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# Mechanism of *Cordyceps sinensis* in atherosclerosis treatment based on network pharmacology and molecular docking analysis

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***Author contributions***

Qi-Qing Cheng and Shi Wang initiated the work, and designed the idea. Ping Li and Zi-Yu Cui prepared and collected material and data. Jin-Rong Lang and Yue Hao wrote the paper. All authors reviewed the article. All authors read and approved the final authors.

***Competing interests***

The authors declare no conflicts of interest.

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***Abbreviations***

*C. sinensis*, *Cordyceps sinensis*; AS, atherosclerosis; TCM, traditional Chinese medicine; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PPI, protein-protein interaction; TCMSP, Traditional Chinese Medicines Systems Pharmacology Database and Analysis Platform; BPs, biological processes; CCs, cellular components; MFs, molecular functions; OB, oral bioavailability; DL, drug likeness.

***Citation***

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***Abstract***

**Background:** The present study intented to delve into the molecular mechanism of *Cordyceps sinensis* (*C. sinensis*) in treating atherosclerosis by combining network pharmacology and molecular docking analysis. **Methods:** We searched the databases including Traditional Chinese Medicines Systems Pharmacology Database and Analysis Platform, PubChem, and PharmMapper to screen out the active chemical ingredients of *C. sinensis* and the corresponding targets. The String database was used for the matching normalization of results, and the software Cytoscape 3.7.2 was adopted to establish the *C. sinensis*-active components-targets of action-disease network. The databases of Online Mendelian Inheritance in Man database, GeneCards, Therapeutic Target Database, and DisGNET were searched to yield the major targets of atherosclerosis (AS), which were matched with the active component targets of *C. sinensis* to identify the potential therapeutic targets. The String database was utilized to set up the protein-protein interaction network, and Cytoscape software was applied for topological analysis, which was followed by the Gene Ontology analysis and Kyoto Encyclopedia of Genes and Genomes signaling pathway analysis based on the DAVID database. Finally, the core components of *C. sinensis* and the targets of action were confirmed via molecular docking on AutoDock Vina and PyMOL. **Results:** In total, 7 bioactive ingredients of *C. sinensis* were identified from Traditional Chinese Medicines Systems Pharmacology Database and Analysis Platform database and 319 predicted targets were obtained, 231 of which were associated with AS. The core targets involved in AS treatment with *C. sinensis* included MAPK1, SRC, PIK3R1, AKT1, and HSP90AA1. The enrichment analysis unveiled the primary pathways involved in these processes, such as pathways in cancer and lipid and atherosclerosis. Moreover, through molecular docking, it was found that the active ingredients of *C. sinensis* presented with strong binding capacities with their corresponding targets, and the strongest binding capacity was observed between peroxyergosterol and SRC. **Conclusions:** The present study revealed at the molecular level that *C. sinensis* played its role in AS treatment through multiple drug active components, targets of action and pathways, which would point out the direction and provide theoretic basis for future research.

**Keywords:** *Cordyceps sinensis*; atherosclerosis; network pharmacology; molecular docking

## *Introduction*

Atherosclerosis (AS) is an intricate systemic, chronic inflammatory, progressive and age-related arterial intimal disease [1], and it's currently a common etiological factor underlying critical cardiovascular diseases [2–4]. The characterization of AS is the accumulation of immune cells and lipids in the vascular walls, and the pathological process of AS mainly involves metabolic disorders, inflammatory responses, foam cell formation, and so on. Recently, the incidence of AS has kept increasing and the age of onset has shown a younger trend. Statins are the first-line clinical drugs against AS, but there are still some problems in terms of medication safety [5, 6]. Hence, it is necessary to develop more alternative drugs to expand clinical drug options against this disease.

As traditional Chinese medicine (TCM) advances, more and more investigations have noted that TCMs play a vital part in the inhibition of inflammatory responses, improvement of lipid metabolism, and amelioration of endothelial dysfunction [6–8]. *Cordyceps sinensis* (*C. sinensis*) has been listed as one of the three well-known supplements in China, along with ginseng and velvet antler. Meanwhile, it's also a precious and valuable TCM with more than three hundred years medicinal history in China. Dongchong Xiacao is its Chinese name, because its appearance is complex of grass-like fungal stromata on dead ghost moth caterpillar. In the early stage, due to the endangered wild resources of *C. sinensis*, its output was greatly limited and its price was really high. Now, the artificial cultivation of *C. sinensis* has made breakthrough progress with a great improvement in the yield and quality [9], so we can develop its wider therapeutic effects and uses.

Network pharmacology is a predictive approach that combines pharmacology and computer science to explain the mechanism of drug actions on diseases [10]. Through network visualization, the potential targets of active ingredients of drugs can be screened, and then the mechanism of drug action can be explored from a holistic perspective [11]. Molecular docking is a simulation calculation method to study the affinity and interaction between small molecules and proteins [12, 13], which further verify the network pharmacology results. These two methods complement each other to promote the modernization of TCM [14], to find a modern pharmacological mechanism for the traditional efficacy, and to provide effective tools for the exploration of new disease mechanisms and targets. This combination method has been successfully used to discover the mechanism of Dongcong Xiacao treatment for a variety of diseases, including depression [15], renal ischemia-reperfusion injury [16], and diabetic kidney [17]. And *C. sinensis* also has been proved to have the effects of increasing the content of superoxide dismutase, scavenging oxygen free radicals and anti-lipid oxidation, as well as hypolipidemic effect by suppressing the synthesis of cholesterol and activating lipoprotein lipases on vessel walls and in plasma, which suggests its potential to prevent atherosclerosis. However, the material basis and action mechanism of Dongcong Xiacao to treat AS have not been specified yet. Therefore, we plan to apply this combination approach to explore the action mechanism and target protein of *C. sinensis* in AS treatment.

As shown in Figure 1, in our research, network pharmacology was adopted to identify the bioactive ingredients, target proteins and functions of *C. sinensis* in AS treatment; Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were applied to reveal associations among active ingredients, intersection targets and pathways; molecular docking analysis was conducted to visualize interactions between core active ingredients and AS-related targets. Therefore, this study determined the possible core ingredients, core target proteins and action mechanisms of *C. sinensis* in treating AS via the combination of network pharmacology and molecular docking, thus combining TCM theories with pharmacological mechanisms for further research and shedding light on clinical applications.

## *Materials and methods*

### Screening of active ingredients of *C. sinensis* and acquisition of related targets

Oral bioavailability ≥ 30% and drug likeness ≥ 0.18 were set as filtering conditions, effective components of *C. sinensis* and their corresponding PubChem CID numbers were searched through Traditional Chinese Medicines Systems Pharmacology Database and Analysis Platform (TCMSP) database, and then the obtained PubChem CID numbers were uploaded to PubChem database to acquire their SDF format files. Finally, the SDF format files of the active ingredients of *C. sinensis* were imported into PharmMapper database to determine the possible targets of *C. sinensis*. After the species of "*Homo sapiens*" was chosen, the obtained targets were normalized using the String database.

### Acquisition of AS target proteins

We entered the keyword "atherosclerosis" into Genecards database [18], Online Mendelian Inheritance in Man database [19, 20], Therapeutic Target Database [21, 22] and DisGNE [23, 24] so as to find out therapeutic targets. The yielded targets were consolidated and the duplicates were removed, which was followed by the normalization of target names through the Uniport database [25].

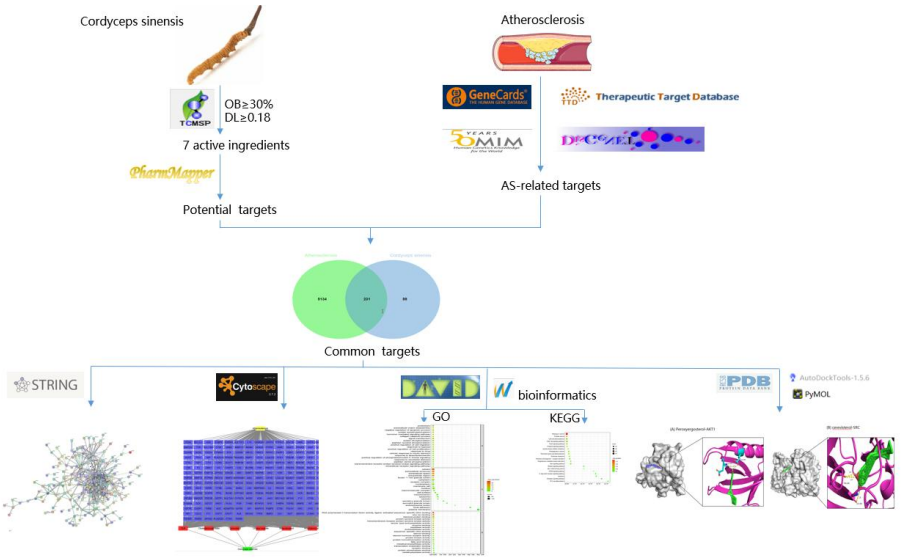


**Figure 1 Analysis flow chart of *C. sinensis* in AS treatment.** *C. sinensis*, *Cordyceps sinensis*; AS, atherosclerosis; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; OB, oral bioavailability; DL, drug likeness.

**Establishment of "Dongchong Xiacao-component-target-atherosclerosis" network**

The target genes of Dongcong Xiacao and disease genes were uploaded into the Venny database to identify intersection targets and illustrate the Venn diagram. Besides, the software Cytoscape 3.7.2 was applied to establish the "Dongchong Xiacao-component-target-atherosclerosis" network.

**Establishment and analysis of the protein-protein interaction (PPI) network**

The intersection targets were entered into the String database to establish the PPI network. "*Homo sapiens*" and "high confidence" were set as species and confidence level respectively. The highly disconnected nodes were hidden, and other parameters were defaulted. In addition, the TSV files were downloaded, and the target-related topological parameters were analyzed and ranked according to degree values using Cytoscape 3.7.2.

**GO and KEGG functional enrichment analyses**

The selected intersection targets were uploaded to DAVID database, followed by GO enrichment and KEGG pathway enrichment analyses on potential targets. The top 20 biological processes (BPs), cellular components (CCs), molecular functions (MFs) and pathways ranked by *P*-value were selected for visualized analysis and processing using the online mapping tool of Bioinformatics.

**Molecular docking analysis of active ingredients and core AS-related targets**

In the PPI network, top five core target proteins having highest degree values were molecularly docked with the corresponding active components to predict the active component-target binding activity. The 3D crystal structures of the core components and targets were obtained from Pubchem and Protein Data Bank databases, which was followed by molecular docking and visualized display via the software of AutoDock Vina and PyMOL, respectively.

## *Results*

**The selection of active ingredients and potential action targets of Dongcong Xiacao**

We searched the TCMSP database with the oral bioavailability (OB) and drug likeness (DL) set at ≥ 30% and ≥ 0.18 respectively. We have found out 7 active ingredients of *C. sinensis*, including peroxyergosterol and cerevisterol, and their detailed information was shown in Table 1. Accordingly, we also screened 319 corresponding targets.

**Acquisition and screening of disease targets for atherosclerosis**

With the search term of "atherosclerosis", the searching of 4 databases (GeneCard, Online Mendelian Inheritance in Man database, Therapeutic Target Database and DisGNE) yielded 4890, 3, 35, and 2044 targets, respectively. After merging and de-duplication, a total of 5365 AS targets were found in total.

**Establishment of "Dongcong Xiacao-component-target-atherosclerosis" network**

The yielded active component targets and disease targets were intersected using the Venny database, which yielded 231 intersection targets (Figure 2). The drug Dongchong Xiacao, its active ingredients, target proteins and disease atherosclerosis were uploaded into Cytoscape software to draw "Dongcong Xiacao-component-target-atherosclerosis" network, which was shown in Figure 3. In the network, *C. sinensis*, components, targets, and AS were represented by green, red, blue, and yellow nodes, respectively.

**PPI network establishment for therapeutic targets of *C. sinensis* on AS**

The 231 intersection targets were uploaded to the String database. Then, the species "*Homo sapiens*" was chosen, the confidence level was defined at high confidence of 0.9, and highly disconnected nodes were hidden. As shown is Figure 4, PPI network included 231 nodes and 554 edges, with the average node value reaching 4.8. Topographic analysis was conducted on the 231 targets using Cytoscape 3.7.2 software, and the ranking was conducted according to degree value. When the degree values of the targets were higher, the more important they were in the PPI network. Based on the analysis, the top 5 targets in the ranking of degree values were identified, as shown in Table 2, which were MAPK1, SRC, PIK3R1, AKT1 and HSP90AA1. It was speculated that these five target proteins were potentially the core potential targets in AS treatment.

**Table 1 Active ingredients of *Cordyceps sinensis***

| Mol ID | Molecule name | OB (%) | DL |
|---|---|---|---|
| MOL001439 | Arachidonic acid | 45.57 | 0.20 |
| MOL001645 | Linoleyl acetate | 42.10 | 0.20 |
| MOL000358 | Beta-sitosterol | 36.91 | 0.75 |
| MOL011169 | Peroxyergosterol | 44.39 | 0.82 |
| MOL008998 | Cerevisterol | 39.52 | 0.77 |
| MOL008999 | Cholesteryl palmitate | 31.05 | 0.45 |
| MOL000953 | Cholesterol | 37.87 | 0.68 |

OB, oral bioavailability; DL, drug likeness.

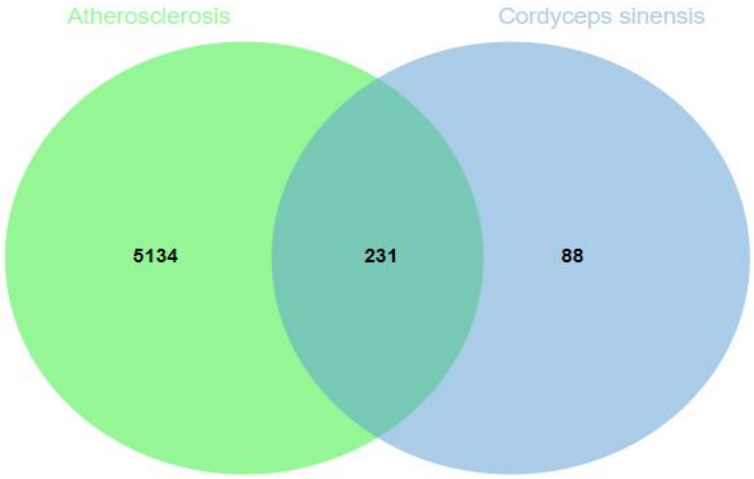


**Figure 2 Venn diagram of intersection targets of *C. sinensis* and AS.** The green circle represented AS targets, and the blue circle stood for the targets of *C. sinensis*. Finally, 231 interaction targets were acquired. *C. sinensis*, *Cordyceps sinensis*; AS, atherosclerosis.

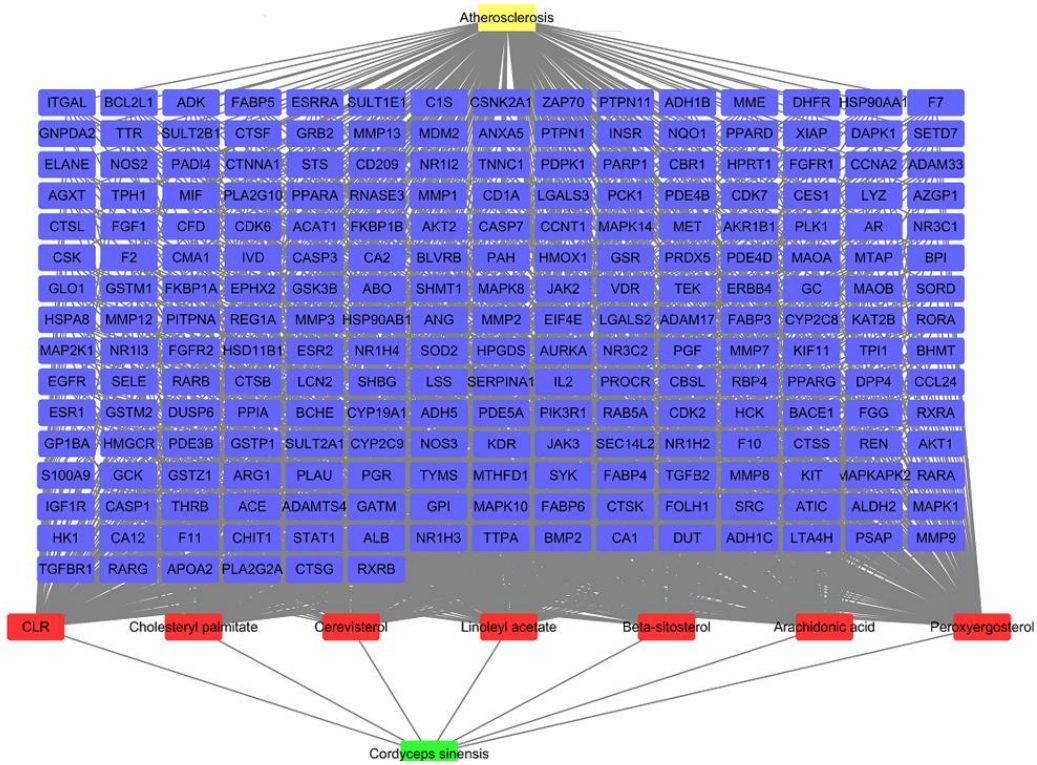


**Figure 3 Drug-component-target-disease network.** The red nodes represented active components of *C. sinensis*, which was consisted of 7 components. AS (yellow node) and *C. sinensis* (green node) have 231 intersection targets (blue nodes). *C. sinensis*, *Cordyceps sinensis*; AS, atherosclerosis.

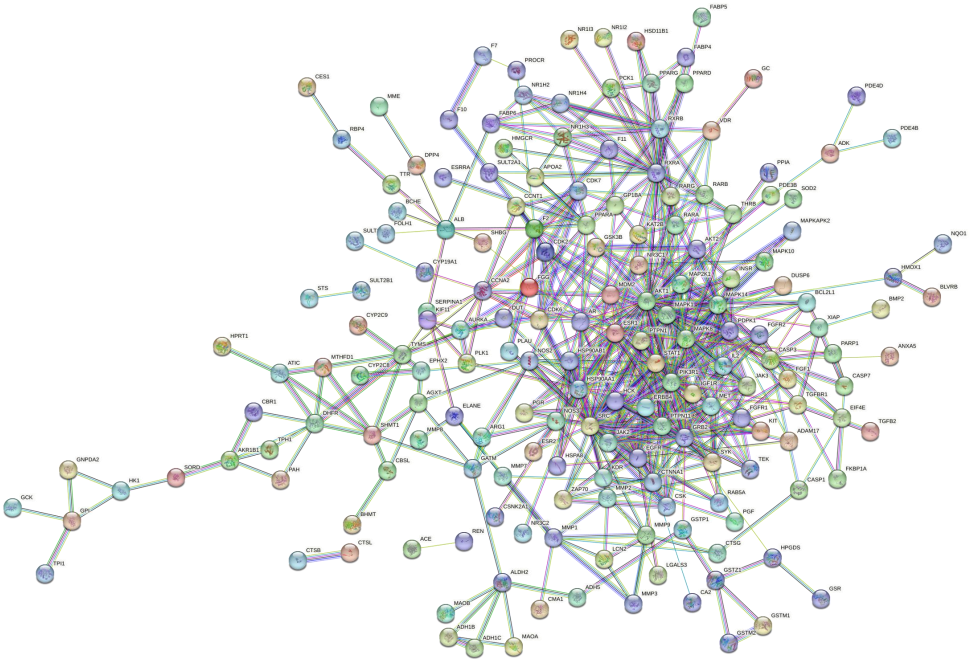

**Figure 4 PPI network for therapeutic targets of *C. sinensis* and AS.** PPI, protein-protein interaction; *C. sinensis*, *Cordyceps sinensis*; AS, atherosclerosis.

**Table 2 Core targets of *C. sinensis* in AS treatment**

| Target name | Degree |
|---|---|
| MAPK1 | 37.0 |
| SRC | 36.0 |
| PIK3R1 | 33.0 |
| AKT1 | 31.0 |
| HSP90AA1 | 28.0 |

*C. sinensis*, *Cordyceps sinensis*; AS, atherosclerosis.

### GO and KEGG functional enrichment analyses

GO enrichment analysis is consisted of 3 parts: BP, CC, and MF. As illustrated in Figure 5, it was discovered that BP is primarily correlated with proteolysis, protein autophosphorylation and signal transduction. CC mainly responded to cytosol, extracellular exosome, cytoplasm and nucleus, and the MF were mainly focused on identical protein binding and protein tyrosine kinase activity.

KEGG enrichment analysis result in Figure 6 indicated that the pathways of AS treatment with *C. sinensis* were mainly enriched in pathways in cancer and lipid and atherosclerosis, as well as PI3K-Akt and prolactin signaling pathway.

### Molecular docking of core components and targets

Molecular docking was performed between the 5 core targets of MAPK1, SRC, PIK3R1, AKT1, and HSP90AA1 and their corresponding active components (Table 3). Whether the small- and large-molecule proteins could bind to each other was principally evaluated by binding energy. The binding energy values of < 0 indicated that small-molecule proteins could bind spontaneously to large-molecule ones, and a smaller binding energy value demonstrated the stronger binding capacity, which meant that it was easier for small-molecule proteins to bind to large-molecule ones. Molecular docking (Table 3, Figure 7) revealed that all the 5 core target proteins could favorably bind to their corresponding active components, among which the strongest binding capacity was observed between SRC and peroxyergosterol, with the binding energy being –12.2 kcal/mol (1 cal = 4.4 J).

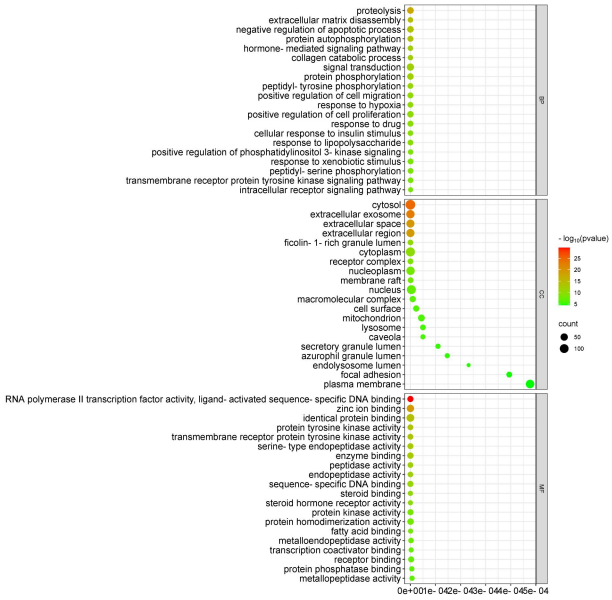


**Figure 5 Bubble diagram of GO enrichment analysis about the action targets of *C. sinensis* and AS.** GO, Gene Ontology; *C. sinensis*, *Cordyceps sinensis*; AS, atherosclerosis; BP, biological process; CC, cellular component; MF, molecular function.

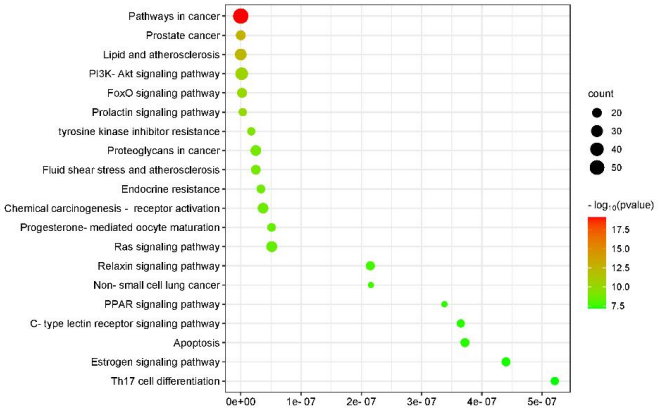


**Figure 6 Top 20 pathways for KEGG enrichment analysis of *C. sinensis* action.** KEGG, Kyoto Encyclopedia of Genes and Genomes; *C. sinensis*, *Cordyceps sinensis*.

**Table 3 Molecular docking results of core targets**

| Active components | Binding Energy (kcal/mol) | | | | |
|---|---|---|---|---|---|
| | AKT1 | MAPK1 | SRC | PIK3R1 | HSP90AA1 |
| Arachidonic acid | –4.7 | –5.6 | –5.4 | –4.7 | –5.0 |
| Linoleyl acetate | –5.3 | –5.6 | –6.2 | –5.4 | –4.9 |
| Beta-sitosterol | no | –9.2 | –10.9 | –9.2 | –8.2 |
| Peroxyergosterol | –9.8 | –10.6 | –12.2 | –9.8 | –10.3 |
| Cerevisterol | no | –9.8 | –11.4 | –9.6 | –9.6 |
| Cholesteryl palmitate | no | –7.7 | –8.5 | –6.6 | –7.0 |
| Cholesterol | no | –9.5 | –11.2 | –9.6 | –9.5 |

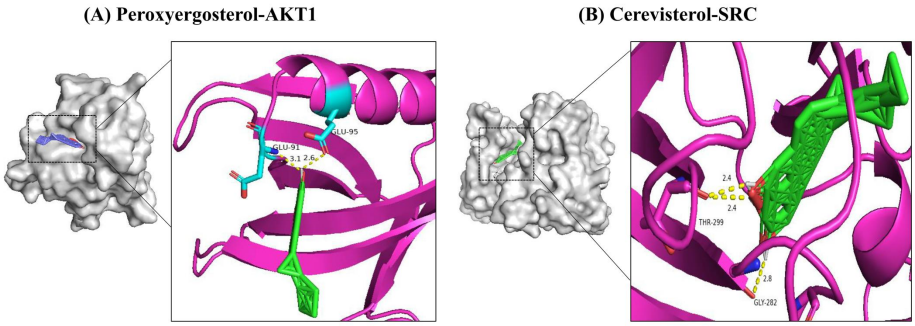


**Figure 7 Molecular docking diagram of (A) peroxyergosteral-AKT1 and (B) cerevisterol-SRC**

### *Discussion*

AS is a chronic inflammatory disease featuring lipid metabolic disorders, and is also the major cause of cardiovascular or cerebrovascular diseases like coronary heart disease and stroke. The complexity and variability of AS pathogenesis have posed great challenges for the treatment. Statins are currently the predominant drugs against AS in clinical practices, but these drugs are single-target and the long-term administration may trigger liver and kidney damage [26, 27]. In this context, the investigation for novel methods of AS prevention and control is still ongoing [28, 29].

A growing body of researches suggest that multi-target therapy is a promising drug discovery strategy with higher efficiency and lower toxicity than monotherapy. TCMs, with multiple components and targets, are associated with diverse mechanisms of action [30]. Due to the multi-component nature, the molecular mechanisms of TCMs in disease treatment are difficult to elucidate. The recent rise of network pharmacology undoubtedly provides a novel analytical approach for exploring the mechanisms of multi-target diseases and pharmacological effects of multi-target drugs. *C. sinensis* has the functions of tonifying kidneys, nourishing livers, stopping bleeding, and resolving phlegm. Its obvious protective effect against AS was confirmed by modern studies. For example, the compound *C. sinensis* oral liquid was found to diminish lipid deposition and macrophage infiltration and inhibit the formation of AS plaques [31]. It was also revealed that *C. sinensis* polysaccharides elevated the content of superoxide dismutases and catalase, and possessed the anti-lipid peroxidation ability [32]. Besides, another study showed that cordycepin, an active component of *C. sinensis*, suppressed lipopolysaccharide-induced inflammatory and matrix responses [33]. All these findings provided new thoughts for the prevention and control of atherosclerosis with *C. sinensis*, but the underlying molecular mechanisms of *C. sinensis* in AS treatment remain ambiguous.

Therefore, network pharmacological tools were adopted in the present study to systematically predict the underlying action mechanism of *C. sinensis* to treat AS. A total of 5365 AS targets were obtained, and 7 major active ingredients of Dongcong Xiacao were identified, which corresponded to 319 drug targets. Among them, 231 potential targets of action were involved in AS treatment. By constructing the PPI network, the 5 core targets involved in AS treatment with *C. sinensis* were screened out, including SRC, HSP90AA1, AKT1, MAKP1 and PIK3R1. SRC is a migration-related non-receptor tyrosine kinase that is essential in the processes of immunoinflammatory responses, such as promotion of phagocytosis, generation of inflammatory cytokines, induction of cell proliferation, migration, and apoptosis [34]. The uptake of oxidized low-density lipoproteins by macrophages is considered to be crucial in the occurrence of arterial inflammation [35], which is strongly associated with NF-κB activation. Suppression of SRC kinase activity can hinder NF-κB activation, thus slowing down AS progression [36]. Over-expressed in AS plaques, the HSP90 protein family is associated with inflammation. Studies have proved that HSP90AA1 expression is down-regulated with HSP90 inhibitors, the specific inhibitory effect of which can facilitate Nrf2 activation and repress NF-κB expression in plaques [37], thereby significantly reducing lesions. The serine/threonine protein kinase AKT1 is responsible for the functional regulation of endothelial cells and vascular smooth muscle cells. In vascular smooth muscle cells, the loss of AKT1 expression can lead to plaque vulnerability manifestations, including fibrous cap thinning and core area necrosis [38, 39]. Furthermore, AKT1, a key node in PI3K-PKB/Akt and pPI3K/Akt/mTOR signaling pathways, participates in the development and progression of AS. MAPK1, also known as ERK2, is a participant in the generation of pro-inflammatory cytokines and is very important for regulating cell proliferation and migration. As a key target of VEGF signaling pathway, MAPK1 is also involved in the division and migration of vascular endothelial cells and plays an important role in promoting angiogenesis [40]. The last core target, PIK3R1, participates in the lipid-induced activation of macrophages during AS [41]. The identification of the above 5 core target proteins can help elaborate on the anti-AS mechanism of *C. sinensis*.

According to KEGG pathway enrichment analysis, AS treatment with *C. sinensis* might be associated with pathways in cancer and lipid and atherosclerosis, as well as PI3K-Akt, prolactin and Ras signaling pathways. PI3K-Akt signaling pathway is the convergence point for multiple AS-affecting factors to stimulate intracellular signals. The anti-atherosclerosis effect of PI3K/Akt signaling pathway is achieved mainly through the following ways: (1) P13K/Akt signals up-regulate the intracellular expression of factors such as NF-κB, to directly suppress the proliferation of vascular smooth muscle cells. (2) P13K/Akt signals induce the expression of matrix metalloproteinase-2 (MMP-2) and MMP-9, thereby affecting plaque formation and progression of, so that inhibiting this pathway can slow down AS development and progression. AS firstly appears in regions with turbulent blood flow and low shear stress, such as arterial branches or bends, while under low shear stress, the pro-inflammatory factors and apoptotic genes in vascular endothelial cells are up-regulated, which facilitates the onset and development of AS and even results in the higher risk of plaque ruptures [42, 43].

Compound Dongchong Xiacao oral liquid has already been proved effectively inhibit the formation of AS plaque in *ApoE* knock-out (*ApoE*-/-) mice, and its mechanism may be related to reducing the levels of triglycerides, low-density lipoprotein cholesterol and total cholesterol in serum, and decreasing the plaque area of thoracic aorta, but the specific active ingredients and targets have not been revealed [44]. This study discovered the potential core ingredients and action targets of *C. sinensis* in AS treatment, which provided the important reference for the subsequent development of anti-atherosclerosis drugs derived from *C. sinensis*.

### *Conclusion*

In conclusion, based on the core signaling pathways like lipid and atherosclerosis, PI3K-Akt, prolactin and Ras, *C. sinensis* modulates the synergistic interactions among the core targets such as MAPK1, SRC and PIK3R1, to play a role in AS treatment. However, there are some limitations to the current study. Because the accuracy and

completeness of existing databases are still imperfect, retrieval results obtained from various databases may be different. In addition, although multiple targets and pathways can be identified using network pharmacological techniques, the derived mechanism of action still requires further validation.

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