Exploration on the mechanism of *Radix Astragali-Caulis Spatholobi* by Qi-invigorating and blood-activating combination for the treatment of atherosclerosis based on network pharmacology

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**Author contributions**
Hai-Hua Lv conceived this study, carried out this study, and drafted the manuscript. Chen-Chen Huang and Ying-Jun He designed the study, collected and analyzed the data. Hong-Jie Liao and Ting Zhao directed the drawing and reviewed the article critically. Suo-Yi Huang was responsible for this manuscript and reviewed the article critically. All authors read and approved the final manuscript.

**Competition of interests**
The authors declare no conflicts of interest.

**Abstract**
The objective of this study was to investigate the main active ingredients, potential targets, and possible mechanisms of action of the combination of *Radix Astragali* and *Caulis Spatholobi* for the treatment of atherosclerosis using network pharmacology. The study aimed to provide a reference basis for the development of new formulations and clinical use of Chinese medicine. The main components of *Radix Astragali* and *Caulis Spatholobi* were obtained from the TCMSP, BATMAN-TCM database, and literature reports. The targets corresponding to the main components were imported into the Uniprot database to standardize the names, and target information was supplemented with the Swiss Target Prediction database. Disease-related targets were obtained from DrugBank, OMIM, CTD, GeneCards, and DisGeNET online databases. Venn tools were used to obtain the potential targets of *Radix Astragali* and *Caulis Spatholobi* for the treatment of AS. The intersecting genes were imported into the STRING 11.5 database to construct protein-protein interaction network maps and analyze their interactions. Cytoscape 3.7.1 software was used to mine their core targets. GO function and KEGG signaling pathway enrichment analysis were performed using the DAVID v2023q1 database. The results were imported into the “Bioinformatics Cloud Platform” to generate enrichment bubble maps. Finally, the “component-target-pathway” diagram was constructed using Cytoscape 3.7.1 software. The study found that 78 major active ingredients and 527 potential targets were obtained from *Radix Astragali* and *Caulis Spatholobi*. The main active components of the two in combination for the treatment of AS are quercetin, stigmasterol, kaempferol, luteolin, formononetin, etc. The key targets involve CDKN1A, EZF1, CDK4, CDK2, CDK1, RB1, TP53, CDKN1B, IL6, JUN, etc. The main pathways involved the AGE-RAGE signaling pathway in diabetic complications, cancer pathway, etc. The biological processes involved include positive regulation of gene expression, negative regulation of apoptotic process, etc. The study initially verified the feasibility of the combination of *Radix Astragali-Caulis Spatholobi* by Qi-invigorating (promoting human metabolic activity) and blood-activating for the treatment of AS. It demonstrated that the combination of Chinese medicine has multi-level, multi-target, and multi-pathway mechanisms of action to treat the disease, providing a reference basis for the development and utilization of new drugs.

**Keywords:** network pharmacology; Qi-invigorating; blood-activating; atherosclerosis
Introduction

With the gradual improvement of the economic living standards in China, people's lifestyles have changed, and various undesirable factors have emerged. According to the statistical yearbook released by the National Bureau of Statistics of China from 2010 to 2020, cardiovascular diseases are the leading causes of death in China, accounting for more than 40% of all causes of death from diseases. This has become a major public health problem that restricts social development. Therefore, early intervention and treatment are crucial for better patient prognosis. Atherosclerosis (AS) is one of the most common and important cardiovascular diseases and is the main pathological basis of cardiovascular disease [1]. The pathogenesis of AS is still unclear, but it is believed to be related to inflammatory response, abnormal lipid metabolism, oxidative stress, endothelial cell damage, platelet agglutination, and many other factors. Traditional Chinese medicine believes that AS belongs to the category of “chest arthralgia,” “blood arthralgia,” and “pulse arthralgia,” and it is differentiated as “heart blood stasis syndrome.” Blood stasis is the standard, and Qi-deficiency (sub-health in modern medicine) is the root. Therefore, Qi-invigorating (promoting human metabolic activity) medicine combined with blood-activating medicine is commonly used to treat AS in clinics [2].

Radix Astragali is the dried root of Mongolian milkvetch or membranous milkvetch [3]. It has a sweet taste, a slightly warm nature, and belongs to the spleen and lung meridians. It is known for its effects of Qi-invigorating and Yang-tonifying (improving human immunity), benefiting Qi (traditional Chinese medicine believes that Qi constitutes the basic substance of the human body and maintains vital activities) and blood, invigorating spleen and promoting diuresis, benefiting Qi and consolidating exterior, detoxification, and pus discharge. It is classified as a Qi-invigorating drug in traditional Chinese medicine. Caulis Spatholobi is the dried vine stem of Spatholobus suberectus Dunn, a member of the Leguminosae family [4]. It has a bitter, slightly sweet taste, a warm nature, and belongs to the liver and kidney meridians. It is known for its effects of activating blood and regulating menstruation, unblocking veins, nourishing blood and replenishing blood, and is classified as a blood activator in traditional Chinese medicine. Recent literature on the treatment of AS with the combination of Qi-invigorating and blood-activating traditional Chinese medicine reveals that Qi-invigorating drugs are mostly studied around Radix Astragali, Radix Ginseng, Radix Angelicae sinensis, and their effective components, while blood-activating drugs are mostly studied around Radix Salviae Ligustirae, Radix Notoginseng, Flos Carthami, Radix chuanxiong, and their effective components. Experiments have shown that the effect of Qi-invigorating drugs combined with blood-activating drugs in the treatment of AS is better than that of Qi-invigorating drugs or blood-activating drugs alone [5]. Radix Astragali has been studied extensively for its therapeutic effects on cardiovascular diseases, and its various active ingredients have shown good therapeutic effects on AS. Caulis Spatholobi is known as the “holy medicine of blood”, and its extract has been shown to reduce the pathological damage of AS [6]. Therefore, we speculate that the combination of Qi-invigorating drug Radix Astragali and blood-activating drug Caulis Spatholobi can play a role in preventing and treating AS, and the effect is better than that of a single medicine.

In recent years, the Chinese medicine industry has received strong support from the state, leading to a transformation of the pharmacological effects of Chinese medicine from traditional empirical medicine to modern pharmacology. As a result, Chinese medicine is playing an increasingly important role in clinical treatment. There are certain rules for the combination of Chinese medicines, which can not only reduce the toxic side effects of Chinese medicines but also enhance their efficacy. Therefore, the development of new combinations of Chinese medicines and the study of their mechanism of action are current problems that need to be addressed. This paper aims to explore the mechanism of action of the combination of Radix Astragali and Caulis Spatholobi in the treatment of AS using the network pharmacology method. The findings of this study can serve as a reference for future experimental verification and clinical application.

Materials and methods

Acquisition of main components and targets of Radix Astragali and Caulis Spatholobi

The Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, https://tcmsp-e.com) was used to retrieve the active components of Radix Astragali and Caulis Spatholobi [7]. The active components were screened based on their absorption, distribution, metabolism, and excretion (ADME) process, with oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18 as the criteria [8]. The Bioinformatics Analysis Tool for Molecular mechanism of Traditional Chinese Medicine (Batman-TCM, http://bionet.nctsb.org/batman-tcm/) database was used to obtain the main active ingredients and their action targets, with Score cutoff ≥ 39 and P value < 0.05 as the screening criteria [9, 10]. The obtained protein targets were imported into the Universal Protein Resource (UniProt) database, with “Reviewed” and “Human” selected as the screening condition for target name specification. The main active ingredients were identified as Astragalus polysaccharide and Astragaloside, supplemented by literature [11–13]. The Swiss Target Prediction database (http://www.swistargetprediction.ch/) was used to complement the target information [14]. Finally, the main active ingredients and targets obtained above were summarized and de-duplicated.

Acquisition of disease targets

The DrugBank database (https://go.drugbank.com), Online Mendelian Inheritance in Man (OMIM, https://omim.org) database, Comparative Toxicogenomics Database (CTD, https://ctdbase.org), GeneCards database, and Disease Gene Network (DisGeNET, https://www.disgenet.org) database were searched using “Atherosclerosis” as the keyword to identify disease-related targets. In the disease databases, if the number of target genes obtained is high, screening can be performed by taking the median combined with the reference Score value [15–20]. The targets obtained from the above five databases were combined and subjected to an aggregation and de-duplication process to obtain the AS disease targets.

Construction of protein-protein interaction (PPI) network and mining of core targets

To further clarify the interactions between the drug targets of Radix Astragali and Caulis Spatholobi with AS disease targets, Venn diagrams were plotted for their targets, and intersected using an online tool (https://bioinfoogg.cnb.csc.es/tools/venny/index.html) [21]. The intersected targets were then imported into the STRING 11.5 platform (https://www.string-db.org/), with “Organism” set to “Homo sapiens” [22]. After obtaining the results, the “highest confidence 0.900” was selected, and the free nodes in the hidden network diagram were chosen, leaving the rest as default. The PPI network graph was constructed, and the tsv file was exported for analysis using the MCC algorithm of the Cytohubba plugin in Cytoscape 3.7.1 software. The top 10 targets were screened for interaction analysis.

Gene ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis

To investigate the biological processes and signaling pathways involved in the treatment of AS by Radix Astragali and Caulis Spatholobi, the intersecting genes obtained in Construction of PPI network and mining of core targets were imported into the DAVID Bioinformatics Resources (DAVID, https://david.ncifcrf.gov/) v2023q1 database [23]. “Official Gene symbol” was selected as the gene identifier, and the species was set to “Homo sapiens.” P < 0.01 was used as the screening condition, and the top 10 AS-related biological processes and top 16 signaling pathways were selected as the filtering condition. The Bioinformatics Cloud Platform
(http://www.bioinformatics.com.cn) was used to draw the enrichment bubble map, with the X-axis set to Gene ratio and the Y-axis set to biological process or signaling pathway. The color of the bubble changed according to the size of \( -\log_{10}(P \text{ value}) \), and the size of the bubble was related to the number of genes involved in the process, with larger bubbles indicating more genes involved.

**Construction of “component-target-pathway” diagram**

To construct a “component-target-pathway” diagram for the treatment of AS with *Radix Astragali* and *Caulis Spatholobi*, Cytoscape 3.7.1 software was used. The current mapping relationship was set to change with the linkage density, with higher linkage density resulting in larger nodes, indicating their importance in participating in the biological process.

**Results**

**Screening results of main active components and targets of *Radix Astragali* and *Caulis Spatholobi***

There are 57 main active components and 412 potential targets of *Radix Astragali*, and 42 main active components and 272 potential targets of *Caulis Spatholobi*. During the process of standardized targeting, it was found that some target genes were not from humans, and these genes were eliminated in the subsequent research process. After the screening process, 78 components were identified in *Radix Astragali* and *Caulis Spatholobi*, including 5 common components and 527 potential targets. These components were labeled separately to facilitate subsequent mapping.

**Screening of disease targets**

The keyword “Atherosclerosis” was used to search the disease target database, resulting in 47 targets retrieved from the DrugBank database and 219 targets retrieved from the OMIM database. However, the GeneCards database, CTD database, and DisGeNET database retrieved more targets, with 1488, 424, and 239 targets obtained by selecting the median and reference Scores value, respectively. The targets obtained from these databases were combined and deduplicated, resulting in a total of 1834 targets that were closely related to AS.

**PPI network construction and core targets mining**

The drug targets obtained in Screening results of main active components and targets of *Radix Astragali* and *Caulis Spatholobi* and the disease targets obtained in Screening of disease targets were plotted in a Venn diagram, and their intersection was taken (see Figure 1). There were 196 intersecting targets between the corresponding targets of *Radix Astragali* and *Caulis Spatholobi* and disease targets. These 196 targets were then imported into the STRING 11.5 database, and the results were shown in Figure 2 according to the setting conditions in Construction of PPI network and mining of core targets. The tsv file was exported and processed as described in Construction of PPI network and mining of core targets, and the top 10 targets were identified as CDKN1A, E2F1, CDK4, CDK2, CDK1, RB1, TP53, CDKN1B, IL6, and JUN (as shown in Figure 3).

![Figure 1 Venn diagram of targets of *Radix Astragali*, *Caulis Spatholobi* and AS. AS, atherosclerosis.](image1.png)

![Figure 2 PPI network diagram of common targets of *Radix Astragali*, *Caulis Spatholobi* and AS. PPI, protein-protein interaction; AS, atherosclerosis.](image2.png)
GO function and KEGG enrichment analysis results

The DAVID v2023q1 database was utilized to analyze the biological processes and signaling pathways of the targets of *Radix Astragali* and *Caulis Spatholobi* combination for the treatment of AS. After exporting the tsv file and drawing the enrichment bubble map with the assistance of the “Bioinformatics Cloud Platform”, the results indicated that several targets were closely associated with AS. The biological processes involved in treating AS with *Radix Astragali* and *Caulis Spatholobi* combination include positive regulation of gene expression, negative regulation of apoptosis process, positive regulation of RNA polymerase II promoter transcription, inflammatory response, etc., as shown in Figure 4A. KEGG enrichment results suggest that these targets are involved in signaling pathways such as AGE-RAGE signaling pathway in diabetic complications, cancer pathway, lipid and atherosclerosis, FoxO signaling pathway, etc., as illustrated in Figure 4B. The functions of the relevant targets for the treatment of AS mainly focus on enzyme binding, identical protein binding, RNA polymerase II transcription factor activity, ligand-activated sequence-specific DNA binding, protein binding, etc., as depicted in Figure 4C.

Construction of “component-target-pathway” diagram

The targets and pathways of *Radix Astragali* and *Caulis Spatholobi* in treating AS were constructed using Cytoscape 3.7.1 software. The “component-target-pathway” diagram is presented in Figure 5, with node size set according to the Degree value. The results indicate that HQ15 (quercetin), JXT1 (stigmasterol), HQ10 (kaempferol), JXT19 (luteolin), and common component C (formononetin) are the primary components of *Radix Astragali* and *Caulis Spatholobi* in treating AS.
while PTGS2, ESR1, and PTGS1 are the main targets involved in the pathway. Among them, HQ15 (quercetin) had the highest Degree value of 149, suggesting that quercetin is the most important active substance for treating AS in this process.

**Discussion**

AS is a complex cardiovascular disease with multiple pathogenic factors, including lipid infiltration, inflammatory response, thrombosis and platelet aggregation, and endothelial damage. While each theory can explain the pathogenesis from a certain perspective, none of them can provide a comprehensive overview of AS [24]. With the development of Chinese medicine, the use of Chinese herbal medicine in clinical practice has become increasingly widespread, and the method of benefiting Qi and invigorating blood is increasingly used in the treatment of AS. *Radix Astragali*, a commonly used herbal medicine to tonify Qi, contains polysaccharides, saponins, flavonoids, and amino acids, which have been found to have various effects such as cardiovascular protection, regulation of immune metabolism, organ protection, antiviral, and anti-oxidative stress protection [25, 26]. Caulis Spatholobi, a commonly used blood invigorator, contains flavonoids, phenolic acids, alkaloids, terpenoids, and other components with antitumor, anti-inflammatory, antioxidant, and hepatoprotective effects [27]. Both herbs have been shown to have good effects in treating AS individually, and it is presumed that their combination to benefit Qi and invigorate blood will be more effective than using either herb alone. However, due to the complex composition of Chinese medicines and the unclear mechanism of interaction among the components, this paper systematically investigates the *Radix Astragali -Caulis Spatholobi* combination for the treatment of AS using a network pharmacology approach to explore its main active ingredients, core targets, signaling pathways, and the biological processes involved.

The results of this research indicate that there are 78 main active ingredients in the combination of *Radix Astragali* and *Caulis Spatholobi*, among which HQ15 (quercetin), JXT1 (stigmasterol), HQ10 (kaempferol), JXT19 (luteolin), and common component C (formononetin) may be the most important for the treatment of AS. Quercetin has been extensively studied in the treatment of atherosclerosis. Zhang M et al. suggested that quercetin could reduce inflammation of the vascular wall by regulating lipid metabolism and lowering IL-1 levels to reduce AS plaque regression [28]. Lv L demonstrated that quercetin could inhibit the proliferation of aortic wall fibroblasts, smooth muscle cells, and collagen synthesis and secretion through the PI3K/Akt/NF-κB pathway, thereby slowing down the progression of AS [29]. Sabeva NS et al. found that
stigmasterol could promote cholesterol excretion in mouse peritoneal macrophages, reduce TNF-α, IL-6, and IL-1β levels, and have a potential role in the treatment of atherosclerosis [30]. Zhao P demonstrated that forononoinet could regulate lipid metabolism by upregulating the expression of SR-B1 and ABCA1 proteins to prevent the formation of AS lesions [31]. Li XY showed that kaempferol could regulate lipids by increasing the amount of cholesterol excreted by macrophages and inhibit macrophage foaminess to combat atherosclerosis [32]. Feng Z et al. suggested that kaempferol could reduce the formation of AS by activating the PI3K/AKT/Nrf2 pathway to improve vascular morphology, regulate lipid levels, and inhibit ROS production, inflammation, and apoptosis levels [33]. Luteolin may protect the cardiovascular system and thus antagonize the development of AS by inhibiting TNF-α to slow down inflammation, scavenging ROS to inhibit oxidative stress, activating the PI3K/Akt signaling pathway, inhibiting the TLR-4/NF-κB signaling pathway, and downregulating P53 protein expression, among other pathways [34]. There are many more studies and discussions related to the above major active components, and only some of the ideas related to AS are listed here.

A total of 527 targets were screened for Radix Astragali and Caulis Spatholobi, and then compared with closely related targets in the AS disease database, resulting in 196 common genes. CDKN1A, E2F1, CDK4, CDK2, CDK1, RB1, TP53, CDKN1B, IκB, JUN, PTGS2, ESR1, PTGS1, and other targets may be the core targets of Radix Astragali and Caulis Spatholobi pairing for the treatment of AS. Abnormal proliferation of vascular smooth muscle cells is a key factor in the development of AS, and current studies have shown that factors involved in cell cycle regulation include three main categories: CDK, cyclin, and CDK1 [35]. CDKN1A is the most widely known cell cycle inhibitor protein with kinase activity, which effectively inhibits the activity of the CDK family, blocks DNA replication, and plays an important regulatory role in cell proliferation and differentiation [36]. CDK1, CDK2, and CDK4 mainly participate in cell cycle regulation, induce mitosis, and initiate DNA replication. The latter two mainly act in the G1 and S phases [37]. E2F1, as a member of the E2F family, is involved in the regulation of the G1 and S phases of the cell cycle and DNA synthesis-related genes, which are mainly regulated by the RB1 gene. In the cell cycle, RB is first phosphorylated, E2F1 is activated to induce CDK2 production, and the protein kinase complex composed of CDK2 and cyclin further contributes to the phosphorylation of RB, thus driving the cell cycle to continue. The overexpression of E2F1 contributes to the abnormal proliferation of smooth muscle cells leading to the formation of AS [38]. The TP53 is an essential molecule in cell proliferation and apoptosis, and its absence drives vascular smooth muscle cell proliferation to accelerate atherosclerosis formation [39]. AS is also a chronic inflammatory disease, and TNF-α, IL-1β, IL-6, and IL-4 are involved in the inflammatory response of the body as inflammatory cytokines, affecting the cardiovascular system [40, 41]. Elevated levels of these cytokines cause smooth muscle cell degeneration and necrosis, destabilize plaque, and contribute to the development of AS, which can lead to dilated cardiomyopathy, myocardial infarction, and even heart failure and other cardiovascular diseases. The JUN is a member of AP-1, and persistently high levels of c-Jun/AP-1 early in immunoinflammatory AS lesions can lead to increased athromatous plaque instability [42]. PTGS1 and PTGS2 are not directly involved in the biological processes of AS, but proceed through the expression of their products COX-1 and COX-2. During platelet activation, arachidonic acid can synthesize TXA2 through COX-1, causing platelets to clump and form thrombi [43]. COX-2 acts during the development and progression of AS, mainly through mechanisms such as inflammatory cytokines that stimulate the vascular wall and cause vascular smooth muscle cells to migrate and proliferate [44]. Studies have shown that estrogen levels and the formation of atherosclerosis are negatively correlated, and the mechanism of action may be that estrogen combined with ESR1 protects the cardiovascular system by reducing the uptake of low-density lipoprotein, the release of inflammatory factors, and preventing the proliferation of vascular smooth muscle cells [45].

Based on the results of GO functional enrichment, it is suggested that the mechanism of action of Radix Astragali and Caulis Spatholobi with AS is closely related to cell growth and metabolism, and various biomolecules are involved in the regulation, constituting a complex network metabolic map. The results of KEGG pathway enrichment suggest that the AGE-RAGE signaling pathway in diabetic complications, cancer pathway, lipid and atherosclerosis, FoxO signaling inhibits PI3K/AKT signaling pathway, TNF signaling pathway, and other pathways are important for the treatment of AS using Radix Astragali and Caulis Spatholobi. Diabetes is one of the high-risk factors for atherosclerosis, and diabetic patients are highly susceptible to vascular complications such as atherosclerosis. Long WP showed that AGE is involved in MMP-2 expression, inflammatory response, and apoptosis of smooth muscle cells within atherosclerotic plaques in diabetic patients through the RAGE pathway, providing a new pathway for the treatment of diabetic-induced vascular complications with Chinese medicine [46]. Abnormal lipid metabolism is one of the factors in the formation of atherosclerosis, which can be manifested as elevated levels of TC, TG, and LDL-C. The PI3K-Akt signaling pathway participates in cell growth metabolism and inflammatory factor release, playing an important regulatory role and is a key pathway to induce apoptosis in vascular endothelial cells, closely related to the formation of AS [47, 48]. Li LJ et al. demonstrated the feasibility of anti-ApoC3 mice via the PI3K/Akt/FoxO1 signaling pathway, and this pathway could improve vascular endothelial matrix remodeling by regulating lipid levels and MMP2/9 expression in mice, thus alleviating the pathological injury of AS in mice [49]. In the TNF signaling pathway, TNF-α mediates the inflammatory response of AS, which is present in AS plaques and closely related to plaque stability, and itself promotes the release of other inflammatory factors, accelerating the formation of AS [50]. IL-17 is an important cytokine secreted by helper T cells 17 and is involved in immune cell and immune factor interactions, inflammation development, plaque formation, and other aspects involved in the formation and development of AS [51].

Conclusion

In conclusion, this research systematically investigated the main active substances, main targets, and signaling pathways of Radix Astragali and Caulis Spatholobi combination for the treatment of AS by combining the lipid infiltration theory, inflammatory response theory, thrombosis and platelet aggregation theory, endothelial damage theory, plaque theory, and other pathogenesis of AS through the method of network pharmacology. The study proved that the combination of Chinese herbal medicine has a multi-level, multi-target, and multi-pathway mechanism of action for the treatment of AS. The feasibility of the combination of these two herbs in the treatment of AS was initially verified, providing a basis for the next experimental validation. However, it is worth noting that network pharmacology is a means to predict the feasibility of drug treatment based on big data and computer technology and does not represent the real situation. Chinese herbal medicine is a complex substance rich in multiple components, and various components will interact with each other after entering the human body, affecting its therapeutic effect. Therefore, in-depth research is still needed to solve these problems. Additionally, the study found that the Radix Astragali and Caulis Spatholobi combination can not only treat AS but also has a potential role in the treatment of tumors. The two are involved in the signaling pathways of many tumors, including prostate cancer, and can potentially be used in the treatment of tumors.

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