A Network Pharmacology Analysis to Reveal the Molecular Mechanism of Zhizi-Danshen on Coronary Heart Disease

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Research

Keywords: Network Pharmacology, Zhizi, Danshen, Molecular Mechanism, Coronary Heart Disease

DOI: https://doi.org/10.21203/rs.3.rs-85979/v1

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Abstract

Objective

Our study aimed to investigate the potential mechanisms of the herb pair Zhizi-Danshen (ZD) for coronary heart disease (CHD) using network pharmacological data mining technology.

Methods

The Traditional Chinese Medicine System Pharmacology (TCMSP) database was used to collect the active ingredients of ZD and predict ZD-related target proteins. Afterwards, we identified CHD-related targets from DisGeNET database, NCBI gene database, and TTD database. The common targets both from ZD and CHD were screened by Venny2.1, which were then imported into the String database for protein-protein interaction (PPI) analysis. Finally, the GO and KEGG enrichment analysis were performed by R software, and the network construction was established using Cytoscape3.7.2.

Results

We obtained 199 possible targets from 62 candidate ingredients of ZD and 1033 CHD-related targets, with 83 overlapping common target genes. Then, 11 core targets were acquired from PPI network analysis. Further, GO analysis showed that these common targets mainly influenced receptor ligand activity, cytokine activity, cytokine receptor binding, steroid hormone receptor activity, and peptide binding. KEGG pathway analysis indicated that ZD affected CHD through seven important pathways linked to vascular endothelial function regulation (fluid shear stress and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, HIF-1 signaling pathway), inflammatory effects (IL-17 signaling pathway, TNF signaling pathway, Toll-like receptor signaling pathway), and hormone regulation (relaxin signaling pathway).

Conclusions

This study revealed the potential pharmacological mechanisms of ZD against CHD, which were mainly associated with regulation of vascular endothelial function and inflammatory effects, promotion of vasodilatation, and prevention of cardiac fibrosis. Moreover, it provided a novel conception for the development of alternative therapies on CHD.

Introduction

Coronary heart disease (CHD) attracts global concern because of its high morbidity, mortality, and recurrence rate, accounting for the vast majority of cardiovascular events [1-2]. It originates from longstanding coronary atherosclerosis, with the clinical manifestations of angina, myocardial infarction, chronic arrhythmia, heart failure, and even sudden death [3-5]. Currently, western medicine is the main therapeutic way to prevent the progression of CHD. However, there still exists some minuses with modern medicine such as inevitable side effects, high drug cost, and multiple drugs taken as lifelong therapy [6-
Moreover, the hypothesis of "one drug, one target, one disease" is no longer applicable for chronic and complex diseases including CHD due to treatment restriction in recent years [8]. Thus, it is essential to seek multi-target and safe therapeutic interventions in order to improve the survival rate of CHD patients and reduce the social and economic burden.

It is true that Traditional Chinese Medicine (TCM), as a complementary and alternative therapy of modern medicine, has a unique curative effect in the treatment of various diseases [9]. Compared with the single target and high selectivity of Western medicine, TCM possesses the advantages of multi-component, multi-target, multi-pathway, and small side effects, which has always been the focus of new drug investigation [10-11]. According to Chinese medicine theory combined with modern research, "blood stasis" together with "heat toxin" are considered as important factors in the pathogenesis of CHD [12]. Chinese herbs *Gardenia jasminoides* (Chinese name Zhizi) and *Salvia miltiorrhiza* (Chinese name Danshen) both from the oldest Chinese book of material medica “Shennong Herbal Classic” have the effects of antifebrile and detoxification, and activating blood circulation to dissipate blood stasis, thus being widely used in cardiovascular diseases [13-14]. Additionally, pharmacological studies have shown that Zhizi can inhibit inflammation, nourish the liver and gallbladder, protect endothelial cells, and prevent atherosclerosis [15-16]. And Danshen is often used as intravenous herbal medicine to treat angina pectoris and acute myocardial infarction owing to the functions of protecting myocardium, inhibiting platelet aggregation, lowering blood pressure, and performing antioxidation [17-18]. Further, some active ingredients of Zhizi and Danshen have been shown with cardioprotective effects. For example, crocetin, the effective component of Zhizi, could reduce activity of serum creatine kinase (CK) and lactate dehydrogenase (LDH), and increase myocardial tissue ATP, thereby improving myocardial ischemia [19]. Salvianolate extracted from Danshen reduced myocardial infarction area by increasing activity of superoxide dismutase (SOD) and thioredoxin, raising glutathione concentration, and decreasing malondialdehyde (MDA) concentration [20]. Therefore, we believe that the herb pair Zhizi-Danshen (ZD) is beneficial for the treatment of CHD. However, due to their complex chemical compounds, the molecular mechanism of anti-CHD remains unclear, which needs to be further elucidated.

Network pharmacology is an emerging approach to drug design integrating systems biology and network analysis, which promotes the transformation from “one target, one drug” model to a new “network target, multi-component therapy” model [21-22]. The core concept of network pharmacology that focuses on integrity and systematization coincides with holism in TCM, and the combination of both establishes a new method to TCM network pharmacology. Besides, it reveals the complicated interactions between Chinese herbs, organism, and diseases from the system perspective and molecular level by predicting the targeted distribution and pharmacological effects of TCM compounds [22-23]. In this study, we used network pharmacology approach to construct visualization network and comprehensively demonstrate the active ingredients and molecular details of ZD against CHD. The compounds of ZD and target proteins were identified from the network databases. The core targets were screened through PPI network, and the underlying mechanism of ZD acting on CHD was investigated in terms of molecular function and signaling pathways by enrichment analysis. The current study provided the pharmacological basis for the
multi-component, multi-target and multi-pathway therapeutic effects of ZD against CHD, suggesting the possibility for clinical application and new drug research.

**Methods**

**Active Compound of ZD and Target Prediction**

The active compounds of ZD were acquired from Traditional Chinese Medicine System Pharmacology (TCMSP [http://tcmspw.com/tcmsp.php]) database. This database [24] is a systematic pharmacology platform that reveals the mechanisms of TCM by identifying drug-target network and drug-disease network, and covers pharmacokinetic properties including absorption, distribution, metabolism, and excretion (ADME). The basic properties of chemical compounds such as molecular name, molecular weight (MW), oral bioavailability (OB), drug likeness (DL), and oil-water partition coefficient (AlgP) can be obtained from TCMSP database. Specifically, OB mainly affects the performance of drugs, which is the ability of drugs absorbed into the blood circulation [25]. DL describes the possibility of compounds to become drugs, and help to optimize pharmacokinetics and drug properties [26]. AlgP reflects the distribution of drugs in oil-water phases. The smaller the value, the better the water solubility is [27]. We consulted relevant literatures which suggested compounds of Zhizi with OB $\geq 10\%$, DL $\geq 0.18$, AlgP $\leq 5$ and Danshen with OB $\geq 30\%$, DL $\geq 0.18$, AlgP $\leq 5$ were regarded as candidate active ingredients [28-29].

Furthermore, the target proteins corresponding to compounds were gained after clicking “Related Targets”. We then converted these target names to official gene names in Uniprot KB (https://www.uniprot.org/) database with “Homo Sapiens” species.

**CHD-related Target Prediction**

The possible CHD-related targets were collected from three public databases including DisGeNET (https://www.disgenet.org/), NCBI Gene (https://www.ncbi.nlm.nih.gov/gene), and TTD (http://db.idrblab.net/ttd/) with the keywords “coronary heart disease”. Subsequently, we aggregated these targets and removed duplicates.

**Common Targets Screening**

Both the ZD-related targets and CHD-related targets obtained above were imported into Venny2.1 (https://bioinfogp.cnb.csic.es/tools/venny/) to draw venny diagram, and the overlapping part showed the common targets of compounds and diseases.

**Protein-Protein Interaction**

Protein-Protein interaction (PPI) were performed by importing the common targets into String (https://string-db.org/) database with the species restricted to “Homo Sapiens” and a highest confidence core >0.9 [30]. Besides, the results were exported in TSV format.
**Functional Enrichment Analysis**

Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were carried out using the clusterProfiler package in R3.6.2. To elucidate the action mechanism of ZD in the treatment of CHD, we performed enrichment analysis on molecular functions and signaling pathways of the candidate targets with $p$ value <0.05 for significance, and the results were plotted as bubble chart.

**Network Construction and Analysis**

Cytoscape 3.7.2 was used to construct three kinds of networks including compound-target network, PPI network, and ZD-CHD network. The “degree” represents the number of edges connecting to the nodes, which is a crucial topological parameter to evaluate the significance of proteins in a visual network [31]. We considered the target with degree greater than twofold of the average as the core gene [32].

**Results**

**Compound-Target Network**

According to the screening criteria of OB, DL, and AlgP, 9 and 54 chemical components from Zhizi and Danshen were collected in the TCMSP platform. Thus, total 62 active ingredients in ZD were obtained, of which isoimperatorin is the shared ingredient of both. The characteristics of these compounds are shown in Table 1.

Next, potential targets related to the compounds were also identified from the TCMSP database. After being checked by Uniprot KB, 199 predictive targets were explored. The compound-target network of ZD were constructed using Cytoscape3.7.2, including 261 nodes and 894 edges (Figure 1).

**Analysis of Targets on CHD**

Based on DisGeNET, NCBI Gene, and TTD database, we collected 912, 377, and 2 targets, respectively. The detailed information of target genes were listed in Supplementary Table S1. After merging the genes from the three databases, a total of 1033 underlying action targets were identified. We then utilized the venny2.1 platform to draw a venny diagram (Figure 2), and found 83 targsers were common to ZD and CHD (Supplementary Table S2). We speculate that these target genes may play an important role for ZD in the treatment of CHD.

**Protein-Protein Interaction (PPI) Network**

We imported the 83 common targets into the String database to acquire target proteins interactions. Subsequently, the PPI network was further visualized using Cytoscape3.7.2 by importing the results previously saved in TSV format. In addition, the network could be adjusted according to the degree which was calculated by NetworkAnalyzer tool. The smaller the degree, the smaller size and brighter color of
node is; otherwise, the larger size and darker color of node is in the network. The PPI network is shown in Figure 3 with 74 nodes and 230 edges.

Core target Screening

The topology analysis indicated the average degree in the PPI network was 6.2. Consequently, we selected the gene with degree > 12.4 as the core target. As shown in Table 2, the core genes in descending order were TNF (degree=27), IL6 (degree=18), AKT1 (degree=17), CXCL8 (degree=16), MAPK14 (degree=15), FOS (degree=14), VEGFA (degree=14), IL1B (degree=13), IL4 (degree=13), MAPK8 (degree=13), and RXRA (degree=13).

GO and KEGG Enrichment analysis

To further clarify the effects of ZD on CHD in molecular function and metabolic pathways, we used the cluster profiler package in R platform for GO and KEGG enrichment analysis. The results obtained were in ascending order of p value and met the criterion of $p < 0.05$. Afterwards, we chose the top 20 significant enrichment results for analysis. The color and size of the nodes were determined according to the value of “p.adjust” and “count”.

GO functional annotation analysis showed 107 enrichment results on molecular functions. The putative targets of ZD anti-CHD mainly affected receptor ligand activity, cytokine activity, cytokine receptor binding, steroid hormone receptor activity, and peptide binding (Figure 4).

Meanwhile, there were 130 signaling pathways enriched through KEGG pathway analysis. The top 20 significant pathways were shown in Figure 5. As a result, pathways closely associated with ZD anti-CHD can be divided into three functional modules: vascular endothelial function regulation (fluid shear stress and atherosclerosis; AGE-RAGE signaling pathway in diabetic complications, HIF-1 signaling pathway), inflammatory effects (IL-17 signaling pathway, TNF signaling pathway; Toll-like receptor signaling pathway) and hormone regulation (relaxin signaling pathway).

ZD-CHD Network and Analysis

The ZD-CHD network was established to intuitively explain the molecular mechanism of ZD against CHD, which was composed of 62 active ingredients, 83 common targets, and 20 pathways, and included 165 nodes and 695 edges (Figure 6). The visual network demonstrated that ZD may play a therapeutic role through the synergistic effect of multiple compounds with related targets and pathways. Besides, quercetin (degree=67), kaempferol (degree=27), luteolin (degree=22), tanshinone Ila (degree=18) were considered as representative compounds of ZD since they connected the most number of common target genes in the network.

Discussion
The occurrence of CHD seriously endangers human's health worldwide. As is known to us, TCM has been used to treat CHD for thousands of years. Currently, TCM advances with the times and has enriched and developed the previous theories based on macroscopic syndrome differentiation and microscopic pathology, thus forming a unique treatment system for CHD [33]. However, due to the complexity of the active components in TCM, the specific mechanism through which it acts on CHD remains unclear. Fortunately, the emergence of network pharmacology makes up for the deficiency. It attempts to analyse the underlying mechanisms of TCM acting on diseases through the virtual screening of potential active compounds, target proteins, and signaling pathways. Hence we conducted a comprehensive study on the molecular mechanism of ZD against CHD using the strategy of network pharmacology.

In the present study, a total of 62 compounds were screened by excavating the active ingredients of ZD. As shown in Figure 6, quercetin, kaempferol, luteolin, and tanshinone Ila were identified as representative compounds. Previous studies have reported that quercetin and kaempferol are flavonoids from Zhizi and have biological activities against CHD such as anti-oxidation, anti-inflammation, inhibition of platelet activation, and relaxation of blood vessels[36]. Meanwhile, luteolin is a polyphenolic compound from Danshen, which exerts cardiovascular protective effects for the roles of reducing oxidative stress, and inhibiting inflammation and apoptosis[37]. Tanshinone Ila is another compound existed in Danshen that can perform anti-ischemia, anti-arrhythmia, anti-atherosclerosis, and anti-coagulation[38]. The above active ingredients provided basis for the pharmacological activities of ZD acting on CHD.

Analysis of the PPI network based on the common targets of ZD and CHD indicated that TNF, IL6, AKT1, CXCL8, MAPK14, FOS, VEGFA, IL1B, IL4, MAPK8, and RXRA were selected as the core targets. These target genes were mainly linked to the release and inhibition of inflammation and regulation of angiogenesis, which explained the effects of anti-CHD at the molecular levels. For instance, TNF is a cytokine produced by activated macrophages. Further, TNF-α is an important pro-inflammatory cytokine which participates in the vasodilatation formation and mediates the recruitment of neutrophils and macrophages to sites of inflammation by stimulating endothelial cells to produce adhesion molecules[39]. IL6, an inflammatory mediator released by neutrophils, monocytes and cardiomyocytes, is associated with the thrombosis of atherosclerotic plaque. It has been reported that the elevated level of IL-6 is related to acute myocardial ischemia and serve as an indicator of recurrent CHD among patients[40]. Moreover, there are various pro-inflammatory cytokines including IL1B and CXCL8, which involved in the process of plaque formation and rupture via different pathways[41-42]. However, IL4 is an anti-inflammatory cytokine that inhibits the expression and release of inflammatory cytokines such as IL-1, IL-6, and TNF-α[43-44]. Szkodzinski et al.[45] have determined prognostic implications of IL-4 in developing severe cardiac dysfunction in the course of acute myocardial infarction (AMI). In addition, AKT1 is the main isomer in vascular endothelial cells, which plays a crucial role in cardiac growth, contraction and coronary angiogenesis[46]. MAPK14, also named as p38α MAPK, is a member of p38 MAPK family. Studies have found that cardiac myocyte p38α kinase regulates angiogenesis via myocyte-endothelial cell cross-talk during stress-induced remodeling in the heart[47]. VEGFA is a mitogen that promotes vascular endothelial cell proliferation and angiogenesis[48]. It has been suggested that endothelial dysfunction caused by VEGFA may increase the risk of CHD[49]. Furthermore, the
combination of VEGFA and its receptor VEGFR2 can activate downstream signaling pathways such as MAPK, Akt to stimulate angiogenesis[50].

Through KEGG pathway enrichment analysis, seven signaling pathways including fluid shear stress and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, HIF-1 signaling pathway, IL-17 signaling pathway, TNF signaling pathway, Toll-like receptor signaling pathway, and relaxin signaling pathway were relevant to vascular endothelial function regulation, inflammatory effects, and hormone regulation. It is worth mentioning that endothelial dysfunction plays a significant role in the progression of atherosclerotic plaque which is a main factor resulting in developing CHD. Endothelial shear stress heavily influences endothelial function, and low shear stress with the proatherogenic effect can be independent predictor of revascularization[51]. Additionally, low shear stress may drive epicardial endothelial dysfunction and atherosclerosis progression, thereby causing more advanced phenotypic manifestations of CHD[52]. Studies have shown that low shear stress activated the expression of vascular cell adhesion molecule 1 (VCAM-1) which was induced by cytokines such as IL-1 and TNF-α, making the markedly greater monocyte binding to the carotid[53-54]. Nevertheless, the activation of AKT1 mediated by fluid shear stress can promote cell survival in endothelial cells[55]. Advanced glycation end products (AGEs) interacting with a cell surface receptor, RAGE was reported to evoke inflammatory and thrombogenic reactions, which contributed to the development of CHD[56]. Research found that AGE/RAGE induced the activation of the ERK/MAPK signaling pathway, ultimately leading to activate nuclear factor NF-κB, thus increasing production of proinflammatory and proatherogenic mediators [57]. Moreover, regulating the AGE/RAGE pathway may be able to treat cardiac ischemic–reperfusion injury, diabetic cardiomyopathy, and inflammatory heart diseases[58]. Hypoxia-inducible factor 1 (HIF-1) signaling pathway plays an important regulatory role in the hypoxia response. It can upregulate the expression of angiogenic factors such as vascular endothelial growth factor (VEGF) to promote angiogenesis. Besides, HIF-1 activates inducible nitric oxide to increase blood flow and reduce ischemic injury[59-60].

In addition, recent studies supported the involvement of chronic inflammation in the progression and initiation of atherosclerosis, which resulted in various cardiovascular diseases[61]. IL-17, derived by T helper-17 (Th17) cells, is involved in inflammatory pathology of various diseases [62]. It promotes the release of proinflammatory cytokines (IL6, TNF-α, IL1B) and chemokines (IL8, CXCL1) to mediate inflammation. Studies found IL-17 signaling activated downstream pathways such as NF-kB and MAPK to stimulate cytokines with relevance to atherosclerosis [63]. Further, it was identified that downregulating IL-17 expression could suppress inflammation and improve heart function[64]. TNF signaling also induces inflammatory response by activating the expression of proinflammatory cytokines and transcription factors[65]. For example, TNF combined with TNF receptor 1 (TNFR1) mediated the activation of NF-kB, which was involved in the pathological process of cardiovascular disease such as ischemia-reperfusion, heart failure, and ventricular remodeling[66]. Moreover, Toll-like receptor (TLR), belongs to pattern recognition receptors, can activate expression of a series of genes related to inflammation and immune response[67]. TLRs have eleven types, of which TLR4 plays an extremely important role in CHD[68]. It was reported that TLR4 interacting with some other pathways such as
PI3K/Akt and MAPK activated a variety of downstream transcriptional factors, and initiated inflammatory response. [69].

Finally, relaxin signaling is a pathway associated with hormone regulation. Produced by the heart, relaxin coupling with its cognate receptor mediates the production of cyclic adenosine monophosphate (cAMP), and activation of nitric oxide (NO) pathway, PI3K/Akt pathway, MAPK pathway, and nuclear factor NF-κB, of which NO production plays a central role in cardioprotection[70]. Some experiments have found that relaxin is able to promote vasodilatation and angiogenesis, inhibit inflammation, and ameliorate ischemia/reperfusion injury because of the upregulated expression in ischemic heart disease [71]. Besides, in cardiac ischemia model, relaxin was verified to reduce interstitial collagen accumulation and cardiac hypertrophy, thus exerting antifibrotic effects[72].

**Conclusions**

To summarize, the present network pharmacology analysis revealed the potential mechanisms of ZD in the treatment of CHD through components and targets screening, functional enrichment analysis, and network construction. As a result, quercetin, kaempferol, luteolin, and tanshinone IIa as the major active ingredients of ZD were predicted to prevent CHD via regulating vascular endothelial function and inflammatory effects, promoting vasodilatation, and preventing cardiac fibrosis, which acted on the key targets such as TNF, IL6, AKT1, CXCL8, MAPK14, and VEGFA. Therefore this study demonstrated the multi-component, multi-target and multi-pathway mechanisms of ZD against CHD, and provided a possible direction for the development of alternative therapies for CHD. In the future, we will strive to clarify our findings with basic experiments in vivo.

**Abbreviations**

ZD: Zhizi-Danshen; CHD: coronary heart disease; TCM: Traditional Chinese Medicine; CK: creatine kinase; LDH: lactate dehydrogenase; SOD: superoxide dismutase; MDA: decreasing malondialdehyde; TCMSP: Traditional Chinese Medicine System Pharmacology; MW: molecular weight; OB: oral bioavailability; DL: drug likeness; AlgP: oil-water partition coefficient; PPI: Protein-Protein interaction; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; VCAM-1: vascular cell adhesion molecule 1; AGEs: Advanced glycation end products; HIF-1: Hypoxia-inducible factor 1; VEGF: vascular endothelial growth factor; Th17: T helper-17; TNFR1: TNF receptor 1; TLR: Toll-like receptor; cAMP: cyclic adenosine monophosphate; NO: activation of nitric oxide.

**Declarations**

**Acknowledgements**

Not applicable.

**Authors’ contributions**
S-YH and W-SL conceived the research methods. WN and D-YC collected and analyzed the data. ZQ and S-JP coordinated and inspected all aspects of the research design. S-YH and W-SL drafted the manuscript. All authors read and approved the final manuscript.

Availability of data and materials
The data and materials generated or analyzed during this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Not applicable.

Consent for publication
The manuscript is approved by all authors for publication.

Competing interests
The authors declare no conflicts of interest.

Funding
This work was supported by the National Natural Science Foundation of China (grant number: 81873274).

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Tables

TABLE 1: Characteristics of active ingredients in ZD
| Molecular Name                                         | Mol ID     | Source  | MW   | AlgP | OB%  | DL  |
|-------------------------------------------------------|------------|---------|------|------|------|-----|
| crocetin                                              | MOL001406  | Zhizi   | 328.44 | 4.58 | 35.30 | 0.26|
| ammidin                                               | MOL001941  | Zhizi   | 270.30 | 3.65 | 34.55 | 0.22|
| geniposide                                            | MOL004557  | Zhizi   | 388.41 | -2.25 | 14.64 | 0.44|
| quercetin                                             | MOL000098  | Zhizi   | 302.25 | 1.50 | 46.43 | 0.28|
| kaempferol                                            | MOL000422  | Zhizi   | 286.25 | 1.77 | 41.88 | 0.24|
| isoirimperatorin                                      | MOL001942  | Zhizi   | 270.30 | 3.65 | 45.46 | 0.23|
| chrysin                                               | MOL002560  | Zhizi   | 254.25 | 2.60 | 22.61 | 0.18|
| 5-hydroxy-7-methoxy-2-(3,4,5-trimethoxyphenyl)chromone | MOL003095  | Zhizi   | 358.37 | 2.80 | 51.96 | 0.41|
| 3-methylkempferol                                     | MOL007245  | Zhizi   | 300.28 | 1.84 | 60.16 | 0.26|
| 1,2,5,6-tetrahydrotanshinone                          | MOL001601  | Danshen | 280.34 | 2.98 | 38.75 | 0.36|
| sugiol                                                | MOL002222  | Danshen | 300.48 | 4.99 | 36.11 | 0.28|
| dehydrotanshinone Ila                                 | MOL002651  | Danshen | 292.35 | 4.22 | 43.76 | 0.40|
| digallate                                             | MOL000569  | Danshen | 322.24 | 1.53 | 61.85 | 0.26|
| luteolin                                              | MOL000006  | Danshen | 286.25 | 2.07 | 36.16 | 0.25|
| 5,6-dihydroxy-7-isopropyl-1,1-dimethyl-2,3-dihydrophanthen-4-one | MOL007036  | Danshen | 298.41 | 4.38 | 33.77 | 0.29|
| 2-isopropyl-8-methylphanthenrene-3,4-dione            | MOL007041  | Danshen | 264.34 | 4.16 | 40.86 | 0.23|
| 3α-hydroxytanshinone Ila                              | MOL007045  | Danshen | 310.37 | 3.56 | 44.93 | 0.44|
| (E)-3-[2-(3,4-dihydroxyphenyl)-7-hydroxy-benzofuran-4-yl]acrylic acid | MOL007048  | Danshen | 312.29 | 3.21 | 48.24 | 0.31|
| 4-methylenemiltirone                                  | MOL007049  | Danshen | 266.36 | 4.33 | 34.35 | 0.23|

TABLE1: Continued.
| Molecular Name                                                                 | Mol ID   | Source  | MW     | AlgP | OB| DL |
|-------------------------------------------------------------------------------|----------|---------|--------|------|---|----|
| 2-(4-hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-7-methoxy-3-benzofurancarboxaldehyde | MOL007050 | Danshen | 356.40 | 3.58 | 62.78 | 0.40 |
| formyltanshinone                                                             | MOL007058 | Danshen | 290.28 | 3.36 | 73.44 | 0.42 |
| 3-beta-Hydroxymethylenetanshiquinone                                         | MOL007059 | Danshen | 294.32 | 3.16 | 32.16 | 0.41 |
| methylenetanshinquinone                                                      | MOL007061 | Danshen | 278.32 | 4.26 | 37.07 | 0.36 |
| przewalskin a                                                                | MOL007063 | Danshen | 398.49 | 2.25 | 37.11 | 0.65 |
| przewalskin b                                                                | MOL007064 | Danshen | 330.46 | 3.18 | 110.32 | 0.44 |
| przewaquinone b                                                              | MOL007068 | Danshen | 292.30 | 2.99 | 62.24 | 0.41 |
| przewaquinone c                                                              | MOL007069 | Danshen | 296.34 | 3.31 | 55.74 | 0.40 |
| (6S,7R)-6,7-dihydroxy-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione | MOL007070 | Danshen | 312.34 | 2.34 | 41.31 | 0.45 |
| przewaquinone f                                                              | MOL007071 | Danshen | 312.34 | 2.07 | 40.31 | 0.46 |
| sclareol                                                                     | MOL007077 | Danshen | 308.56 | 4.27 | 43.67 | 0.21 |
| tanshinaldehyde                                                              | MOL007079 | Danshen | 308.35 | 3.83 | 52.47 | 0.45 |
| danshenol b                                                                   | MOL007081 | Danshen | 354.48 | 2.59 | 57.95 | 0.56 |
| danshenol a                                                                   | MOL007082 | Danshen | 336.41 | 2.01 | 56.97 | 0.52 |
| salvilenone                                                                   | MOL007085 | Danshen | 292.40 | 4.26 | 30.38 | 0.38 |
| cryptotanshinone                                                             | MOL007088 | Danshen | 296.39 | 3.44 | 52.34 | 0.40 |
| dan-shexinkum d                                                               | MOL007093 | Danshen | 336.41 | 2.83 | 38.88 | 0.55 |
| danshenspiroketallactone                                                     | MOL007094 | Danshen | 282.36 | 3.24 | 50.43 | 0.31 |

TABLE1: Continued.
| Molecular Name                                                                 | Mol ID   | Source   | MW    | AlgP | OB% | DL   |
|-------------------------------------------------------------------------------|----------|----------|-------|------|-----|------|
| deoxyneocryptotanshinone                                                      | MOL007098 | Danshen | 298.41 | 4.32 | 49.40 | 0.29 |
| dihydrotanshincractone                                                        | MOL007100 | Danshen | 266.31 | 2.77 | 38.68 | 0.32 |
| dihydrotanshinone I                                                           | MOL007101 | Danshen | 278.32 | 2.86 | 45.04 | 0.36 |
| epidanshenspiroketalactone                                                    | MOL007105 | Danshen | 284.38 | 2.37 | 68.27 | 0.31 |
| isocryptotanshi-none                                                          | MOL007108 | Danshen | 296.39 | 3.59 | 54.98 | 0.39 |
| isotanshinone II                                                              | MOL007111 | Danshen | 294.37 | 4.66 | 49.92 | 0.40 |
| milstonone I                                                                  | MOL007119 | Danshen | 312.39 | 3.33 | 49.68 | 0.32 |
| milstonone II                                                                 | MOL007120 | Danshen | 312.39 | 2.14 | 71.03 | 0.44 |
| miltipolone                                                                   | MOL007121 | Danshen | 300.43 | 2.74 | 36.56 | 0.37 |
| miltirone                                                                     | MOL007122 | Danshen | 282.41 | 4.73 | 38.76 | 0.25 |
| neocryptotanshinone II                                                         | MOL007124 | Danshen | 270.35 | 3.61 | 39.46 | 0.23 |
| neocryptotanshinone                                                           | MOL007125 | Danshen | 314.41 | 3.01 | 52.49 | 0.32 |
| 1-methyl-8,9-dihydro-7H-naphthol[5,6-g]benzofuran-6,10,11-trione              | MOL007127 | Danshen | 280.29 | 3.21 | 34.72 | 0.37 |
| prolithospermic acid                                                          | MOL007130 | Danshen | 314.31 | 2.77 | 64.37 | 0.31 |
| (2R)-3-(3,4-dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acryloyl]oxy-propionic acid | MOL007132 | Danshen | 360.34 | 2.69 | 109.38 | 0.35 |
| salvianolic acid g                                                             | MOL007141 | Danshen | 340.30 | 2.20 | 45.56 | 0.61 |
| salvianolic acid j                                                             | MOL007142 | Danshen | 538.49 | 3.78 | 43.38 | 0.72 |
| salvilenone I                                                                  | MOL007143 | Danshen | 270.40 | 2.88 | 32.43 | 0.23 |
| salvionone                                                                    | MOL007145 | Danshen | 268.38 | 4.05 | 31.72 | 0.24 |

TABLE1: Continued.
| Molecular Name                                                                 | Mol ID     | Source  | MW    | AlgP | OB%  | DL  |
|------------------------------------------------------------------------------|------------|---------|-------|------|------|-----|
| (6S)-6-hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone | MOL007150 | Danshen | 312.34 | 2.42 | 75.39 | 0.46 |
| tanshindiol b                                                                | MOL007151 | Danshen | 312.34 | 2.34 | 42.67 | 0.45 |
| przewaquinone e                                                              | MOL007152 | Danshen | 312.34 | 2.34 | 42.85 | 0.45 |
| tanshinone Ila                                                               | MOL007154 | Danshen | 294.37 | 4.66 | 49.89 | 0.40 |
| (6S)-6-(hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione | MOL007155 | Danshen | 310.37 | 3.57 | 65.26 | 0.45 |
| tanshinone VI                                                                | MOL007156 | Danshen | 296.34 | 2.44 | 45.64 | 0.30 |

**TABLE 2: The 11 core targets and topological parameters of PPI network**

| Number | Target name | Degree | Betweenness Centrality | Closeness Centrality |
|--------|-------------|--------|------------------------|----------------------|
| 1      | TNF         | 27     | 0.25                   | 0.54                 |
| 2      | IL6         | 18     | 0.08                   | 0.47                 |
| 3      | AKT1        | 17     | 0.13                   | 0.46                 |
| 4      | CXCL8       | 16     | 0.11                   | 0.46                 |
| 5      | MAPK14      | 15     | 0.07                   | 0.46                 |
| 6      | FOS         | 14     | 0.08                   | 0.44                 |
| 7      | VEGFA       | 14     | 0.13                   | 0.47                 |
| 8      | IL1B        | 13     | 0.01                   | 0.43                 |
| 9      | IL4         | 13     | 0.06                   | 0.43                 |
| 10     | MAPK8       | 13     | 0.07                   | 0.45                 |
| 11     | RXRA        | 13     | 0.16                   | 0.44                 |