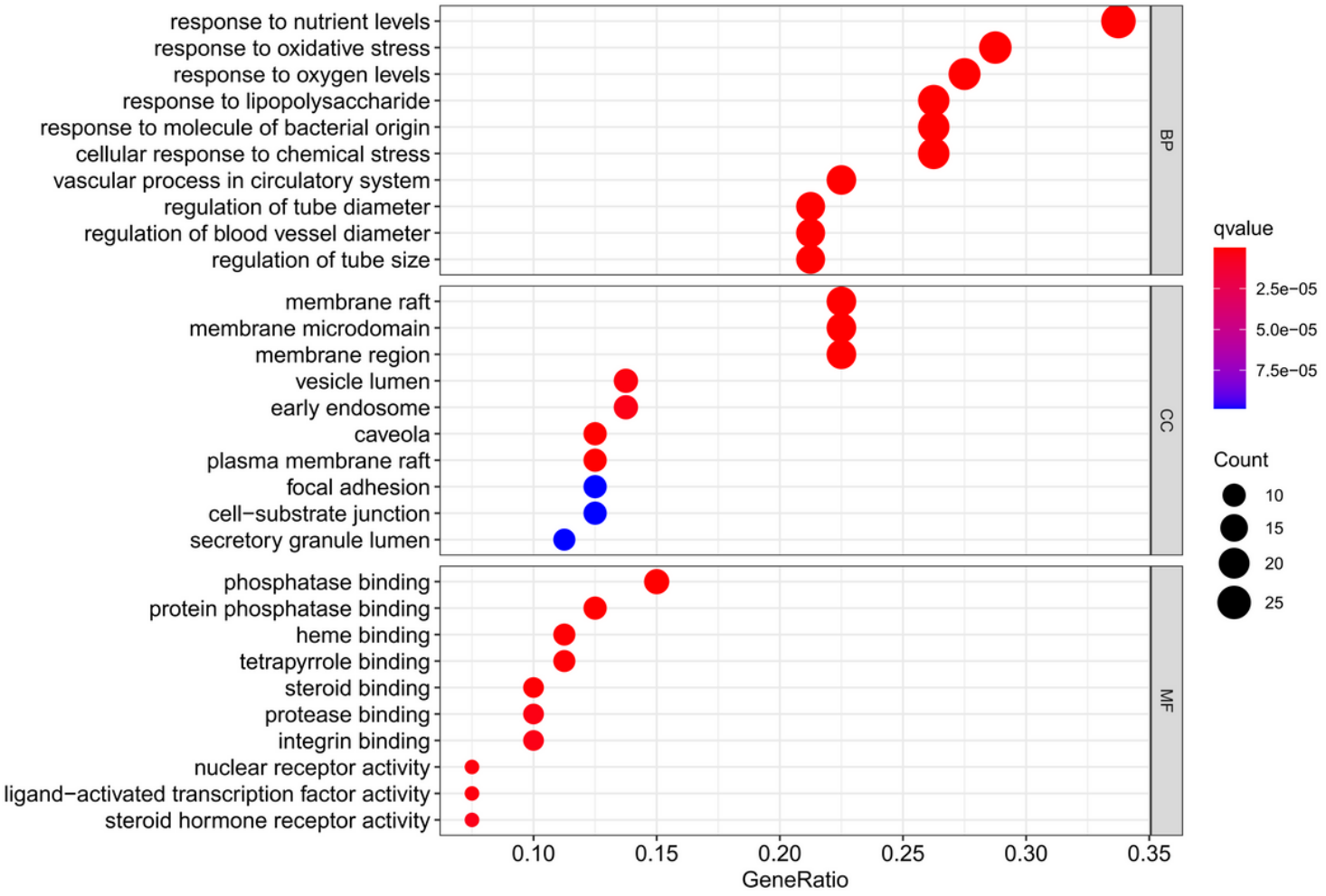

Figure 7

The top 10 of GO enrichment analysis.

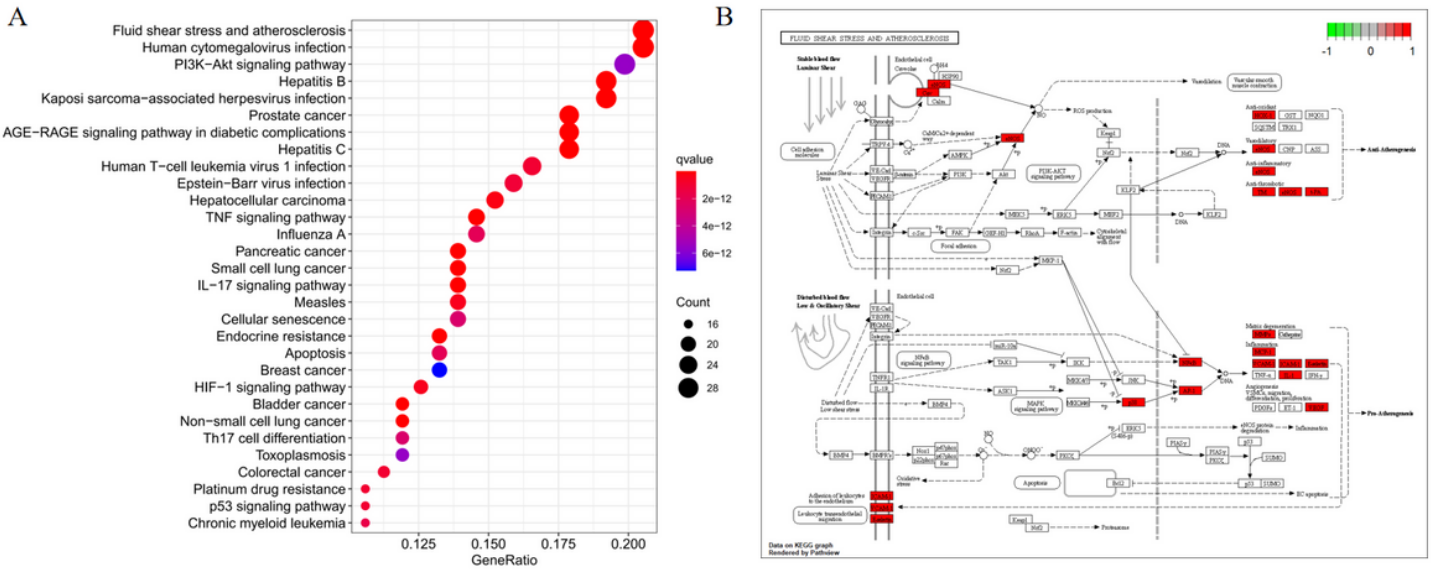

Figure 8

KEGG enrichment analysis and pathway map. A, KEGG enrichment analysis of the target enes. Gene ratio refers to the ratio of enriched genes to all target genes. Counts refer to the number of the enriched genes. B, Pathway map of fluid shear stress and atherosclerosis as the most significant enriched pathway

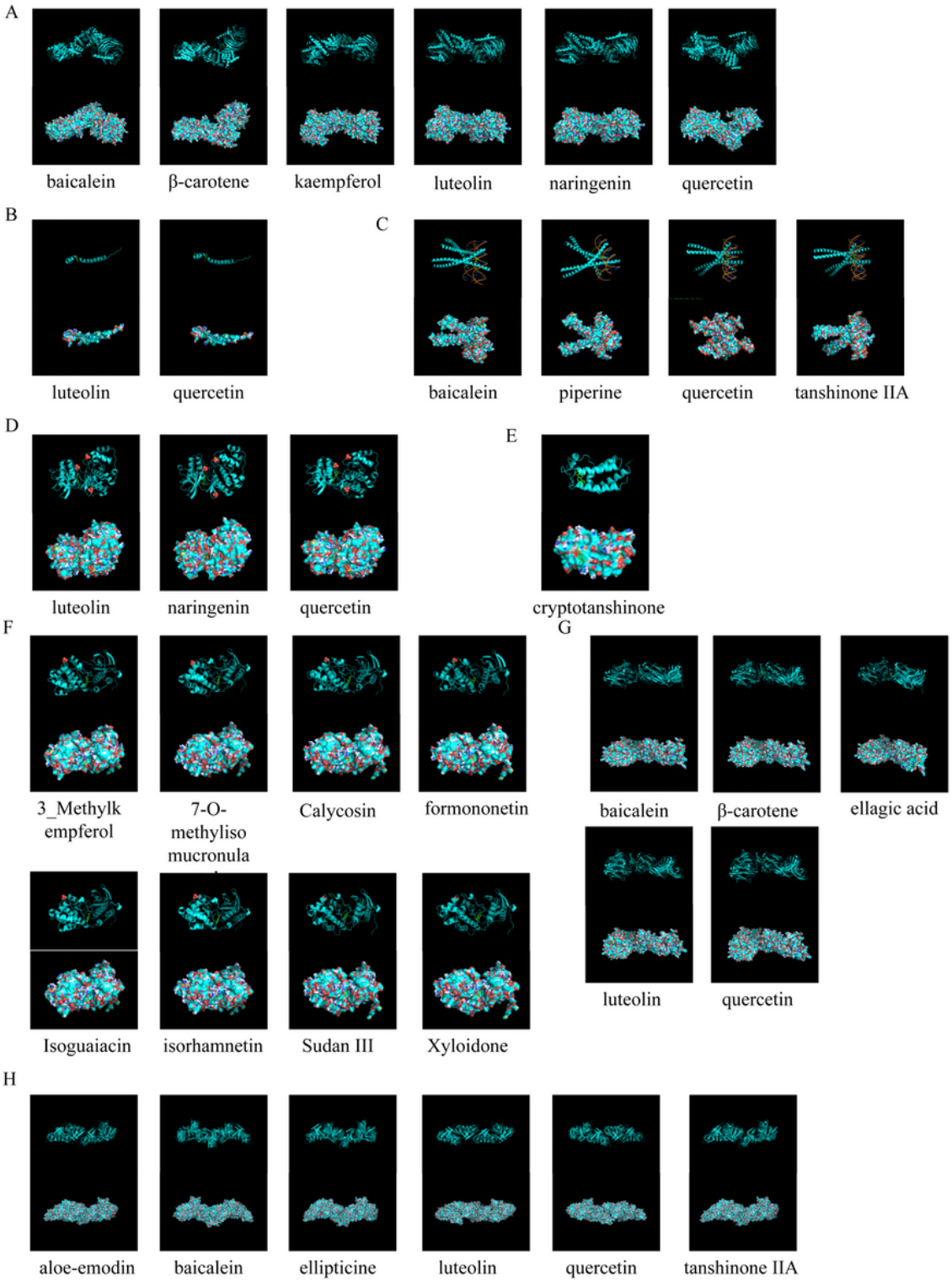

Figure 9

Screening of the key genes in the subnetwork and further molecular docking. A, Molecular docking between the six small molecule ligands and protein 5WBL (encoded by AKT1). B, Molecular docking between the two small molecule ligands and protein 2RGP (encoded by EGFR). C, Molecular docking between the four small molecule ligands and protein 1FOS (encoded by FOS). D, Molecular docking between the three small molecule ligands and protein 3W55 (encoded by MAPK1). E, Molecular docking

between the one small molecule ligands and protein 6NUQ (encoded by STAT3). F, Molecular docking between the eight small molecule ligands and protein 3L8X (encoded by MAPK14). G, Molecular docking between the five small molecule ligands and protein 2VPF (encoded by VEGFA). H, Molecular docking between the six small molecule ligands and protein 7BWN (encoded by TP53). On the top shows the 3D structure of ligands and receptors, at the bottom shows the surface of the receptor and 3D structure of the ligands. AKT1: AKT Serine/Threonine Kinase 1, EGFR: Epidermal Growth Factor Receptor, FOS: Proto-oncogene c-Fos, MAPK1: Mitogen-activated protein kinase 1, MAPK14: Mitogen-activated protein kinase 14, STAT3: Signal transducer and activator of transcription 3, TP53: Cellular tumor antigen p53 and VEGFA: Vascular endothelial growth factor A.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- sTable1.xls
- sTable2.xls
- sTable3.xls
- sTable4.xls