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Network Pharmacology Study on Hypoglycemic and Lipid-Regulating Mechanism and Pharmacodynamic Material Basis of Crataegi Fructus

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Abstract

Objective: To use the method of network pharmacology to predict the mechanism of Crataegi fructus hypoglycemic and lipid regulation and its pharmacodynamic material basis.

Methods: Traditional Chinese Medicine Systems Pharmacolog Database (TCMSP), Traditional Chinese Medicine Integrative Database (TCMID), Bioinformatics Analysis Tool for Molecular mechanism (BATMAN), and GeneCards databases were used to mine the active components of Crataegi fructus and their targets for hypoglycemic and lipid-lowering.

The String database was used to obtain the Protein-Protein Interaction (PPI) relationship. Cystoscope software was used to construct the PPI and component-target network of Crataegi fructus, and the core targets, key components were screened out, and the Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) signaling pathways of key targets were enriched and analyzed using the Database for Annotation, Visualization and Integrated Discovery (DAVID) database. Finally, the molecular docking verification was carried out using AutoDockTools-1.5.6 software.

Results: 152 common targets of Crataegi fructus and hyperlipidemia and 464 targets of hyperglycemia were analyzed and screened out four core active components of Crataegi fructus including kaempferol, quercetin, epicatechin and ursolic acid were screened, and five important targets were Insulin resistance (INS), protein kinase B(AKT1), interleukin- 6(IL6), tumor protein p53(TP5 3) and Tumor Necrosis Factor (TNF). Six signaling pathways involved in the regulation of hypoglycemia and lipid regulation, including phosphatidylinositol 3 kinase-protein kinase B(PI3K-AKT), hypoxia-inducible factor -1(HIF-1), Adenosine 5'-Monophosphate-Activated Protein Kinase (AMPK), TNF, INS signaling pathways, etc. Molecular docking results showed that the core active components of Crataegi fructus had good binding activity to the target.

Keywords: Crataegi fructus; Hypoglycemic and lipid-lowering; Network pharmacology; Signaling pathway.

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Background

Crataegi fructus is the dried and mature fruit of crataegus pinnatifid a. bge. var. major n. e. br. of Rosaceae or Crataegus pinnatifida Bge, with the effects of «promoting digestion, invigorating stomach, moving qi, removing blood stasis, turbidity and lipid-lowering» etc [1]. Modern studies have shown that it mainly contains flavonoids and their glycosides, polyphenols, triterpenoids and organic acid compounds and other active components. Previous studies have shown that *Crataegi fructus* has a wide range of pharmacological effects, the *Crataegi fructus* extract has a significant hypoglycemic and lipid lowering effect [2-4]. SHIH et al. [5] gavaged a certain amount of aqueous extract of *Crataegi fructus* into mice and found that it could reduce glucose production and triglyceride synthesis and improve insulin resistance by inducing phosphorylation of AMPK. AIERKEN et al. [3] showed that *Crataegi fructus* extract not only reduced the blood glucose level of Type 2 diabetes mellitus (T2DM) model mice, but also increased the release of pancreatic plasma insulin level.

In addition, modern pharmacological studies have shown that *Crataegi fructus* extract can effectively reduce blood lipid levels in rats, inhibit oxidative stress, and improve body fat deposition [6,7]. However, due to the unclear specific components and targets, there has been no in-depth study on lowering blood glucose and regulating lipid, which has affected the exertion of its advantages to a certain extent. Therefore, in this study, the network pharmacology was used to systematically explore the health-care efficacy of *Crataegi fructus* in lowering blood glucose and regulating lipid, in order to further identify the potential action mechanism and pharmacodynamic material basis, and provide further reference for the application of *Crataegi fructus* and the development of health-care functional foods.

Network pharmacology is an emerging discipline that connects drugs and diseases from a systematic and holistic perspective by constructing the network relationship of «drug-component-disease-target-pathway». It is highly consistent with the overall concept and dialectical treatment thought of Traditional Chines e medicine (TCM), and is a new method for the development and modernization of traditional Chinese medicine [8]. In view of this, this study made an in-depth and systematic study on the potential molecular mechanism of hypoglycemic and lipid-lowering of *Crataegi fructus* from the perspective of network pharmacology, in order to provide a reference for further development and applicati on of *Crataegi fructus*.

Materials and methods

Acquisition of Crataegi fructus components and prediction of their targets

The *Crataegi fructus* components were obtained from TCMID (http://www.megabionet.org/tcmid/) [9] and BATMAN (http://bionet.ncpsb.org/batman-tcm/) databases [10], and the corresponding targets of the compounds were obtained from (TCMSP) (http://tcmspw.com/tcmsp.php) [11] and Batman databases. At the same time, the protein database Uniprot (http://www.uniprot.org/uploadlists/) [12] was used to convert them into unified gene names.

Identification of glucose-lowering and lipid-regulating targets of Crataegi fructus

Gene Cards (https://www.genecards.org/) database is a platform that can provide all known human genes in genome, protein group, transcription, heredity and function [13]. Using «Diabetes» and «Hyperlipidemia» as keywords, the target information related to hyperlipidemia and diabetes was collected. The target points of hyperlipidemia, diabetes and *Crataegi fructus*, which were searched in Genecards database, were mapped in Venny 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/), and their common targets were screened out as potential targets for lowering blood sugar and regulating lipid of *Crataegi fructus*.

Construction of the «Ingredient-Target-Disease» network and screening of key targets

To identify the interaction between the hypoglycemic targets and lipid-lowe ring targets of *Crataegi fructus*, the screened targets were introduced into the S TRING network platform (https://string-db.org/) to construct a protein-protein interaction (PPI, the process of combining two or more proteins to determine their biochemical functions) network. The protein type was set as «Homo sapiens», the scoring condition (confidence level) was set as >0.9, and the PPI network format file of the target was exported. The active components, their corresponding *Crataegi fructus* hypoglycemic and lipid-lowering targets and PPI were in putted into Cytoscape 3.2.1 to construct a «component-target-disease» network for hypoglycemic and lipid regulating of *Crataegi fructus*, and the topology analysis of the network was performed using the «Network Analyzer» plug-in. (Degree, DG) and (Between ness Centrality, BC) and (Closeness Centrality, CC) are important topological parameters for evaluating the proportion of a node in a network. DG can reflect the number of links between a node and other nodes in the network. BC reflects the ratio of the number of paths passing through the node to the total number of shortest paths in all the shortest paths in the network. CC is used to measure the importance of nodes. Therefore, the larger the topology parameter of the node is, the more critical the target is in the network [14].

KEGG signal pathway and GO biological process enrichment analyses

The core targets of *Crataegi fructus* identified in «1.2» and «1.3» were analyzed for GO biological process and enrichment of KEGG signaling pathway u sing DAVID database. The target genes with $P<0.05$ were screened to obtain the main signaling pathways and biological processes involved in the efficacy of Fructus Crataegi.

Molecular docking assisted validation

The protein structure file was downloaded from the Protein Data Bank (PDB) website (https://www.rcsb.org/), and the target protein and component were pre-treated using Auto dock 1.5.6 and Discovery Studio 2.5 software. Then Auto dock vina was used to perform molecular docking on the targets and components. The binding energy (affinity, kcal/mol) $\leqq 5$ was considered to be the better binding, and the binding energy $\leqq 7$ was considered to be the better binding [15,16].

Results and analysis

Main components and corresponding targets of *Crataegi fructus*

The 82 components of *Crataegi fructus* were obtained from the two databases, of which 58 components had action targets. After correction and removal of duplicates by Uniprot, a total of 575 targets for *Crataegi fructus* were obtained from the databases of TCMSP and BATMAN.

Component–target network of *Crataegi fructus* for hypoglycemic and lipid-lowering

A total of 1481 and 17157 targets related to hyperlipidemia and diabetes mellitus were obtained from Gene cards database. These targets were mapped to 152 and 464 targets in Venny 2.1.0, respectively. These targets are potential targets for Crataegi fructus hypoglycemic and lipid-lowering.

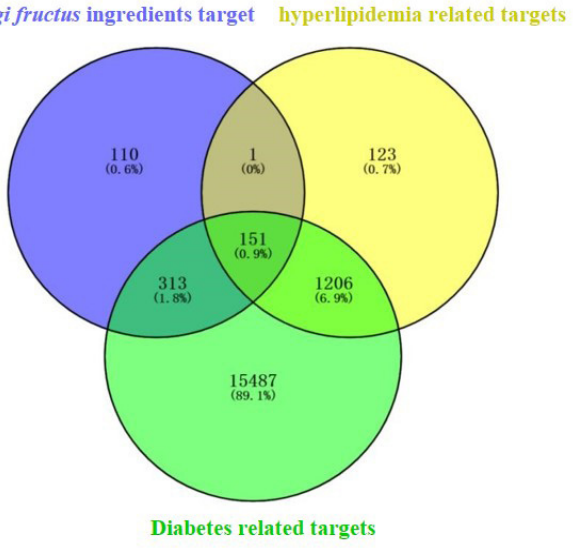

Figure 1: Viability assay in Hela cell cultures. *Arracacia xanthorrhiza Bancr* (AXB) cytotoxic effect on HeLa cells was evaluated by MTT assay. Cells were seeded at 1 x 10^4 per well and treated with increased doses of AXB from 10^{-11} mg/ml to 10^{-1} mg/ml. Experiments were performed in triplicate to evaluate half-maximal inhibitory concentration for AXB.

Screening of key targets of *Crataegi fructus* for hypoglycemic and lipid regulation

In order to better explore the action mechanism of *Crataegi fructus* in lowering blood glucose and regulating lipid, the related targets of *Crataegi fructus* in lowering blood glucose and regulating lipid were input into the STRING database to obtain a target PPI network file, and the active components and target PPI were imported into Cytoscape software to remove the isolated components that did not intersect with the targets, and the target network PPI of *Crataegi fructus* in lowering blood glucose and regulating lipid was drawn (Figures 2,3). The topological analysis results of *Crataegi fructus* hypoglycemic network showed that the median values of DG, CC and BC were 20, 0.415 and 0.001, respectively, and a total of 94 targets met the screening requirements. The results of topology analysis of *Crataegi fructus* lipid regulatory network showed that the median values of DG, CC and BC were 31, 0.488 and 0.002, respectively, and a total of 42 targets met the screening requirements. In addition, 94 key targets of *Crataegi fructus* for lowering blood glucose included 42 potential targets of *Crataegi fructus* for regulating blood lipid, and the first five targets of the network were all INS, AKT1, IL6, TP53, and TNF, indicating that blood glucose was closely related to the occurrence and development of blood lipid and they affected each other, suggesting that these targets were the key to lowering blood glucose and regulating blood lipid of *Fructus Crataegi*.

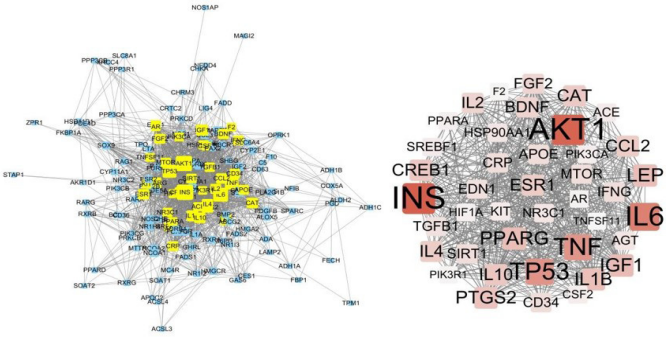

Figure 2: Potential targets PPI and its key target network for *Crataegi fructus* lipid regulation.

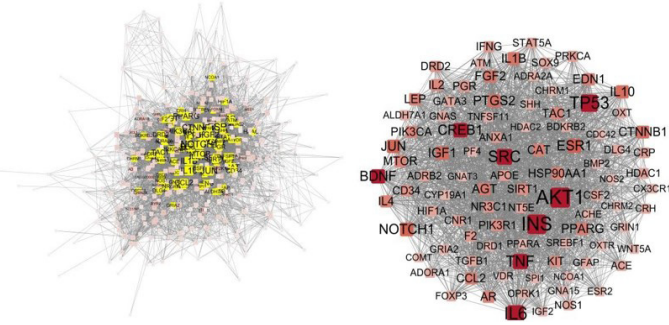

Figure 3: Potential targets PPI and its key target network of *Crataegi fructus* hypoglycemic.

The composition - target network of *Crataegi fructus* is shown in figure 4, in which the triangle represents the *Crataegi fructus* components and the quadrilateral represents the *Crataegi fructus* hypoglycemic and lipid-lowering targets. The inner and outer rings are both potential targets of *Crataegi fructus* hypoglycemic and lipid-lowering, and the inner rings are potential targets of *Crataegi fructus* lipid-lowering. Network topology analysis showed that the average connectivity value, betweenness and near-centrality of the compounds were 5,0.0000459 and 0.43, respectively, indicating that *Crataegi fructus* compound acted on multiple targets. Through network topology parameter screening, there were four important active ingredients, including kahenol (DG= 55), quercetin (DG=21), epicatechin (DG=15) and ursolic acid (DG=14). It was speculated that the above active ingredients were the key components of of *Crataegi fructus* for lowering blood sugar and regulating lipids.

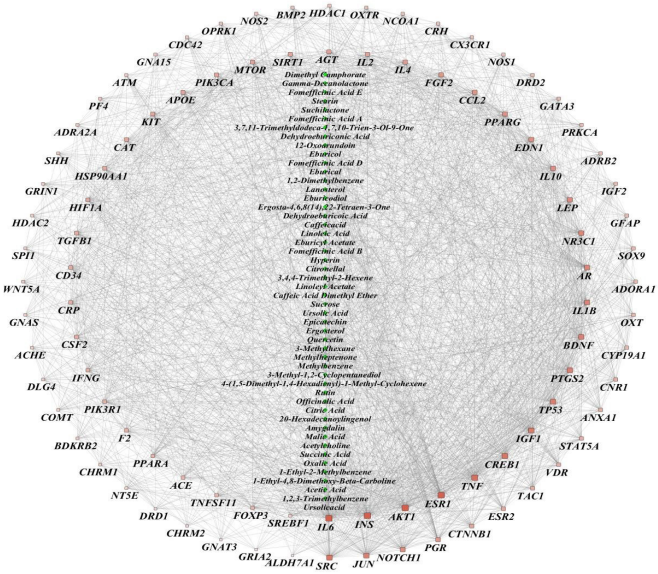

Figure 4: Compound-Target Network.

GO biological process analysis

The GO biological process enrichment analysis was performed on the key targets of *Crataegi fructus* hypoglycemic and lipid regulation, and the top 10 biological processes with P<0.05 were screened out. The visualization results are shown in figures 5,6. These targets are mainly involved in biological processes such as the intervention of immune system processes, cell proliferation and apoptosis and invasion, toxic metabolism and cytokine activity and regulation of their synthesis processes, which are the biological processes in which the key targets of *Crataegi fructus* hypoglycemic and lipid regulation are involved. *Crataegi fructus* may play a role in lowering blood sugar and regulating lipids by intervening in the above biological processes.

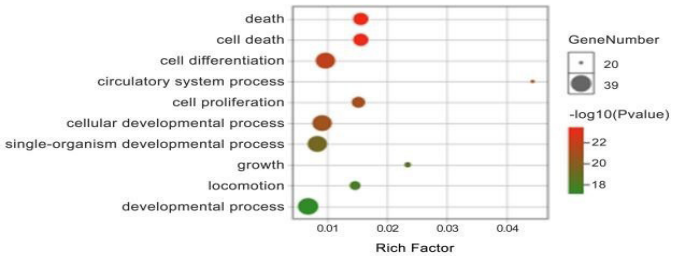

Figure 5: Biological process of hypoglycaemia.

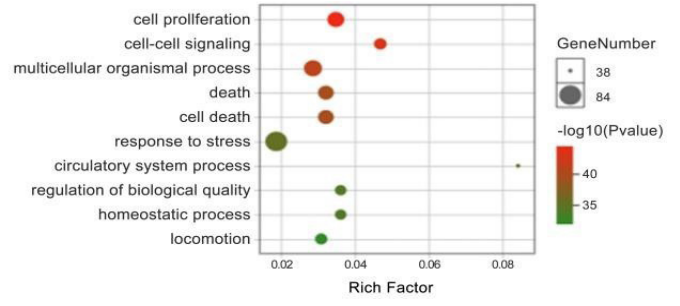

Figure 6: Biological process of lipid regulation.

KEGG signal pathway enrichment analysis

Biological pathways perform specific biological functions through the interactions between the different target proteins they constitute, and are the physiological basis for understanding the clinical manifestations of diseases. Therefore, drug intervention in disease is not only related to target proteins, but also affected by the biological pathway in which the target proteins are located, and the disordered body can be restored to balance through the interaction result, especially for traditional Chinese medicine and compound prescriptions with multi-component, multi-target and multi-pathway characteristics. Therefore, in this study, KEGG signal pathway enrichment analysis was conducted on key targets of *Crataegi fructus* hypoglycemic and lipid-lowering respectively, and the signaling pathways with P<0.05 were screened out, and the first ten pathways were visualized, as shown in figures 7,8. As shown in the bubble chart, *Crataegi fructus* is mainly involved in PI3K-AKT, HIF-1, AMPK, TNF, and INS signaling pathways, among which PI3K-AKT signaling pathway enriched in diabetes is the most significant, while TNF and HIF-1 signaling pathways enriched in hyperlipidemia are the most significant. These results indicated that Fructus Crataegi mainly focused on interfering with PI3K-AKT signaling pathway to achieve the hypoglycemic effect, and its lipid-lowering mechanism mainly focused on inter fering with TNF and HIF-1 signaling pathways. Therefore, the above pathways were most likely to be the key pathways for *Crataegi fructus* to achieve lipid -lowering and hypoglycemic health effects.

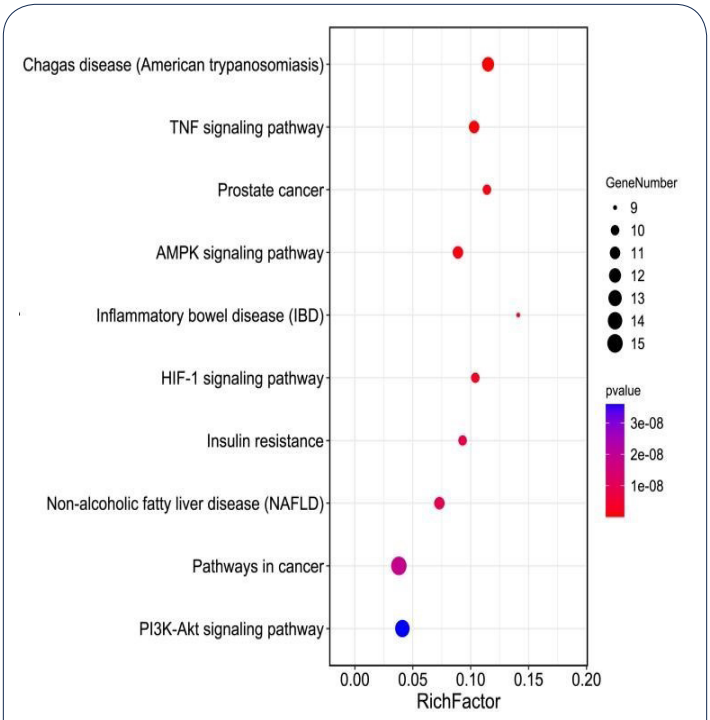

Figure 7: Potential pathways of hypoglycemia.

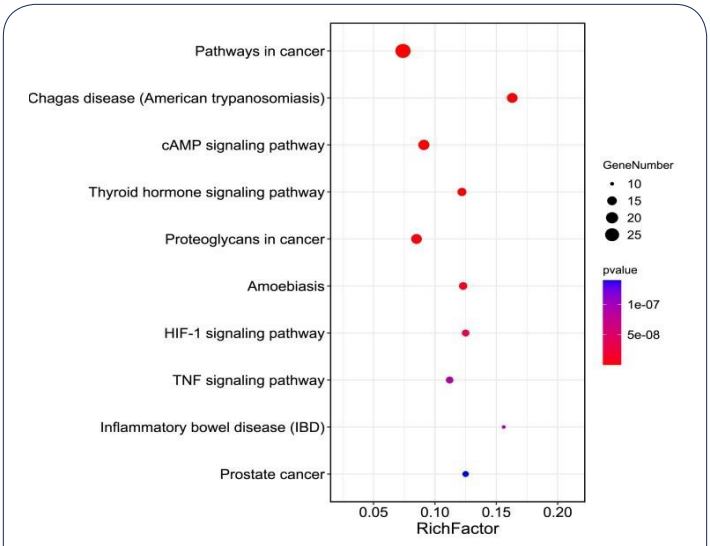

Figure 8: Potential pathways of lipid regulation.

Molecular docking assisted validation

In the composition target network, the top five components with DG value included kaempferol (flavonoids), quercetin (flavonoids), ursolic acid (triterpenoids) and epicatechin (polyphenols). Therefore, the above five targets were selected in the present study to further explore the material basis of *Crataegi fructus* for lowering blood glucose and regulating lipid. The docking results showed that each component had different degrees of binding to each target (Table 1), and there were 4, 3, 2, 1 and 4 compounds with binding energies less than -7.0 kcal/mol with INSR, AKT1, IL6, TP53 and TNF-α, respectively. The binding energies of quercetin to five targets were all less than -7.0 kcal/mol. The best targets combining with the components included INSR, AKT1, and TNF-α, indicating that these components all contributed to different degrees in the process of glucose and lipid reduction and regulation of *Crataegi fructus*. The above targets may play a key role in the health care of hypoglycemic and lipid regulation in *Crataegi fructus*. Figure 9 shows the optimal interaction of each component with the target.

Table 1: Binding energies of kenerl compounds and targets.

Compound	Target	Binding energy / kcal/mol	compound	Target	Binding energy / kcal/mol
Kaempferol	INSR	-8	**Quercetin**	INSR	-7.9
	AKT1	-8.2		AKT1	-8.7
	IL6	-6.6		IL6	-7.4
	TP53	-6.7		TP53	-7.8
TNF-α		-8.3	TNF-α		-9
INSR		-7.3	INSR		-7
AKT1		-8.5	AKT1		-4
Epicatechins IL6		-6.5	**Ursolic acid** IL6		-7
TP53		-5.4	TP53		-5
TNF-α		-8.6	TNF-α		-7
Kaempferol-TNF-α			**Quercetin - TNF -α**		

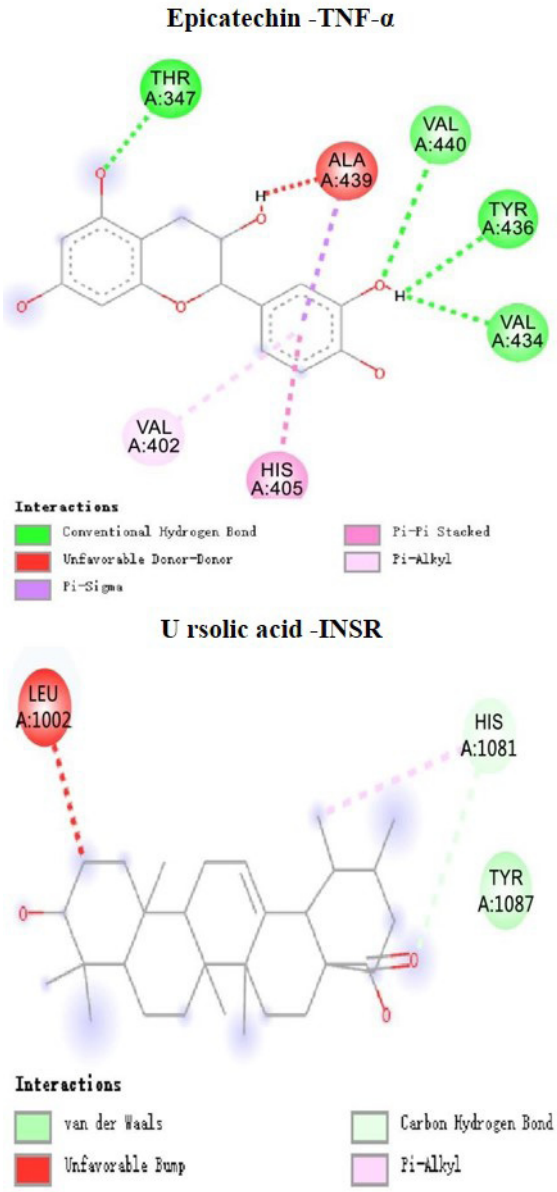

Figure 9: The best interaction between each component and the target.

Discussion

Analysis on the health care mechanism of *Crataegi fructus* in hypoglycemic and lipid-lowering

Literature retrieval and KEGG pathway enrichment analysis showed that the health care effect of *Crataegi fructus* in hypoglycemic and lipid-lowering mainly involved PI3K/AKT, AMPK, TNF, HIF-1, Insulin resistance and other signaling pathways, which were the classical pathways for the occurrence and development of hyperlipidemia and hyperglycemia-related diseases, as well as the important pathway for insulin to regulate lipid, glucose and lipid metabolism. Under physiological conditions, secreted insulin activates the PI3K/AKT signaling pathway and regulates the balance of lipid and glucose metabolism by increasing glucose utilization and reducing gluconeogenesis in liver and muscle, and increasing insulin production in pancreas [17]. HIF-1 in the HIF-1 signaling pathway is a transcription factor that regulates cell response in a hypoxic environment and plays a key role in the regulation of

peroxisome lipid metabolism [18]. HIF-1 activates the expression of visfatin 1 in liver tissues, resulting in the reduction of reactive oxygen species and prevention of liver lipid deposition [19]. Studies have found [20] that in the process of inducing atherosclerosis, inflammatory cytokines, such as VEGF and TNF-α, will induce the formation of vascular thrombosis and lead to a large number of normal apoptosis to aggravate the development of the disease in hyperlipidemia. Clinically, inflammatory factors such as IL6 and TNF-α in the TNF signaling pathway have become important indicators to measure the development of hyperlipidemia, and TNF-α and IL 6 can further accelerate the synthesis of Triglyceride(TG) by stimulating the liver [21,22]. Insulin resistance is closely related to hyperlipidemia [23]. Patients with hyperlipidemia are prone to Insulin resistance. At the same time, insulin resistance makes insulin target cells insensitive to insulin, and plasma glucose cannot be ingested by target cells, resulting in an increase in plasma glucose level. The body needs to ingest excessive glucose in plasma to synthesize fat, which is stored in target cells, to maintain the glucose metabolism balance, thus causing hyperlipidemia. AMPK can prevent the occurrence and development of diabetes and hyperlipidemia-related diseases by regulating glycolipid metabolism, anti-inflammation, and anti-oxidative stress [24]. Therefore, *Crataegi fructus* can exert the effects of regulating apoptosis, inflammation, insulin level and immune function through multiple signaling pathways such as PI3K/Akt, TNF, HIF-1, AMPK, Insulin resistance, in order to deal with the glucolipid metabolism disorder caused by insulin level imbalance, immune function decline and verification.

Analysis of key components of *Crataegi fructus* for hypoglycemic and lipid-lowering

Among 82 components of *Crataegi fructus*, 58 components have action targets, among which 50 components have potential contribution to the health care effect of hypoglycemic and lipid-lowering. The topology analysis of component-target network revealed that the degree values of quercetin, kaempferol, ursolic acid and epicatechin were the largest, suggesting that they had more action targets, and might be important pharmacodynamics substances for reducing blood glucose and regulating lipid of *Crataegi fructus*.

Studies have shown that quercetin has a variety of physiological activities, such as antioxidant, lipid-lowering, hypoglycemic, anti-inflammatory and so on. Ahn et al. [25] confirmed that quercetin can exert its anti-adipogenesis activity by activating AMPK signaling pathway. It has been proved [26] that quercetin can significantly reduce IL6 and TNFα in high-fat and obese rats. Quercetin indirectly affects PI3K/ AKT pathway by regulating ROS, thereby inhibiting inflammation and apoptosis, and ultimately reducing the degree of atherosclerosis. Quercetin can effectively improve hyperglycemia, hyperlipidemia and antioxidant status in type 2 diabetes [27] by influencing insulin system bypass through AMPK pathway to alleviate insulin resistance [28]. Nutrients in the diet, especially functional foods, are beneficial to metabolic-related diseases such as diabetes. Kaempferol, as a dietary polyphenol [29], is reported to have a variety of beneficial effects on human health, including the regulation of lipid and glucose metabolism, through the activation of AMPK to promote lipid metabolism [30] and up-regulation of skeletal muscle PI3K-AKT signaling pathway [31], thereby improving glucose and lipid metabolism disorders and insulin resistance. In addition, kaempferol can also play a role in reducing TG by inhibiting the Akt pathway [32]. Ursolic acid, as a natural Chinese herbal medicine component, can effectively regulate the expression of pro-inflammatory or anti-inflammatory cytokines such as TNFα and IL6 [33,34], which may become an important target for the prevention and treatment of inflammation and other inflammation-induced related diseases. Ursolic acid can also inhibit 3T3-L1 pre-adipocyte differentiation and adipogenesis through APMK pathway [35], thereby inhibiting 3T3-L1 pre-adipocyte differentiation and lipid accumulation by regulating transcription factors and their downstream lipid targets. The mechanism of ursolic acid in relieving insulin resistance in adipose tissues of aged rats is related to the activation of Akt signaling pathway and inhibition of inflammation. Studies in the literature [36,37] have shown that epicatechin can reduce body weight, blood lipid and blood glucose of high-fat diet fed rat model. Long-term administration of catechin can reduce obesity in mice caused by high-fat diet, which may be related to the reduction of fat absorption and promotion of lipolysis. In addition, epicatechin can improve insulin resistance in spontaneous type II diabetes rats [38], which may be related to its effect in inhibiting liver gluconeogenesis. Epicatechin can also compensate for insulin, promote adipocyte differentiation, and enhance insulin sensitivity, which is beneficial to the prevention and treatment of type II diabetes. The molecular docking results are also basically consistent with previous studies, which provide certain evidence support for the prediction results of this time. However, there were few studies on INSR targets and HIF-1 pathway by quercetin, kaempferol, ursolic acid and epicatechin, and few studies on the mechanism of epicatechin on glucose and lipid reduction were conducted, which could provide new ideas for the in-depth study of glucose and lipid reduction in *Crataegi fructus* and worthy of further exploration.

Conclusion

In the present study, network pharmacology was proposed to systematically explore the substance basis, action target and pathway information of *Crataegi fructus* for hypoglycemic and lipid-lowering. The results showed that the potential active components such as quercetin, kaempferol, ursolic acid, and epicatechin in *Crataegi fructus* played key regulatory effects on apoptosis, insulin level imbalance, inflammatory response, and immune function caused by glycolipid metabolism disorder through PI3K/Akt, AMPK, TNF and other signaling pathways. The predicted results can provide theoretical basis and new research direction for the pharmacodynamic substance basis and mechanism of *Crataegi fructu s* hypoglycemic and lipid-lowering, and then provide new reference for the app lication of *Crataegi fructus* and the development of health function food.

Declarations

Conflicts of interest: The authors declare no conflicts of interest.

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