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Exploring the mechanism of sea buckthorn polyphenols for the treatment of hyperlipidemia based on network pharmacology and molecular docking

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Abstract The aim of this study was to explore the mechanism of action of sea buckthorn polyphenols in the treatment of hyperlipidemia through network pharmacology and molecular docking. The TCMSP pharmacology database was used to screen the polyphenols present in sea buckthorn, and then the SwissTargetPrediction and Uniprot databases were used to obtain the potential targets of sea buckthorn polyphenols, which were supplemented by the literature. In total, 7 polyphenols and 154 potential targets were obtained. Through GeneCards, OMIM database, 1 358 hyperlipidemia-related targets were collected. We found that there were 101 targets at the intersection of components and diseases. Through GO and KEGG enrichment analysis, 27 core targets were obtained, which were AKT1, TNF, TP53, IL-6, etc. in order of degree value. 174 pathways were obtained from KEGG enrichment analysis, including AGE-RAGE signaling pathway in diabetic complications, fluid shear stress and atherosclerosis, lipid and atherosclerosis, etc. The molecular docking of the main components to the targets was performed using OpenBabelGUI, AutoDockTools-1.5.6 software. Finally, the results were visualized using Cytoscape 3.9.1 software. The molecular docking results showed that sea buckthorn polyphenols have good binding ability with the key targets. Among them, such as quercetin and kaempferol, have good binding ability with TNF, TP53 and IL-6. For example, TNF binds to quercetin with a binding energy of −5.34 kcal/mol and to kaempferol with a binding energy of −6.22 kcal/mol; TP53 binds to kaempferol with a binding energy of −5.32 kcal/mol; IL-6 binds to quercetin with a binding energy of −5.62 kcal/mol, etc. Therefore, the network pharmacology study showed that the treatment of hyperlipidemia by sea buckthorn polyphenols can be realized by multi-component-multi-target-multi-pathway together, which provides some reference for the later study of sea buckthorn polyphenols in the treatment of hyperlipidemia.

Keywords: molecular docking; network pharmacology; sea buckthorn; polyphenol; hyperlipidemia

1 Introduction

Hyperlipidemia (HLP), medically known as dyslipidemia, usually refers to elevated TG and TC in plasma, including elevated LDL-C and decreased HDL-C [1]. HLP is divided into two categories: Primary and secondary. Primary is related to congenital and heredity, and is caused by genetic defects, abnormalities of receptors, enzymes or apolipoproteins involved in lipoprotein transport and metabolism, or by environmental or unknown factors; secondary occurs mostly in metabolic disorders diseases (diabetes mellitus, hypertension, etc.), or is

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related to other factors, such as age, diet, spirituality, and emotional activity. Clinical manifestations include xanthomas caused by lipid deposition in the dermis and atherosclerosis caused by lipid deposition in the endothelium of blood vessels.

At present, the modern medical treatment of hyperlipidemia is based on TC and LDL-C lowering drugs such as statins and resins, and TG lowering drugs such as fibrates and nicotinic acid [2]. These types of western drugs have certain lipid-lowering effects, but for some patients who are intolerant to lipid-lowering drugs may experience muscle pain or liver and kidney damage, or even death after long-term use. Compared with western drugs, traditional Chinese medicine (TCM) has certain advantages in improving hyperlipidemia, and the drugs used in TCM to treat hyperlipidemia, such as hawthorn, poria, danshen and zedoary, have fewer side effects and relatively less damage to the human body [3, 4]. With the continuous deepening of Chinese medicine research, the study of TCM in treating hyperlipidemia has received more and more attention.

Sea buckthorn, the fruit of *Hippophae rhamnoides* L., family Hippophae. The mature fruit is orange, with oily and smooth surface of pulp and seeds, and the seeds are oval dark brown with sour and astringent taste. China is the country with the richest sea buckthorn resources, accounting for about 90% of the global total, and the area of artificial sea buckthorn forests accounts for 55% of the total area of the country [5]. As a kind of medicinal and food plants, sea buckthorn not only has high ecological significance, but also contains rich bioactive components, known as “persimmon of the north” “golden fruit” and so on. The flavonoids, polysaccharides, polyphenols, vitamins, fatty acids and other bioactive substances in sea buckthorn fruit have the functions of antioxidant, anti-aging, anti-tumor, improvement of intestinal flora, hypoglycemia, immunomodulation, bacteriostasis and so on [6].

Polyphenolic compounds in sea buckthorn mainly include flavonoids and phenolic acids, and the polyphenol content of sea buckthorn leaves is higher than that of sea buckthorn berries, Criste, et al. [7] found that the polyphenol content of four types of sea buckthorn berries ranged from 9.86 to 18.79 mg/g, while the content of sea buckthorn leaves ranged from 40.98 to 48.6 mg/g. Sea buckthorn polyphenol compounds have a wide range of physiological functions, such as anticancer, improving intestinal flora and lowering blood lipids and protecting the liver [8].

Network pharmacology is an emerging discipline that analyzes biological systems through networks and selects specific signaling nodes for multi-target drug molecular design. And molecular docking is an approach that focuses on studying intermolecular (e.g., ligand-receptor) interactions and predicting their binding modes and affinities [9].

In this paper, based on network pharmacology, molecular docking technique was used to explore the mechanism of action of sea buckthorn polyphenols in the treatment of hyperlipidemia, which will provide some reference for the subsequent studies of sea buckthorn polyphenols in the treatment of hyperlipidemia.

2 Material and methods

2.1 Acquisition of main active components and targets

The main chemical constituents of sea buckthorn were retrieved using TCMSP pharmacology database (https://old.tcmsp-e.com/) [10, 11]. Sea buckthorn contains seven polyphenols, namely pelargonidin, isorhamnetin, kaempferol, (+)-catechin, 5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one, ent-epicatechin, quercetin. The target information was normalized by Swiss Target Prediction database (http://www.swisstargetprediction.ch/), UniProt database (https://www.uniprot.org/) to get the predicted targets of the drugs [12].

2.2 Hyperlipidemic target acquisition

A total of 1 358 disease-related targets were obtained by searching GeneCards (https://www.

genecards.org/) and OMIM (https://omim.org/) with the keyword "hyperlipidemia" and excluding duplicates.

2.3 Key target acquisition

In the Venny 2.1.0 online platform (https:// www.liuxiaoyuyuan.cn), component targets and disease targets were entered for venen mapping, and the resulting intersections were key targets.

2.4 Construction and analysis of "component-target interaction network" and "drug-component-target" interaction network

The "component-target" and "drug-component-target" interaction networks of sea buckthorn polyphenols were analyzed using Cytoscape 3.6.1 bioinformatics analysis software.

2.5 Construction and analysis of protein-protein interaction (PPI) network

Protein targets were imported into the String database (https://cn.string-db.org/), and the information was imported and plotted into a PPI network for visualization and analysis using Cytoscape 3.9.1 software.

2.6 Gene ontology and Kyoto encyclopedia of genes and genomes enrichment analysis

To clarify the impact of target protein-target gene interactions in gene function and signaling pathways, we performed GO bioprocess enrichment analysis and KEGG pathway enrichment analysis on the Metscape platform.

2.7 Molecular docking

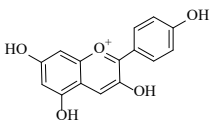
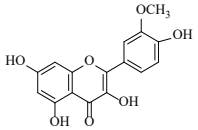
Molecular docking was used to verify the binding of the core target to the compounds. The protein crystal structures of the active ingredients of sea buckthorn polyphenols were obtained from the UniProt database (https://www.uniprot.org/). The structural formulae of the targets were obtained from RCSB PDB (https://www.rcsb.org/).

3 Results

3.1 Network of components and targets

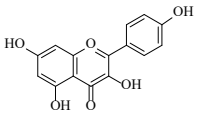
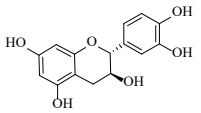
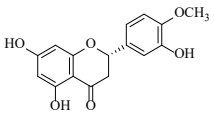
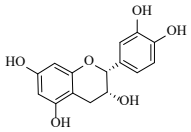
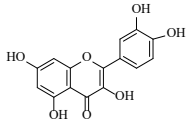
After screening and target prediction, seven polyphenols were obtained from sea buckthorn active ingredients for further study. These are listed in Table 1. A total of 244 potential targets related to sea buckthorn polyphenols were obtained, 154 after removing duplicates. Using Cytoscape 3.6.1 bioinformatics analysis software, the "component-target" interaction network and "drug-component-target" interaction network were constructed based on the degree value, as Fig. 1 shown.

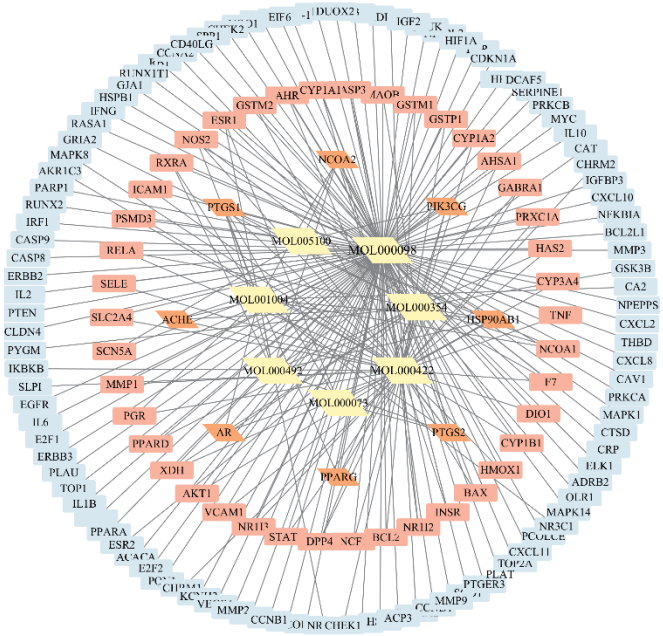
Table 1 Information for the candidate bioactive compounds of sea buckthorn

No.	MOL ID	Compound	Structure
1	MOL001004	Pelargonidin	
2	MOL000354	Isorhamnetin	

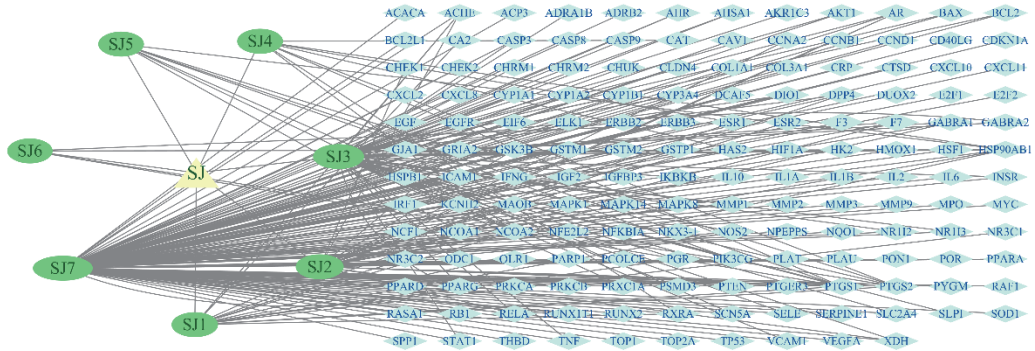
(to be continued)

Continued Table 1

No.	MOL ID	Compound	Structure
3	MOL000422	Kaempferol	
4	MOL000492	(+)-Catechin	
5	MOL005100	5,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one	
6	MOL000073	Ent-epicatechin	
7	MOL000098	Quercetin	



(A)



(B)

A – "Component-Target" interaction network; B – "Drug-Component-Target" interaction network.

Fig. 1 Interaction network diagram

Using "hyperlipidemia" as the keyword in the GeneCards database and the OMIM database, the target names were obtained and a form table was established to eliminate the duplicated targets, and 1 358 related targets were obtained. A total of 101 intersected targets were obtained by intersecting 154 potential targets of polyphenols from sea buckthorn. Finally, Venn diagram was created using Venny 2.1.0, an online platform Fig. 2 shows the result of the Venn diagram.

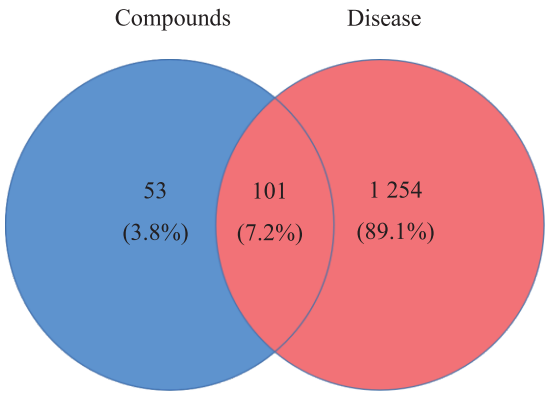


Fig. 2 The Venn diagram of sea buckthorn and disease targets

3.2 PPI network

The 101 targets were entered into the String database to obtain the PPI network of the relevant hyperlipidemia targets of the polyphenols from sea buckthorn. The higher the number of target interaction nodes, the higher the value of degrees of freedom, and the more critical the core position in this network, as shown in Fig. 3.

According to the degree value, the top 10 targets are AKT1, TNF, TP53, IL6, IL1β, PTGS2, ESR1, CASP3, HIF1A, MMP9. Among them, AKT1, TNF, TP53 and IL6 degree values were high, indicating that the above targets may be the core targets of sea buckthorn for the disease, which are important for the therapeutic effect.

3.3 GO and KEGG pathway enrichment

GO enrichment analysis was conducted on potential targets of drug in the intervention of HLP, including BP (biological process), MF (molecular function), and CC (cellular component). The top 10 BP, MF, CC terms are displayed in three-in-one bar chart as shown in Fig. 4A, respectively. In BP, it acts on reactive oxygen species metabolic process, cellular response to chemical stress and regulation of reactive oxygen species metabolic process, etc. At the level of

MF, it acts on membrane raft, membrane microdomain and membrane region, etc. In terms of CC, action on nuclear receptor activity, ligand-activated transcription factor activity and DNA-binding transcription factor binding, etc.

KEGG pathway analysis of 10 core targets (Fig. 4B) showed that related pathways include AGE-RAGE signaling pathway in diabetic complications, fluid shear stress and atherosclerosis, lipid and atherosclerosis, etc.

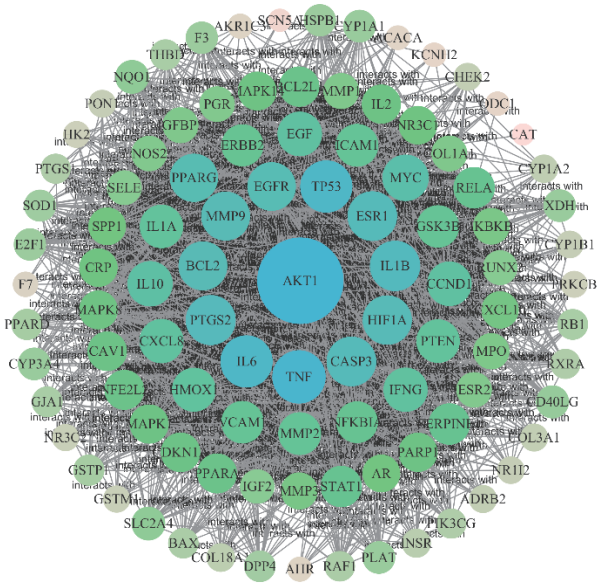
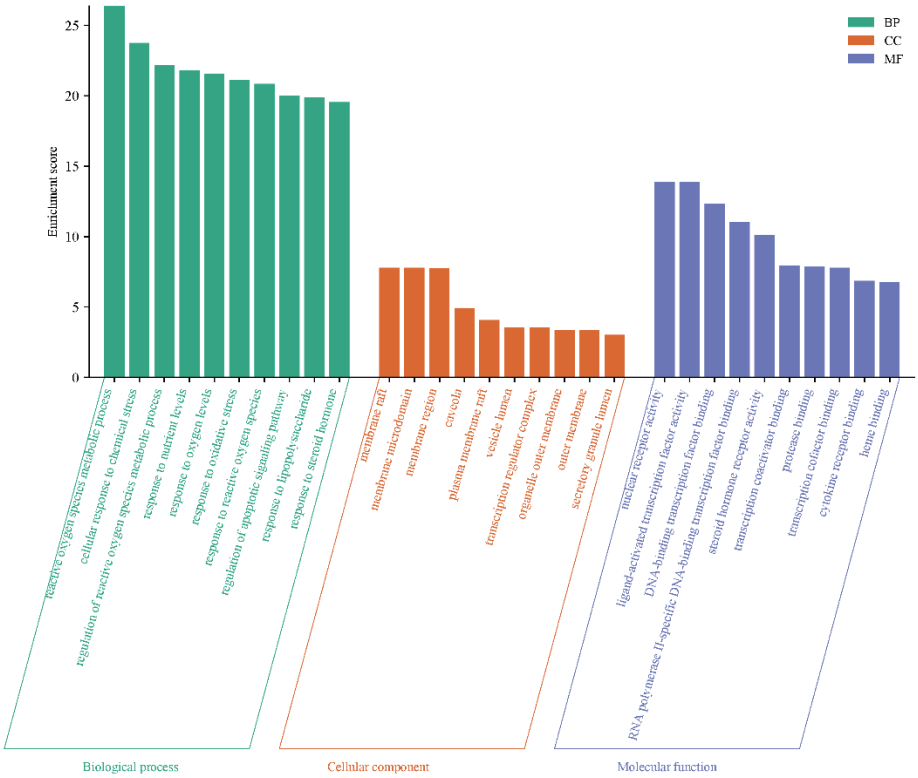
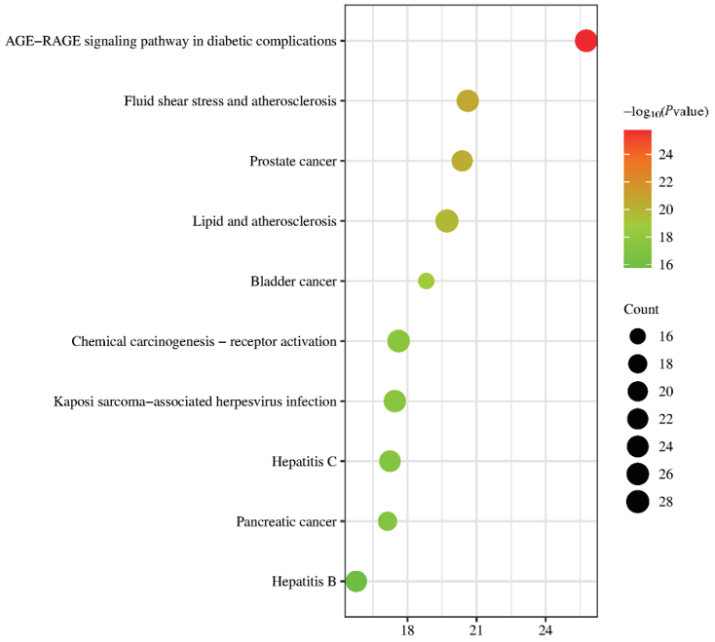


Fig. 3 PPI network of identified major targets



(A)



(B)

A − GO enrichment analysis of intersected targets between drug and disease; B − KEGG enrichment analysis of intersected targets between drug and disease.

Fig. 4 GO and KEGG enrichment analysis

3.4 Molecular docking

In this study, the binding of the core target to the compound was verified using AutoDockTools-1.5.6 and the lowest energy docking model was chosen. When the binding energy is < 0 kcal/mol, the small molecule ligand can spontaneously bind to the protein receptor. If the binding energy is < −5.0 kcal/mol or lower, it indicates that both have good binding ability.

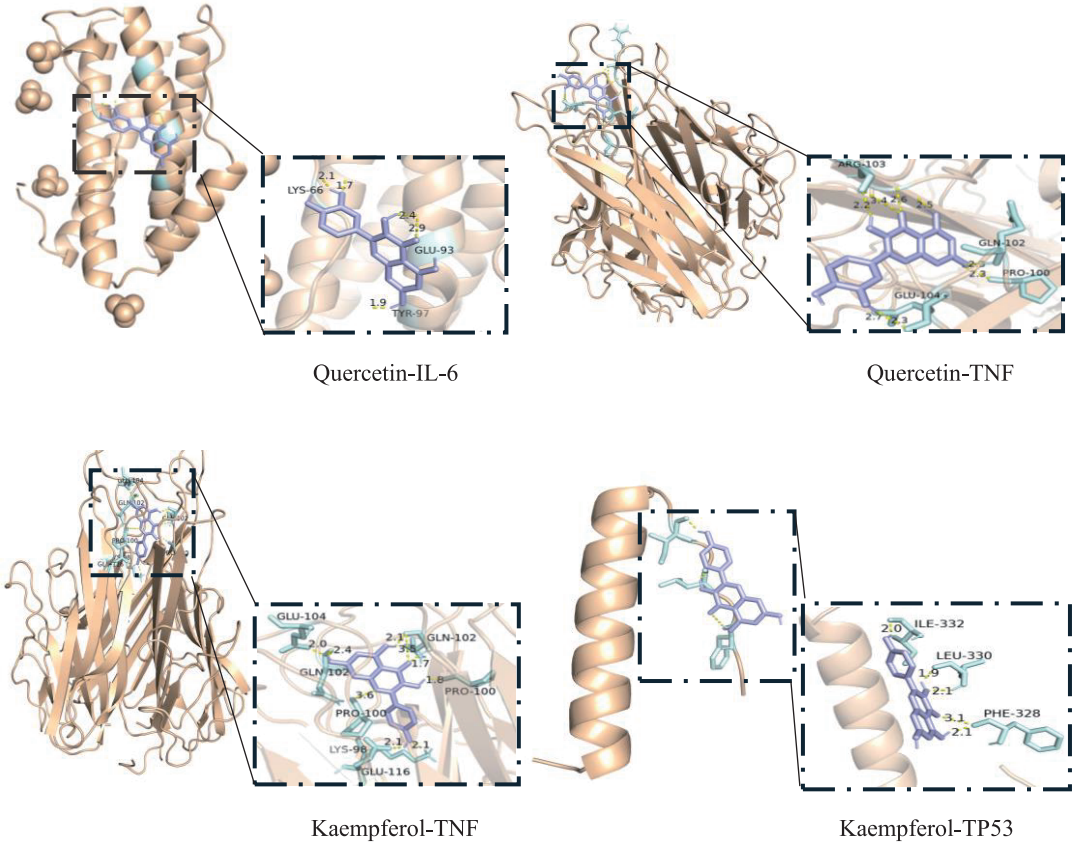
The core targets with the top 4 degree values in the PPI network analysis were AKT1 (PDB ID: 1H10), TNF (PDB ID: 1tnf), TP53 (PDB ID: 1aie), and IL-6 (PDB ID: 1aLu), and the target proteins was obtained from the RCSB PDB (https://www.rcsb.org/) and molecularly docked them with potential active components in sea buckthorn polyphenols.

The results showed that the core target bound well to the compound and exhibited a strong ability to bind to the core target (Table 2). For example, TNF binds to quercetin with a binding energy of −5.34 kcal/mol and to kaempferol with a binding energy of −6.22 kcal/mol; TP53 binds to kaempferol with a binding energy of −5.32 kcal/mol; IL-6 binds to quercetin with a binding energy of −5.62 kcal/mol, etc.

Table 2 Results of molecular docking

Target	Binding energy (kcal/mol)	
	Quercetin	Kaempferol
AKT1 (PDB ID: 1H10)	−3.84 ± 0.06	−3.93 ± 0.04
TNF (PDB ID: 1tnf)	−5.34 ± 0.05	−6.22 ± 0.42
TP53 (PDB ID: 1aie)	−4.56 ± 0.07	−5.32 ± 0.06
IL-6 (PDB ID: 1aLu)	−5.62 ± 0.14	−3.85 ± 0.04

The docking results of the above four groups are shown in Fig. 5 and demonstrate the interaction between the compounds and the residues of the protein binding site.



Quercetin-IL-6 Quercetin-TNF

Kaempferol-TNF Kaempferol-TP53

Fig. 5 Molecular docking and visualization of docking results

Quercetin was linked to residues LYS-66, GLU-93, and TYR-97 of IL-6 through hydrogen bonding, with bond lengths of 2.1 Å, 1.7 Å, 2.4 Å, 2.9 Å, and 1.9 Å, in that order; And quercetin was linked to residues ARG-103, GLN-102, PRO-100, and GLU-104 of TNF, with bond lengths of 2.2 Å, 3.4 Å, 2.6 Å, 2.5 Å, 2.3 Å and 2.7 Å; Kaempferol is linked to residues GLU-104, GLN-102, PRO-100, LYS-98, and GLU-116 of TNF with bond lengths of 2.0 Å, 2.4 Å, 2.1 Å, 3.5 Å, 1.7 Å, 1.8 Å, 3.6 Å, and 2.1 Å; At the last, kaempferol was linked to residues ILE-332, LEU-330, and PHE-328 of TP53 with bond lengths of 2.0 Å, 1.9 Å, 2.1 Å, and 3.1 Å.

The above results strongly suggest that polyphenolic compounds in sea buckthorn may play an important role in the treatment of hyperlipidemia.

4 Discussion

Hyperlipidemia is a common and frequent disease of abnormal fat metabolism in the human organism, belonging to the category of modern medicine, generally accompanied by high TC, high TG, high LDL levels, and is also a common symptom of a variety of cardiovascular diseases, which is known as “the first of all diseases” [13]. Chronic hyperlipemia increases the incidence of vascular endothelial dysfunction and can even induce cardiovascular disease [14].

As a kind of medicine and food, research on sea buckthorn extract has been ongoing in recent years, and its therapeutic effect on hyperlipidemia has been confirmed by several *in vivo* experiments [15].

Sea buckthorn contains a host of bioactives such as flavonoids and polyphenols that can prevent the development of cardiovascular disease. Polyphenols, an active ingredient isolated from sea buckthorn berries (SVP), have been shown to significantly reduce serum lipids, enhance antioxidant enzyme activity, and decrease serum TNF-α and IL-6 levels in rats when treated with orally administered. Sea buckthorn polyphenols also attenuates vascular by decreasing the expression of eNOS, ICAM-1, and LOX-1 mRNAs and proteins in the aorta of hyperlipidemic rats injury. Based on these findings, sea buckthorn polyphenols has antioxidant effects and can effectively improve hyperlipidemia [16].

In vitro, quercetin could not only reduce apoptosis and increase mitochondrial membrane potential, but also reduce ROS production, thus effectively alleviating the senescence of human aortic endothelial cells; *in vivo*, quercetin administration significantly reduced the lipid deposition in the lumen of mouse arteries and attenuated vascular senescence and hyperlipidemia by decreasing the aortic levels of IL-6, soluble intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 levels in the aorta, as well as increasing the density of sirtuin 1, as a means of attenuating vascular aging and hyperlipidemia [17]. In addition, quercetin can improve hyperlipidemia and oxidative stress levels in high-fat diet rats by regulating the AMPK/SIRT1/NF-κB pathway, and inhibit the inflammatory response by decreasing the levels of NF-κB and IL-1β, and elevating the levels of IL-10 [18].

And then, kaempferol not only attenuated ox-LDL-induced inflammation, oxidative stress and apoptosis in human umbilical vein endothelial cells [19], but also normalized the vascular morphology and lipid levels in high-fat diet-ovariectomy-induced mice, and significantly reduced the levels of inflammatory factors and the expression of vascular adhesion molecules, thus inhibiting inflammation and oxidative stress [20].

This is consistent with the core components of sea buckthorn polyphenols for the treatment of hyperlipidemia, which were screened by network pharmacology in this study. Therefore, quercetin and kaempferol are the important active ingredients for the treatment of hyperlipidemia.

TNF, IL-6, TP-53 and AKT1 were screened by the "Disease-Component-Target" network, and were the core targets of quercetin and kaempferol in the treatment of hyperlipidemia, with Degree values of 87, 84, 84 and 89, respectively.

TNF is mainly produced by activated macrophages, NK cells and T-lymphocytes, with TNF-α playing a major role. TNF family protein levels have been used as an important reference indicator in hyperlipidemia-related diseases [21]. TNF-α is a predisposing factor for the abnormal function of coronary artery endothelial cells and the increase of intima-media thickness, which can directly damage the vascular endothelial cells and increase their permeability, enhance the transmembrane capacity of blood cholesterol, and form atherosclerotic plaques in the inner wall of the blood vessels [22]. The TNF signaling pathway is closely associated with hyperlipidemia and atherosclerosis, and TNF-α accelerates lipolysis by inhibiting free fatty acid uptake, inhibiting adipogenesis and differentiation, while decreasing lipoproteinase activity and increasing the activity of hormone-sensitive lipases [23]. TNF-α also exerts its proatherosclerotic effects by directly increasing the transcellular transport of low density lipoprotein particles through endothelial cells [24].

It has been found that IL-6 and TNF are important pro-inflammatory factors, which are closely related to hyperlipidemia, and can promote adipocyte apoptosis, inhibit adipocyte differentiation and synthesis, stimulate the accelerated decomposition of adipocyte lipids, lead to insulin resistance, promote atherosclerosis, and increase the likelihood of developing hyperlipidemia [25]. From the perspective of traditional Chinese medicine, hyperlipidemia is more than a simple vascular disease; It is also a chronic inflammatory disease and reveals the relationship between inflammatory factors and hyperlipidemia and atherosclerosis [26]. Inflammatory factors such as IL-6 stimulate the expression of adhesion molecules, cytokines, and growth factors by vascular endothelial

cells (ECs), and induce the proliferation and migration of ECs, favoring the formation of immature neovascularization in the arterial vascular tunica media and within the plaque [27].

TP53, also known as the tumor protein P53, when it is mutated and becomes dysfunctional, the mevalonate pathway goes out of control, increasing the risk of cancer [28]. In contrast, blocking the mevalonate metabolic pathway reduces cholesterol in the body, suggesting that TP53 can regulate the mevalonate pathway and thus influence the development of hyperlipidemia [29].

The above results indicate that the screening in this study has a certain theoretical basis and can provide a new research direction for the treatment of hyperlipidemia with sea buckthorn.

In summary, the present study applied network pharmacology to analyze the interaction between sea buckthorn polyphenols and common targets of hyperlipidemia, and verified the core components and core targets by molecular docking, so as to predict that the mechanism of sea buckthorn polyphenols in the treatment of hyperlipidemia may be that the two potentially effective components. Quercetin and kaempferol, act through the AGE-RAGE signaling pathway in diabetic complications, fluid shear stress and atherosclerosis, lipid and atherosclerosis, and other core signaling pathways, acting on core targets such as AKT1, TP53, TNF , IL-6, and other core targets and functions.

Although this study embodies the characteristics of multi-components, multi-targets and multi-pathways, and may provide new ideas for the treatment of hyperlipidemia by sea buckthorn polyphenols, there are still some limitations in the current network pharmacology, and some of the results still need to be confirmed by further studies through relevant experiments.

5 Conclusion

In this study, the results of network pharmacology showed that the main active ingredients of sea buckthorn polyphenols for treating hyperlipidemia may be quercetin, kaempferol, etc.; the potential core targets are AKT1, TP53, TNF, IL-6, etc.; the major pathways after enrichment are AGE-RAGE signaling pathway in diabetic complications, fluid shear stress and atherosclerosis, lipid and atherosclerosis, etc.; and quercetin docked with IL-6 and TNF, as well as kaempferol docked with TNF and TP-53, all showed good docking results with binding energies of −5.62 kcal/mol, −5.34 kcal/mol, −6.22 kcal/mol, and −5.32 kcal/mol.

The present study provides a basis for further research on the therapeutic effects of sea buckthorn polyphenolic active ingredients on hyperlipidaemia, with a view to providing a theoretical basis for future in-depth studies on the key mechanisms involved.

Acknowledgments

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