The therapeutic mechanism of black soybean in atherosclerosis based on network pharmacology

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Abstract

Objective: To investigate the cardiovascular mechanism of black soybean, the biological characteristics of black soybean were studied by bioinformatics, and the mechanism of its treatment for atherosclerosis was further determined.

Methods: Firstly, the basic data sets of effective components and corresponding targets of black beans were constructed, and then mapped to the AS background network obtained from DisGeNET database and CTD database. Finally, the potential targets of black beans acting on AS were obtained. After constructing the protein-protein interaction (PPI) network, the topological characteristics of these targets were analyzed. KEGG and GO were enriched to obtain the potential mechanism of black soybean acting on AS.

Results: There were 12 bioactive components reported in black soybean. Among them, beta-sitosterol, stigmasterol and N-(4-hydroxyphenylethyl) ACTINIDINE were the three most active components. There are 19 targets of black soybeans acting on PPI network of AS disease. Among them, ADRB2 and PTGS2 are important targets for black soybeans to alleviate AS. The therapeutic pathways include arachidonic acid metabolism and serotonin synapse.

Conclusion: Black soybean can play a therapeutic role in AS through multi-target and multi-pathway. The application of network pharmacology can quickly clarify the characteristics of functional foods and identify their potential targets and mechanisms for disease treatment.

Key words: Black bean, Cardiovascular disease, Network pharmacology, Mechanism of action

Introduction

Glycine Max is one of the common coarse grains in China. It is the black seed of leguminous plant soybean. Because the seed coat is black, it is named Black bean, also known as black bean, winter bean, et al [1]. Like soybeans, black beans belong to leguminous plants, which are widely distributed in 27 provinces and municipalities in China. They are cultivated in most parts of China, with the highest yield in Northeast China [2]. Black soybean is rich in nutritional value [3]. It also has 36.0% protein, 15.9% fat, 10.2% dietary fiber and 33.6% carbohydrate. At the same time, every 100 g of black soybean contains 224 mg of calcium, 243 mg of magnesium, 1 377 mg of potassium and 500 mg of phosphorus. In addition to the above components, black soybean also contains a large number of vitamins and other trace elements. Compared with other Chinese dietary soybeans, black soybean has a more balanced nutritional component [4].

In addition to the main nutrients mentioned above, black soybean also has its special biological active ingredients, and through these active ingredients, it plays an important nutritional and health function. According to the literature reports, black soybean has a strong protective function against oxidative damage [5], which is mainly realized by the anthocyanins in the skin of black soybean. In addition, isoflavones, vitamin E and rutin in black soybean also have corresponding antioxidant effects. Free radical damage in the body is one of the important mechanisms of cardiovascular disease and cancer. Like soybean, black soybean is also rich in isoflavones [6], which has been proved by experiments to have a wide range of anti-cancer activities. Its anti-cancer spectrum includes breast cancer, prostate cancer and colon cancer.

Atherosclerosis (AS) is the main cause of coronary heart disease, cerebral infarction and peripheral vascular disease. With the sustained development of China's economic level and the continuous improvement of people's living standards, the incidence of AS in China is increasing year by year [7]. The disease can cause a series of malignant diseases of the heart system, and has a greater clinical risk [8]. Dietary factors are one of the important factors of the disease. Therefore, in addition to daily dietary regulation, food with special active ingredients can be developed as raw materials in existing foods to produce supplements or substitutes, thus accelerating the efficiency of lipid metabolism in human body. Compared with drugs, the potential value of developing foods with the function of regulating AS is higher and more acceptable to the people [9]. Similar to black soybean, the pathogenesis of AS is very complex, so it is extremely difficult to find the potential mechanism of black soybean to alleviate AS. How to overlap the relationship between the two and initially determine the common differences between them is the key to solve the above problems. Considering that bioinformatics can carry out large sample and high processing capacity, this method obtains the desired results through cross-comparison analysis of existing databases. Therefore, the application of bioinformatics to deal with the above problems is an effective means to solve the problem [10].

Materials and Methods

Main Components of Black Soybean and Their Molecular Targets

In TCMSP database (http://lsp.nwu.edu.cn/tcmsp.php), the composition and properties of the main components of black soybean were obtained. After sorting out, the corresponding text is formed and subsequent data mining processing is carried out. In the process of predicting the main active ingredients of black soybean, it is necessary to analyze the characteristics of the main ingredients of black soybean. Among them is the oral availability of black soybean ingredients. It is displayed in the database with the value of OB (Oral Bioavailability, OB). According to the OBioavail model [11] in TCMSP database, this study evaluated the absorption characteristics of active ingredients. Generally, 30% is the limit of oral availability. Drug-likeness (DL) refers to the similarity between compounds and known drugs. In this study, 0.18 is taken as the acceptable value. On the other hand, after sorting out all the components of black soybean, we only screened out the main components that have been reported in the known literature and did the next mining research. The analysis of components with potential drug activity was not involved.

In Drugbank database (http://www.drugbank.ca), the molecular target components corresponding to the effective components obtained in 2.1 were sorted out. Because part of the database molecular target information is mouse or rabbit origin, the above molecular targets are mapped in UniProt and mapped to human for subsequent analysis. After sorting out, the data set of molecular targets of black soybean interaction was obtained. A compound-molecule target network was constructed in Cytoscape 3.7.1 software.

Construction of AS Background Network

In order to obtain the background network of AS for subsequent analysis, this study mainly used DisGeNET database (www.disgenet.org) and CTD database (http://ctdbase.org/) to search Atherosclerosis as keywords respectively to obtain the molecular target data set related to AS. Among them, there are 1133 targets in DisGeNET database summary mode and 59 targets in CTD database which have been reported or clinically verified. After deleting the repetitive molecular targets mentioned above, a total of 1135 molecular targets were sorted out and defined as the molecular target data set of AS. The data set is imported into string database to construct the background network of AS.

Mechanisms of Black Bean Acting on AS

The AS background network obtained by 2.3 was mapped by using the data set of black bean molecular targets obtained by 2.2. The potential target of black soybean acting on AS was obtained. The network analysis function of Cytoscape 3.7.1 software was used to analyze the network topological parameters, in order to investigate the target characteristics of black soybean acting on AS. In order to further elucidate the role of target proteins in gene function and signaling pathway, we used webgestalt database (http://www.webgestalt.org/) to enrich the function of the acquired sub-son target, and then constructed a molecular target-KEGG pathway network by using ClueGO plug-in in Cytoscape 3.7.1 software. According to the KEGG pathway and GO function obtained, the potential mechanism of black soybean acting on AS was analyzed.

Results

Main Components of Black Bean and Their Molecular Targets

In TCMSP database, using black bean (Sojae Semen Nigrum) as the key word to search, we can obtain 130 active ingredients which have been reported, and then screen them by oral bioavailability and pharmacokinetics. The total number of ingredients obtained is 12 (see Table 1). In Drugbank, the molecular targets of 12 active ingredients in Table 1 were searched. A total of 114 effective ingredients in black soybean were obtained. After weight reduction, 65 single values were obtained. After crossing the above 12 active ingredients and 65 molecular targets, the prepared interaction relationship is shown in Figure 1.

In Cytoscape 3.7.1, a network of interactions between the above compounds and their molecular targets is constructed, as shown in Figure 1. After the topological analysis of the network, it can be seen that there are 77 nodes in the network, with an average node degree of 2.96. Among them, beta-sitosterol (nodal degree = 38), Stigmasterol (nodal degree = 31) and N-(p-Hydroxyphenethyl) ACTINIDINE (nodal degree = 16) were the three components with the highest biological activity in black soybean. In addition, NCOA2 (nodal degree = 6), PTGS1 (nodal degree = 5) and ADRB2, PTGS2, SCN5A, CHRM1 and CHRM3 are the effective components of the drug. These

Table 1 Main Active Components and Biological Characteristics of Black Bean

No.	Mol ID	name	MW	OB	DL
1	MOL000358	beta-sitosterol	414.79	36.91	0.75
2	MOL009711	Cycloartenone	424.78	40.75	0.79
3	MOL003629	Daidzein-4,7-diglucoside	578.57	47.27	0.67
4	MOL004798	delphinidin	303.26	40.63	0.28
5	MOL000433	FA	441.45	68.96	0.71
6	MOL005030	gondoic acid	310.58	30.70	0.20
7	MOL009722	L-Folinic acid	473.50	31.79	0.74
8	MOL009729	methyl (E)-nonadec-10-enoate	310.58	30.66	0.19
9	MOL009733	methyl 12-oxooctadec-9-enoate	310.53	37.45	0.19
10	MOL009735	N-(p-Hydroxyphenethyl) actinidine	268.41	62.16	0.19
11	MOL009706	Pramoxine	293.45	49.08	0.19
12	MOL000449	Stigmasterol	412.77	43.83	0.76

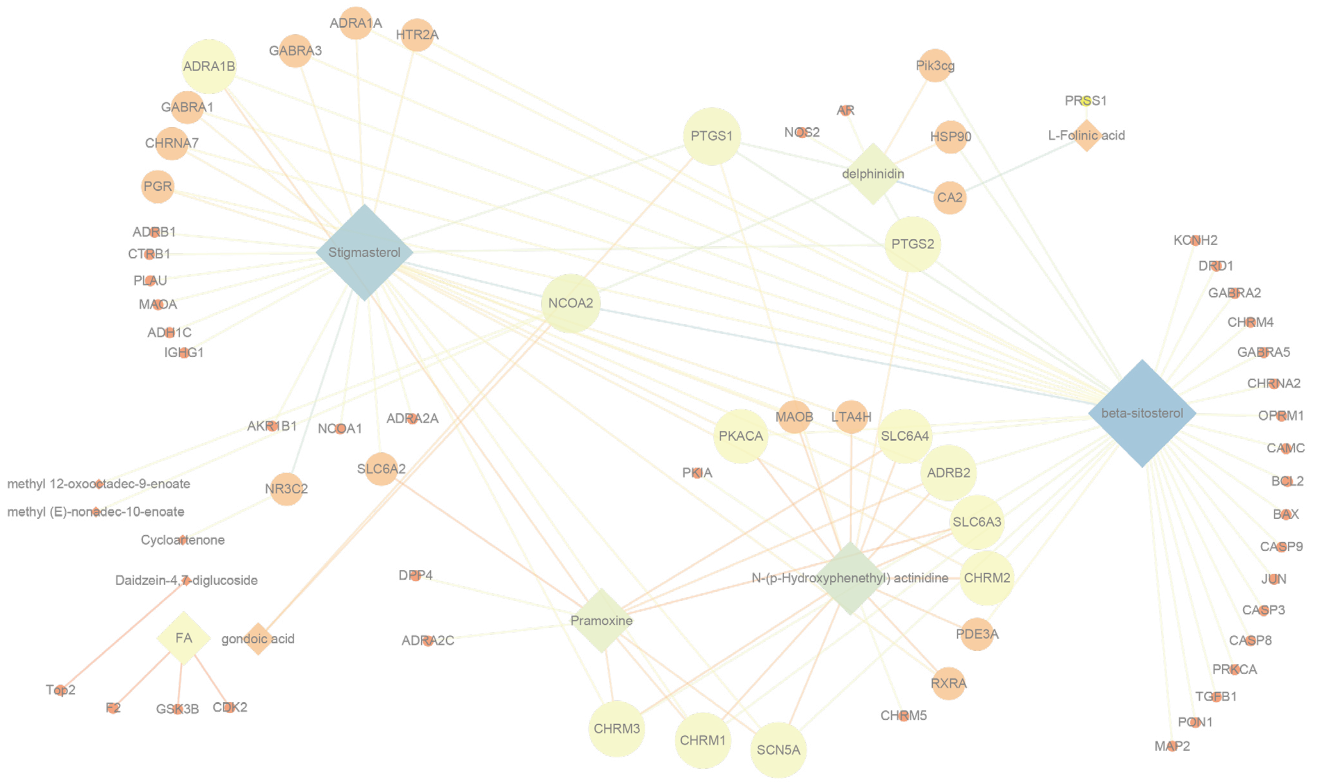

Figure 1 Black Bean Active Component-Molecular Target Network

seven molecules are the main target molecules of black beans.

In this network, there are 114 edges with an average length of 125.75. A total of 61 edges are less than the average length, which proves that the above compounds/molecular targets are closely related.

Black Bean Acts on Molecular Targets Related to AS Diseases

After introducing the AS background network, 65 individual molecular targets obtained in Section 3.1 were used to target. Finally, the molecular targets of black soybean for AS were obtained, as shown in Figure 2 (cluster Marker plug-in processing). Among them, purple red is the potential molecular target of black soybean, totaling 19, and lavender is the main component corresponding to the target, totaling 8.

After the topological analysis of the network (PPI network after eliminating the active components), it can be seen that there are 652 nodes in the network, with an average node degree of 72.97. Among the 19 selected targets, 11 were higher than the average node degree, namely CASP3 (node degree = 260), PTGS2 (node degree = 260), TGFB1 (node degree = 159), F2 (node degree = 158), AR (node degree = 144), GSK3B (node degree = 107), PLAU (node degree = 106), NOS2 (node degree = 104), CASP9 (Node Degree = 97), PON1 (Node Degree = 80), ADRB2 (Node Degree = 74). The results of cross-matching 3.1 showed that PTGS2 and ADRB2 were the main targets of AS. In this network, there are 23788 edges with an average length of 35.53. A total of 6851 edges are less than the average length, which proves that the above compounds/molecular targets are closely related.

The effective components and targets of black soybean were extracted and PPI network was constructed separately (see Figure 3). To further determine the regulation

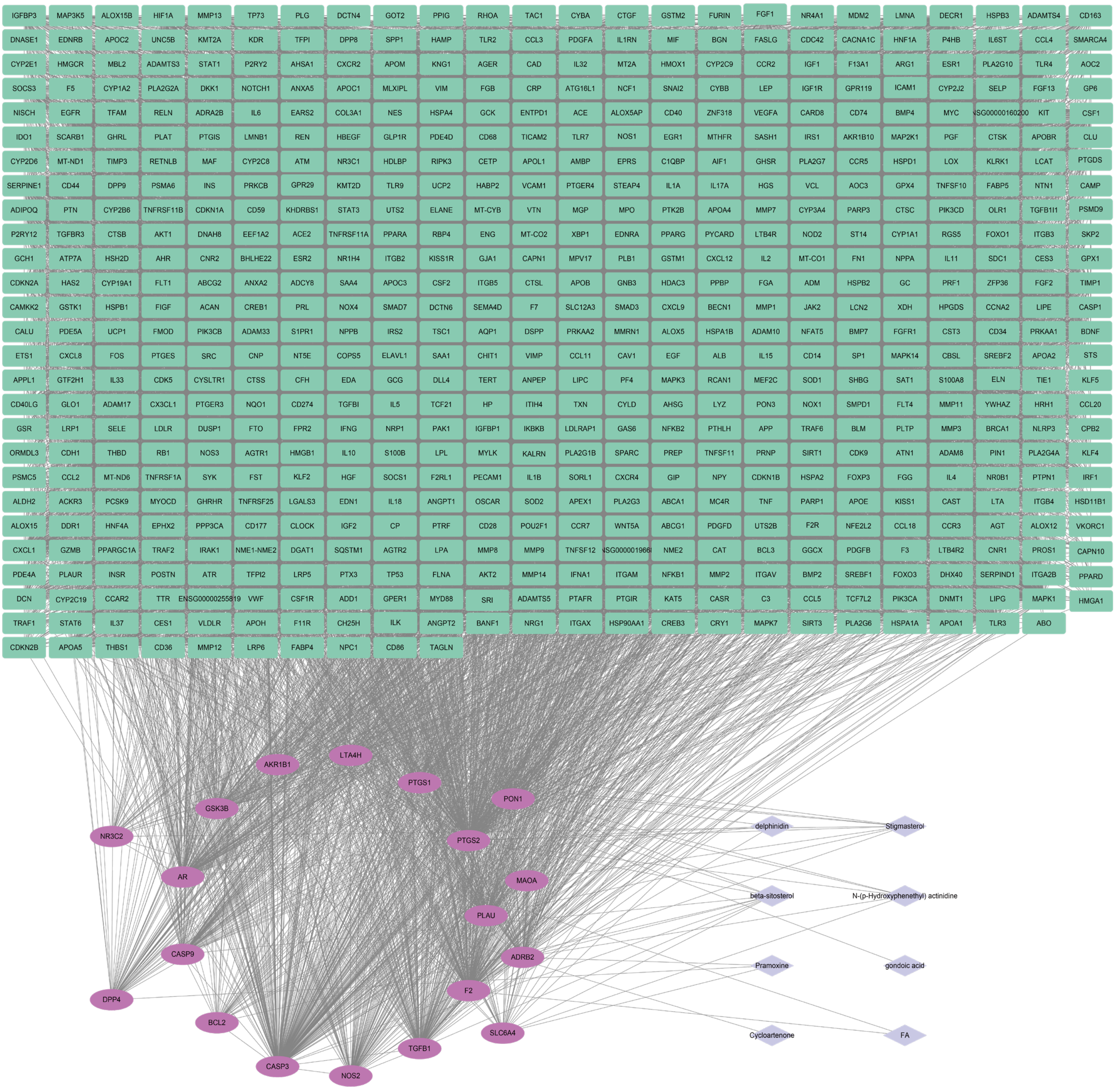

Figure 2 Black soybean acts on AS active component-molecular target network

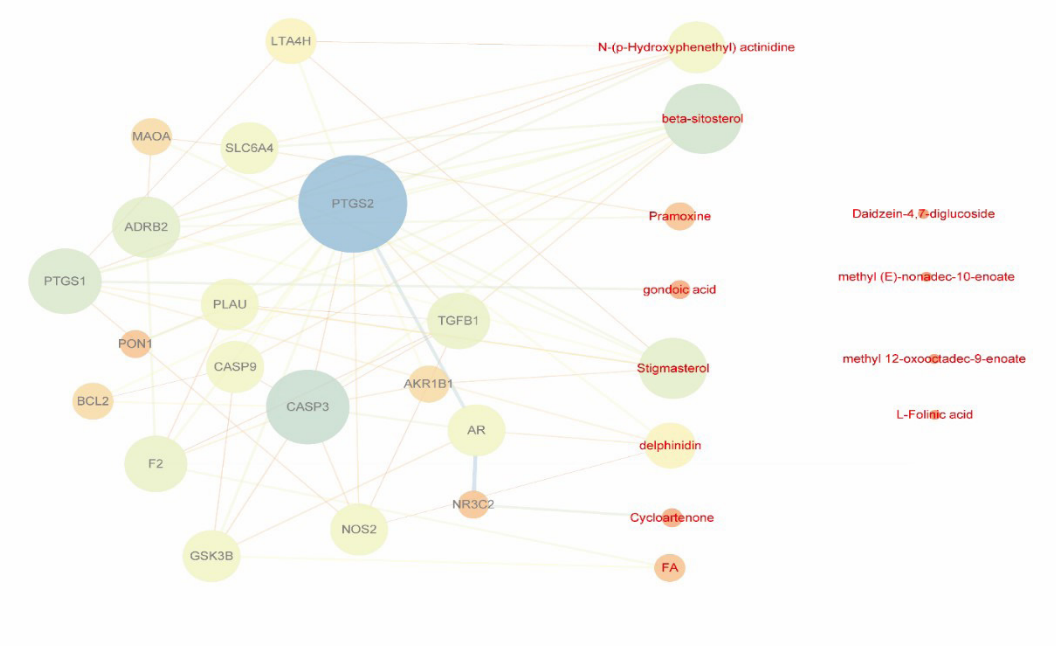

Figure 3 Black soybean acts on AS active component-molecular target network

of active ingredients in black soybean on AS-related targets. After the topological analysis of the network, it can be seen that there are 31 nodes in the network, with an average node degree of 4.33. Among them, beta-sitosterol (nodal degree = 9), Stigmasterol (nodal degree = 7) and N-(p-Hydroxyphenethyl) ACTINIDINE (nodal degree = 5) were the three components with the highest biological activity in black soybean. Further analysis of PPI network relationship of its target points shows that the targets with the highest node degree are PTGS2 (node degree = 15), CASP3 (node degree = 10), PTGS1 (node degree = 8) and ADRB2 (node degree = 7). It is certain that of the 19 molecular targets mentioned above, the four targets mentioned above are the core targets for their regulation. In this network, there are 66 edges, with an average length of 22.73, and 25 edges less than the average length.

Biological Function of Black Bean on Molecular Targets Related to AS Diseases

In order to further systematically analyze the biological function of black soybean in alleviating AS, 19 molecular targets have been identified in this study. According to the results of Figure 4A, according to the research results of webgestalt database, there are 10 pathways to achieve functional enrichment ($p < 0.05$). Further analysis of the 10 pathways indicated that there were three main pathways related to AS, namely Serotonergic synapse pathway, Regulation of lipolysis in adipocytes pathway and Apoptosis pathway.

From the results of Figure 4B, the David database of 19 targets mentioned above was obtained by using clueGO plug-in of Cytoscape 3.7.1. It can be seen that there are 11 paths to achieve functional enrichment ($p < 0.05$). Further analysis of these 11 pathways revealed that there were 5 pathways associated with AS. Combining the results of webgestalt database, the final results are shown in Table 2.

Further enrichment of molecular functions of black soybean targets was carried out. According to the results of webgestalt database, GO functions of 19 targets were enriched. BP (bio-process), MF (molecular function) and CC (cell constituent) functions of these targets were obtained respectively. The results are shown in Figure 5, which including GO-BP (biological process) (5A), GO-CC (cell component) (5B) and GO-MF (molecular function) (5C).

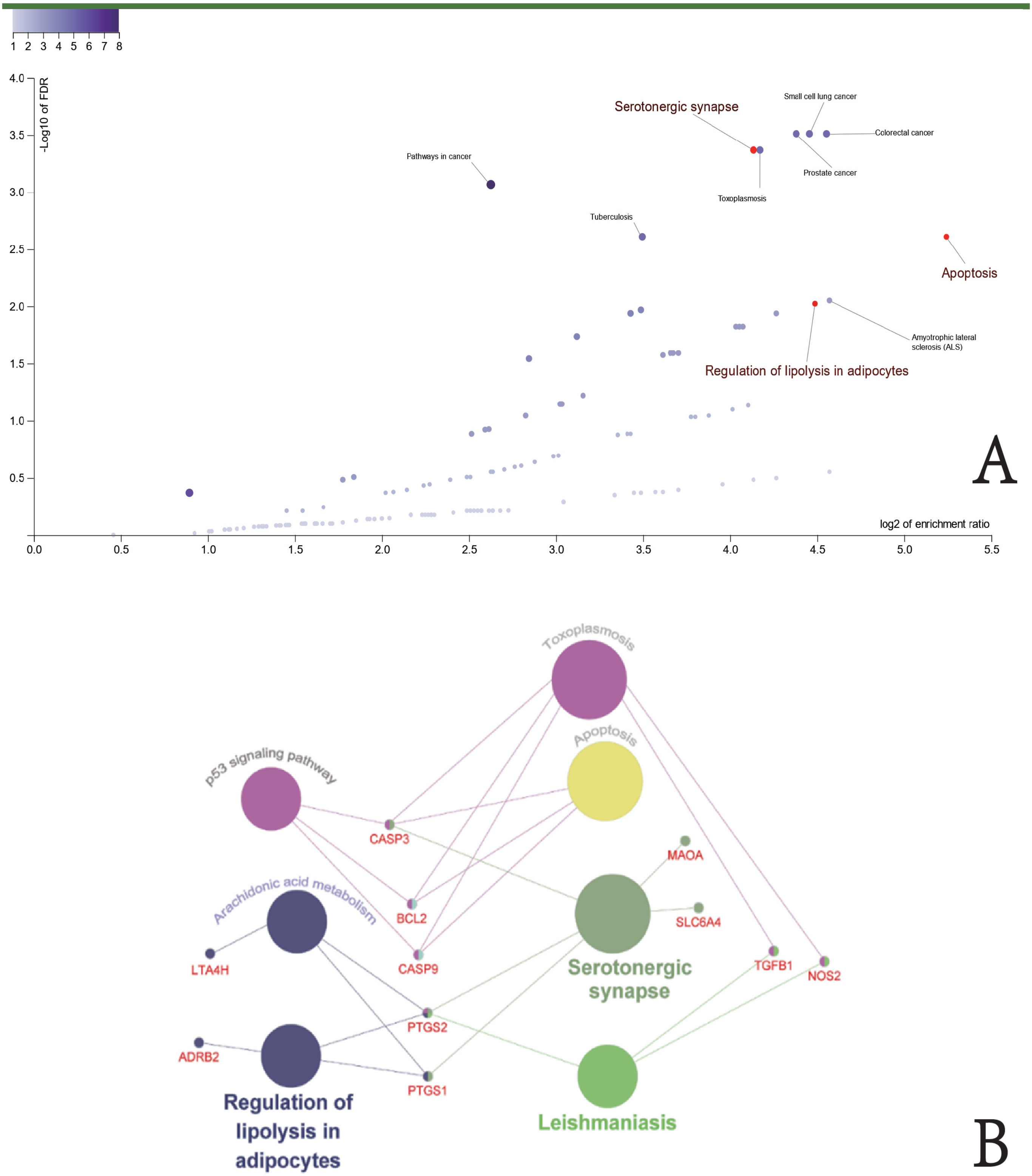

Figure 4 Functional enrichment (KEGG pathway) of black beans acting on AS molecular targets which including (A) WebGestalt result and (B) Cytoscape result.

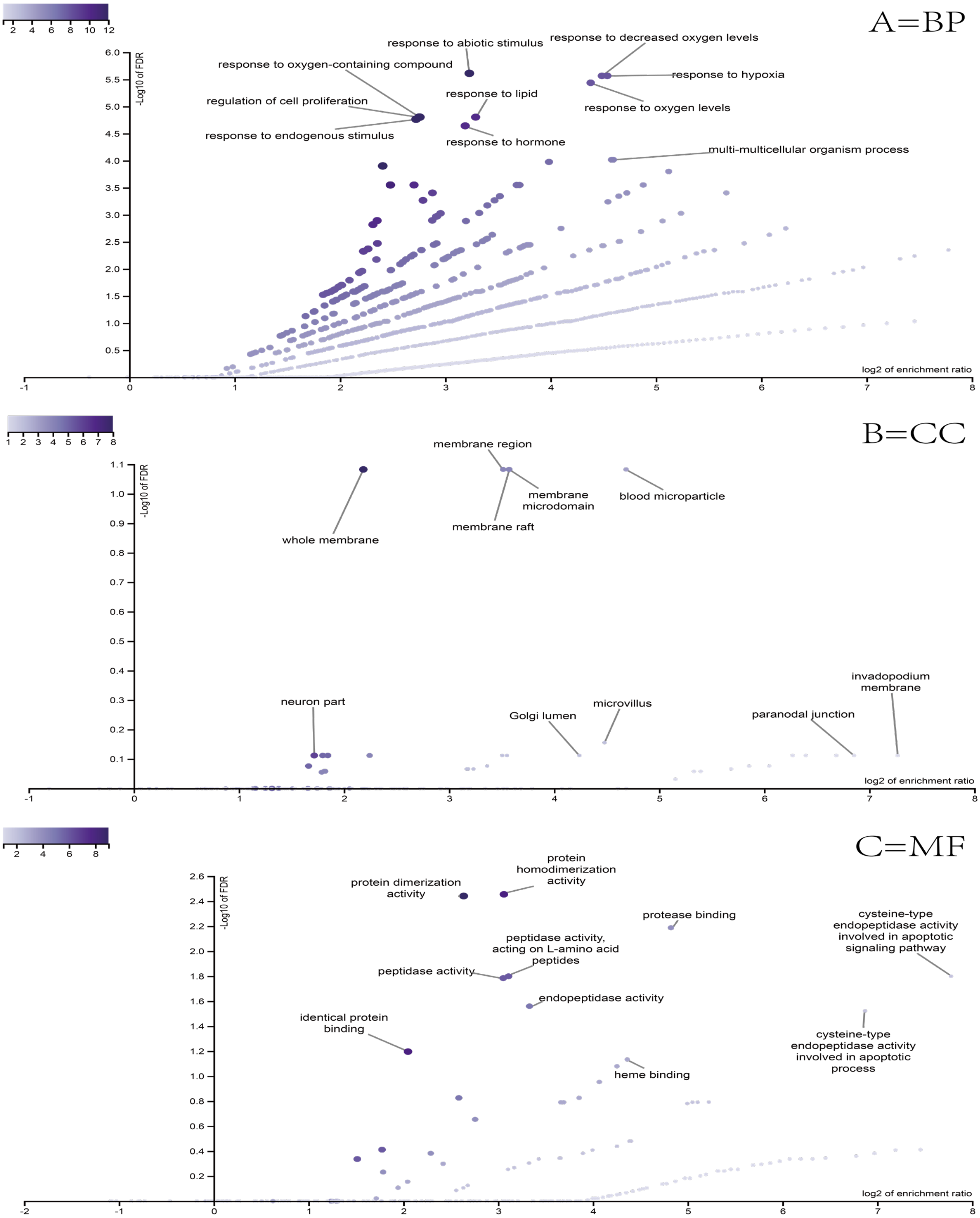

Figure 5 Functional enrichment (GO function) of black beans acting on AS molecular targets which including (A) GO-BP(biological process), (B) GO-CC (cell component) and (C) GO-MF (molecular function).

Discussion

Although there are many studies on the pathogenesis of AS [12]. However, considering the external factors affecting AS, especially the factors such as diet, environment and susceptibility genes, how to quickly establish the disease evaluation system and further improve its pathogenesis and treatment mechanism is the key to reduce the clinical incidence of AS and improve its treatment effect [13]. Considering the importance of diet in the pathogenesis of AS [14]. From the proofreading of dietary adjustment and the evaluation of common foods, on the one hand, it can

Table 2 Functional Analysis of Black Bean on AS Targets

KEEG	GO Term	*P* value	Genes
04726	Serotonergic synapse	< 0.001	CASP3, MAOA, PTGS1, PTGS2, SLC6A4
00590	Arachidonic acid metabolism	< 0.001	LTA4H, PTGS1, PTGS2
04923	Regulation of lipolysis in adipocytes	< 0.001	ADRB2, PTGS1, PTGS2
04115	p53 signaling pathway	< 0.001	BCL2, CASP3, CASP9
04215	Apoptosis	< 0.001	BCL2, CASP3, CASP9

provide a new theoretical basis for daily dietary regulation. On the other hand, through the effective ingredients of common foods, we can find the biomarkers related to AS, which can provide precise reference for clinical evaluation and treatment. In order to identify the potential targets for black soybean to alleviate AS, we studied the biological functions of black soybean, the mapping of AS background network and the enrichment of molecular targets. Using network pharmacology and bioinformatics, the potential mechanism of common food black soybean for AS treatment was investigated. According to the results of the study, we found that there were 12 components with potential oral activity in black soybean. Of the 12 components mentioned above, 8 active components could act on 19 targets reported by AS, respectively. Through further analysis of the target obtained, we determined that black soybean was mainly achieved through five KEGG pathways, such as Serotonergic synapse, in the treatment of AS. Meanwhile, the GO function of black soybean showed that these targets were widely involved in calcium metabolism [15] (GO:0051926, negative regulation of calcium tr). The biological functions of ansport and GO: 0008217 (regulation of blood pressure) are discussed [16]. This study can explain the mechanism of black soybean alleviating AS from the theoretical level, and provide corresponding molecular targets for future research on black soybean diet.

According to the analysis of the effective components in black soybean, beta-sitosterol, Stigmasterol and N-(p-Hydroxyphenethyl) ACTINIDINE were the three components with the highest activity in alleviating AS in black soybean. As a food supplement, beta-sitosterol began to study the treatment of AS as early as 1956 [17]. Current studies show that beta-sitosterol can treat AS mainly by reducing the adhesion of vascular smooth muscle [18], antioxidant [19] and anti-inflammatory activity [20]. Because beta-sitosterol is widely distributed in a variety of foods (mainly legumes), it is one of the important active ingredients in the treatment of AS. Similar to beta-sitosterol, Stigmasterol is often found in legumes. According to the literature, sterols from leguminous plants often have good scavenging capacity of oxidative free radicals, so as to achieve the treatment of AS [21]. The results of this study show that Stigmasterol can achieve AS treatment through multiple targets. According to Li's results, Stigmasterol can inhibit the proliferation of vascular cells, and thus reduce the increase and rupture of AS plaque [22]. N-(p-Hydroxyphenethyl) ACTINIDINE is a kind of alkaloids. Although there are no reports about its treatment of AS, previous studies have shown that berberine [23], indole alkaloids and isoquinoline alkaloids also have good anti-AS activity [24]. It can be inferred that N-(p-Hydroxyphenethyl) actinidine, as one of the alkaloids, has certain potential of anti-AS and can be further studied in the future.

After screening of network pharmacology, PTGS2 and ADRB2 are more closely related to AS than other 17 molecular targets, which can be regarded as the main target of black soybean acting on AS. PTGS2 can express downstream COX-2 gene, and cyclooxygenase (COX) is an important rate-limiting enzyme regulating arachidonic acid synthesis of prostaglandins (PGs) and thromboxane A2 (TXA2). Overexpression of COX-2 in vascular smooth muscle often means vascular injury or increase of inflammatory factors, which may further induce inflammation of vascular wall and subsequent plaque exfoliation and proliferation [25]. There are few studies on ADRB2 and AS. Most of the existing studies focus on the relationship between the polymorphism of ADRB2 and the pathogenesis of diseases, such as asthma [26], obesity and cardiovascular diseases [27]. However, the research on its mechanism is insufficient. Existing studies have shown that ADRB2 exists in various organs innervated by sympathetic postganglionic fibers, and its main function is to combine with adrenaline and norepinephrine. It is mainly mediated by catecholamines, thus regulating the body's physiological functions such as fat metabolism, energy consumption, glycogen decomposition [28]. CASP 3 is an important apoptotic factor, and its CASP family is an important apoptotic pathway factor. Current studies have shown that in the pathogenesis of AS, arterial vessels are often injured by inflammation, and the important pathway to induce cell damage is CASP-3 and CASP-9. With the continuous stimulation of inflammatory response, Casp-3 is activated, which induces the overexpression of CASP-9 downstream, leading to vascular injury [29]. TGFB1 is more used in the study of heart failure [30]. With the decrease of TGFB1, the degree of fibrosis induced by heart failure also decreases [31]. Considering its role in stimulating cell growth and differentiation, it can be inferred that plaque formation is closely related to AS pathogenesis. F2 (Prothrombin) is an important molecular target in the formation of AS [32], which can significantly regulate plaque formation and rupture. In addition, AR, GSK3B and PLAU are also widely involved in the whole disease process of AS. It is certain that black soybean can alleviate AS by regulating the above molecular targets.

In this study, we further enriched the pathways involved in the above targets. According to the results, the above targets were enriched into five corresponding pathways. Serotonergic synapse can regulate the contraction of blood vessels. With the contraction of blood vessels, the vessel lumen becomes smaller and the blood flow becomes slower, leading to the accelerated accumulation of inflammatory factors and cholesterol in blood vessels. PTGS2 and its corresponding COX2 belong to arachidonic acid metabolic pathway. In addition to COX pathway, the LOX pathway and CYP pathway involved in arachidonic acid metabolism pathway are widely involved in various stages of AS, such as plaque formation, adhesion and exfoliation, vascular inflammation, etc. [33]. The regulation of fat metabolism in adipocytes lays particular emphasis on dietary regulation. Diet is very important in the pathogenesis of AS. With the intake of high-fat diet, fat often accumulates. Through the metabolic pathway of fat cells, fat accumulated in the body can be effectively consumed, thus reducing the risk of AS. P53 signaling pathway and cell apoptosis are mainly regulated by CASP-3. Among the potential targets, CASP-9 and BCL-2 belong to CASP family. In the pathogenesis of AS, these two pathways mainly regulate the apoptosis of endothelial cells. Black soybean can protect blood vessels by inhibiting apoptosis.

Conclusion

In this study, the traditional food black soybean was systematically studied by using network pharmacology. By means of bioinformatics, the potential target and corresponding pathway information of black soybean were quickly obtained, which provided sufficient reference and guidance for subsequent experimental research. By means of network pharmacology, a large number of complicated preliminary experiments can be avoided and potential molecular targets can be obtained directly. This method can shorten a lot of research time and energy. However, the functional food research based on network pharmacology is limited by the previous database foundation of food and the limitation of bioinformatics on the one hand; the former needs to be supplemented by the functional study of food compounds and active ingredients, while the latter needs to be carried out by subsequent experiments. Verification. The conclusions of this study need to be verified by further experimental studies. In conclusion, this study provides new research ideas and methods for functional food research. The empirical research methods of traditional Chinese medicine can provide sufficient guidance for follow-up research.

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Competing interests

The authors declare no competing financial interests. Readers are welcome to comment on the online version of this article at https:// www.tmrjournals.com/ fthc

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