



Exploring the mechanism of *Crataegus pinnatifida* fruit flavonoids to improve Alzheimer's disease based on network pharmacology and molecular docking

Dehong Zhang, Xuqian Niu, Rongzheng Deng, Anna Gan, Fei Lin, Jinyu Wang, Bo Wu, Tingxu Yan^{*}, Ying Jia^{*}

Faculty of Functional Food and Wine, Shenyang Pharmaceutical University, Wenhua Road 103, Shenyang 110016, China

Abstract This study aims to explore the mechanism by which flavonoids in *Crataegus pinnatifida* fruit improve Alzheimer's disease (AD) through network pharmacology and molecular docking technology. The flavonoid components present in *Crataegus pinnatifida* fruit were gathered from the HERB, HIT, and ETCM databases, and were further supplemented by relevant published literature. The PubChem and SwissTargetPrediction databases were utilized to predict potential targets, and a “*Crataegus pinnatifida* fruit-active ingredient-target” network was constructed using Cytoscape 3.9.0 software. The GeneCards database was utilized to identify targets associated with AD, which were subsequently intersected with the active targets of *Crataegus pinnatifida* fruit. A protein-protein interaction (PPI) network was constructed using the STRING platform. KEGG enrichment analysis of the core targets was conducted on an online bioinformatics mapping platform, while molecular docking of the primary active components and core targets was executed using AutoDock software. Eight flavonoids and 160 potential targets were identified from *Crataegus pinnatifida* fruit, of which 147 targets were linked to AD. The results of the “*Crataegus pinnatifida* fruit-active ingredient-target” network indicated that quercetin was the principal flavonoid active ingredient. PPI analysis revealed that SRC and EGFR were the key targets, and KEGG analysis identified the main enrichment pathways as Pathways in cancer, PI3K/Akt signaling pathway, and Proteoglycans in cancer. Molecular docking confirmed the strong binding affinity between the core targets and the primary active ingredient. The interaction of quercetin with the key targets SRC and EGFR may represent a significant mechanism by which flavonoids from *Crataegus pinnatifida* fruit contribute to the improvement of AD.

Keywords: *Crataegus pinnatifida* fruit; flavonoids; Alzheimer's disease; network pharmacology; molecular docking

1 Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the core pathological features of β -amyloid ($A\beta$) deposition and hyperphosphorylation of Tau protein, posing a significant global public health Challenge^[1]. Its pathogenesis

is multifaceted, involving various pathological processes, including neuroinflammation, oxidative stress, mitochondrial dysfunction, and neurotransmitter disorders^[2]. Recent analyses of neural topological networks have revealed a degradation of “small world” characteristics and a loss of connection efficiency among core hub nodes in the brain during the early stages of AD, suggesting that the disintegration of neural networks may serve as a precursor to cognitive impairment^[3]. Although existing pharmacological

^{*} Corresponding authors: Wei Zheng (107010005@syphu.edu.cn); Xu Zhao (zhaoxu_1010@163.com).

These authors have no conflict of interest to declare.

interventions, such as anticholinesterase inhibitors and antiglutaminergics, can partially alleviate symptoms, their efficacy is limited, and they cannot reverse the disease's progression^[4]. Therefore, there is an urgent need to explore multi-target intervention strategies.

Crataegus pinnatifida fruit is a widely recognized fruit and traditional Chinese herbal medicine. It is rich in polyphenols, organic acids, and other bioactive compounds, which contribute to its beneficial effects on digestion, lipid metabolism, and antioxidant activity. Research has demonstrated that *Crataegus pinnatifida* can mitigate the pathological processes associated with AD by inhibiting the aggregation of A β , reducing the hyperphosphorylation of tau protein, and enhancing cholinergic system function^[5]. Flavonoids are vital active phenolic compounds found in the fruit of *Crataegus pinnatifida*, known for their significant antioxidant, anti-inflammatory, and neuroprotective effects. These compounds can mitigate damage to nerve cells induced by oxidative stress and inflammation. In recent years, there has been increasing interest in the application of flavonoids for the treatment of AD^[6]. Therefore, the flavonoids present in *Crataegus pinnatifida* fruit hold significant potential for application in the improvement of AD. However, the specific action targets and the multi-component synergistic mechanisms have not been systematically elucidated, which hampers traditional pharmacological methods from fully analyzing its multi-target and multi-channel regulatory network^[7].

Network pharmacology, as an effective approach that integrates systems biology and computational science, offers a novel perspective for analyzing complex disease-drug interactions. By constructing a "disease-target-component" interaction network, the synergistic regulatory effects of multiple components of traditional Chinese medicine on various targets can be systematically revealed. Additionally, molecular docking technology can be used to further verify the binding affinity of active ingredients to key targets, providing molecular level evidence for mechanistic studies^[8]. Consequently, this study systematically explores the multi-target action mechanisms of

flavonoids in the medicinal and edible fruit of *Crataegus pinnatifida* for the improvement of AD, integrating network pharmacology and molecular docking technology to provide a theoretical foundation for the development of multi-target AD improvement drugs derived from natural products.

2 Method

2.1 Crataegus pinnatifida fruit component collection and target prediction

The search term "SHAN ZHA" is used in the HERB (<http://herb.ac.cn/>), HIT (<http://www.badd-cao.net:2345>), ETCM (<http://www.tcmip.cn/ETCM/>) database search, and according to the published literature to supplement^[9-12], to obtain all flavonoids in *Crataegus pinnatifida* fruit, after combined to heavy processing. The screened flavonoids of *Crataegus pinnatifida* fruit were input into PubChem database (<https://pubchem.ncbi.nlm.nih.gov>) to obtain the SMILE structure of the active ingredient. Import SwissTargetPrediction (<http://www.swisstargetprediction.ch/>) database, *Homo sapiens* was selected, the corresponding targets of each component were predicted, the targets with the probability greater than zero were screened, and the active components without targets were deleted. After all the targets were combined and the repetitive items were deleted, a target database of flavonoids in *Crataegus pinnatifida* fruit was established.

2.2 AD targets collection and component targets intersection

With "Alzheimer's disease" as the keyword, Genecards (<https://www.genecards.org/>) and OMIM (<https://www.omim.org/>) were used to screen the related targets, the target information of the two disease databases was combined, and Venn diagram was drawn using RStudio 4.4.2 software, and the AD target database was obtained. The targets of *Crataegus pinnatifida* fruit flavonoids and AD were input into

Oebiotech (<https://cloud.oebiotech.com/task/>) for intersection, Venn diagram was drawn, and all disease targets were obtained.

2.3 Construction of “*Crataegus pinnatifida* fruit-active ingredient-target” network diagram

The corresponding targets and common targets of the active components were integrated, and the network diagram of “*Crataegus pinnatifida* fruit-flavonoid active components-common target” was constructed using Cytoscape 3.7.2 software. Subsequently, the network diagram was subjected to network topology analysis in Cytoscape software to calculate the Degree value of the nodes, and the active components were sequenced according to the Degree value from large to small to obtain the key flavonoid active components of *Crataegus pinnatifida* fruit for improving AD.

2.4 Construction of protein interaction network and screening of core targets

Using STRING (<https://cn.string-db.org/>) database, open Multiple proteins, input the intersection gene of active ingredient and AD, set the species to “Homo sapiens”, set the minimum interaction score to 0.7, hide the unconnected nodes in the network, and download the protein-protein Interaction (PPI) network diagram and TSV file. The TSV file was imported into Cytoscape 3.7.2 software for network topology analysis, the Degree value of the node was calculated, and the PPI core target network map was drawn, at the same time, the core targets were screened.

2.5 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis

The genes intersecting the active components and AD were submitted to the DAVID database (<https://david.ncifcrf.gov/home.jsp>) and the species was selected as “Homo sapiens” for the KEGG pathway

enrichment analysis. The obtained analysis results were ranked according to the significance (FDR value) from small to large, and the items in the top 20 were ranked by bioinformatics online mapping platform (<https://www.bioinformatics.com.cn>) drawing related analysis diagram.

2.6 Molecular docking validation

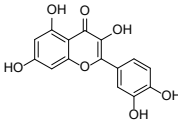
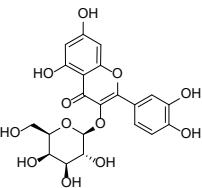
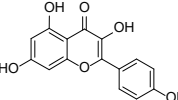
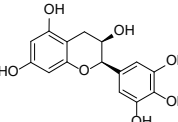
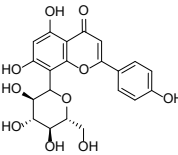
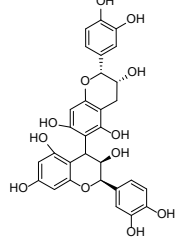
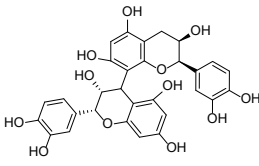
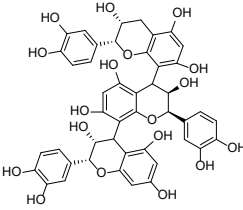
Molecular docking was performed on the screened core targets and key active components, and the SDF file with 3D structure of the main active components was downloaded in the PubChem database and converted into mol2 format by Chem 3D. The gene ID corresponding to the core target protein was obtained through Uniprot, and the pdb format of the 3D structure of the corresponding protein was downloaded in the RCSB-PDB database (<https://www.rcsb.org/>). Water and ligand small molecules in the protein structure were removed by PyMOL software, and the pdb format was derived. Subsequently, the hydrogen atoms in the side chains of amino acids were filled up and butted using AutoDock 4 software to find the binding mode of ligands and proteins and calculate the binding energy. Finally, the visual analysis of the butted results was performed using PyMOL software.

3 Results

3.1 *Crataegus pinnatifida* fruit flavonoids active ingredients and targets

By integrating HERB, ETCM, HIT database and literature supplement, eight effective components of *Crataegus pinnatifida* fruit flavonoids were obtained, as shown in Table 1. The SMILE structure of each component was predicted through PubChem database, and was imported into SwissTargetPrediction platform for screening. After summarizing the targets with probability greater than zero, the repeats and isomers were removed, and 160 genes related to *Crataegus pinnatifida* fruit flavonoids were finally obtained.

Table 1 Main active ingredients of *Crataegus pinnatifida* fruit flavonoids

Code name	Molecule name	MF	Structure
HPS	Quercetin	$C_{15}H_{10}O_7$	
JSTG	Hyperoside	$C_{21}H_{20}O_{12}$	
SNF	Kaempferol	$C_{15}H_{10}O_6$	
EGC	Epigallocatechin	$C_{15}H_{14}O_7$	
MJS	Vitexin	$C_{21}H_{20}O_{10}$	
B5	Procyanidin B5	$C_{30}H_{26}O_{12}$	
B2	Procyanidin B2	$C_{30}H_{26}O_{12}$	
C1	Procyanidin C1	$C_{45}H_{38}O_{18}$	

3.2 Disease target screening

Through the retrieval of GeneCards and OMIM databases, 12622 and 146 disease-related genes were screened, and the intersection was summarized and drawn by RStudio software to draw a Venn diagram. Finally, 12636 disease targets were obtained, and

the AD targets were intersected with 160 targets of *Crataegus pinnatifida* fruit flavonoid active ingredients to obtain 147 intersection genes, which were the potential action targets of *Crataegus pinnatifida* fruit flavonoid ingredients for the treatment of AD. The Venn diagram of the components and disease targets was drawn as shown in Fig. 1.

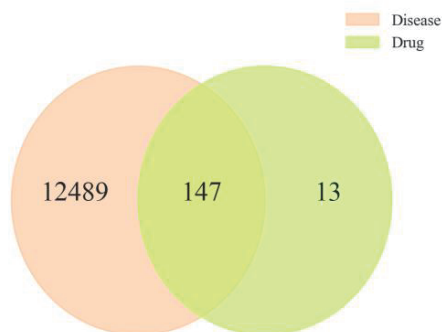


Fig. 1 Venn diagram of “components-targets”

3.3 Network diagram analysis of “*Crataegus pinnatifida* fruit-active ingredient-target”

Using Cytoscape software, the potential targets corresponding to the eight flavonoid active components in *Crataegus pinnatifida* fruit were integrated with the common target of AD, the targets corresponding to the active components were screened as the common target with AD, and the network diagram of “*Crataegus pinnatifida* fruit-active component-target” was constructed, as shown in Fig. 2. The golden nodes in the figure represented the common target of active components in *Crataegus pinnatifida* fruit and AD, and the orange nodes represented eight flavonoid active components in *Crataegus pinnatifida* fruit. The figure revealed the interaction relationship between flavonoid

active components in *Crataegus pinnatifida* fruit and AD target, and indicated that flavonoid components in *Crataegus pinnatifida* fruit could improve AD through multi-component and multi-target action. According to the analysis of network topology, the network diagram consists of 156 nodes and 155 edges. Degree value indicated the number of other nodes connected by a node. The larger the area of the orange node representing the active ingredient in the network diagram was, the more targets corresponding to the active ingredient would be indicated, which was the key active ingredient of *Crataegus pinnatifida* fruit flavonoids in improving AD. It could be seen from the figure that the main key active ingredient of flavonoids in *Crataegus pinnatifida* fruit for improving AD was HPS-quercetin (Degree=74).

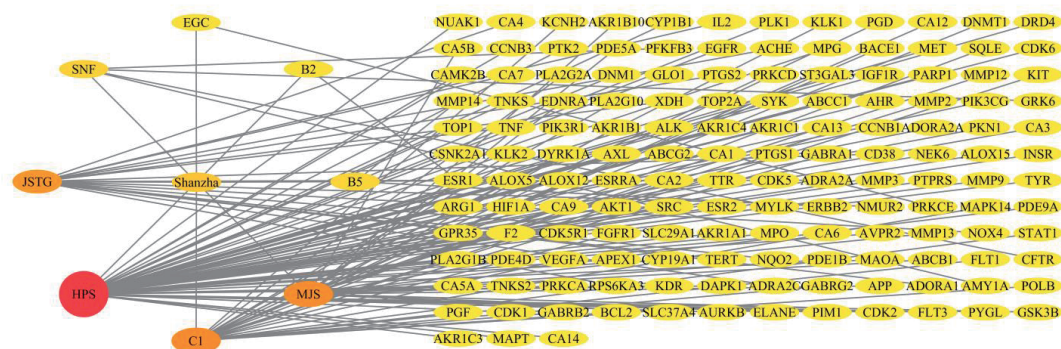
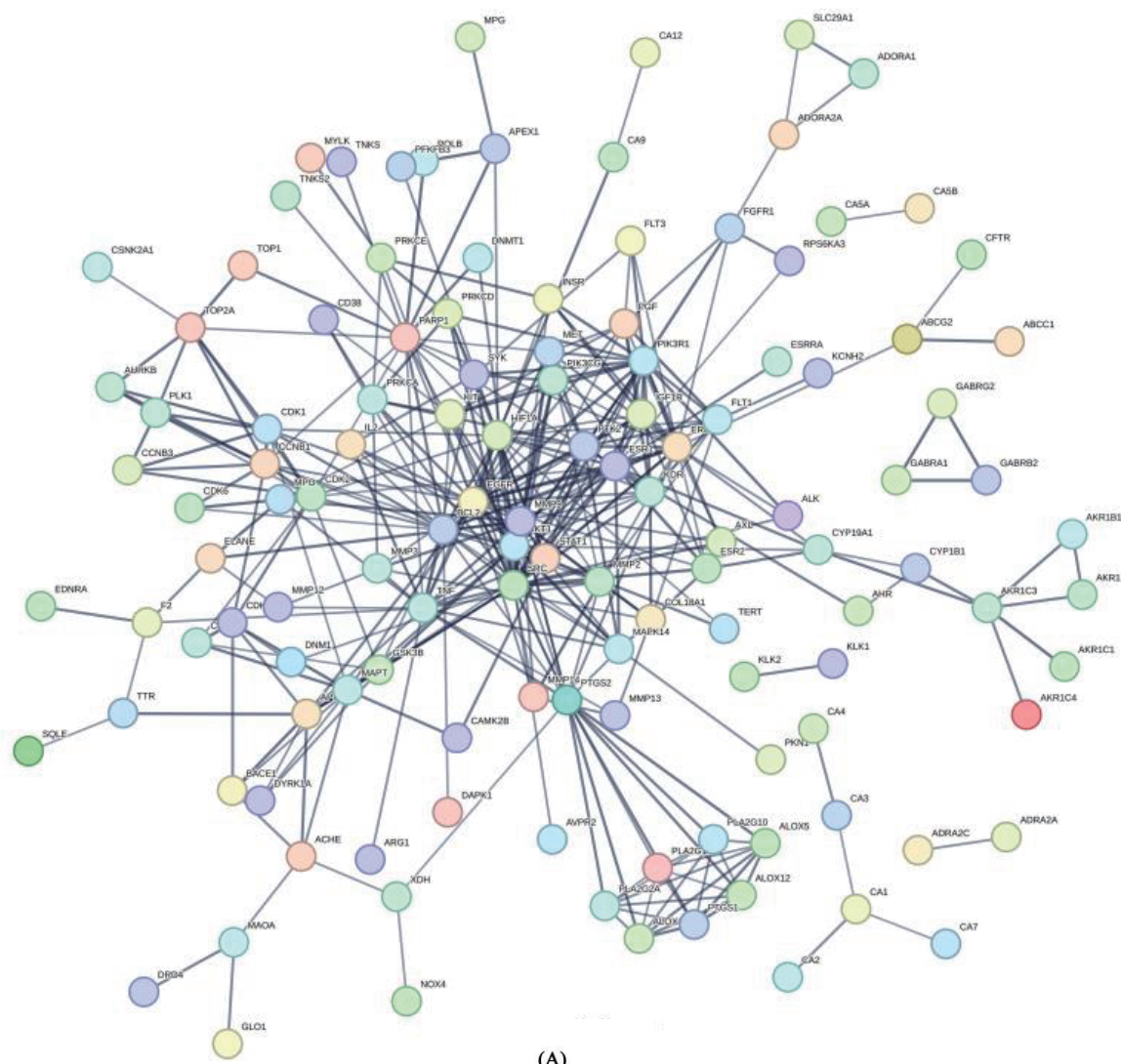


Fig. 2 Venn diagram of “drug component-target”

3.4 PPI protein interaction analysis and core target screening results

The PPI protein interaction analysis of 147 targets of flavonoids in *Crataegus pinnatifida* fruit for improving AD was conducted in STRING database. The PPI protein interaction network diagram was shown in Fig. 3 (A). The analysis results were then imported into Cytoscape software for network topology analysis to calculate the Degree value of each node. The larger the Degree value of a node, the stronger the interaction between the protein corresponding to this node and other proteins would

be, and it would become the core targets. According to the Degree value, the network diagram of *Crataegus pinnatifida* fruit flavonoids improving AD core targets was drawn, and a total of 124 nodes and 376 edges were obtained, as shown in Fig. 3 (B). Each node in the figure represented a target. The larger the area and darker the color of the node indicated that the higher the Degree value of the node was, the more important the target corresponding to the node would be. From the figure, it could be seen that the core targets of flavonoids from *Crataegus pinnatifida* fruit for improving AD were SRC (Degree=32) and EGFR (Degree=31).



(A)

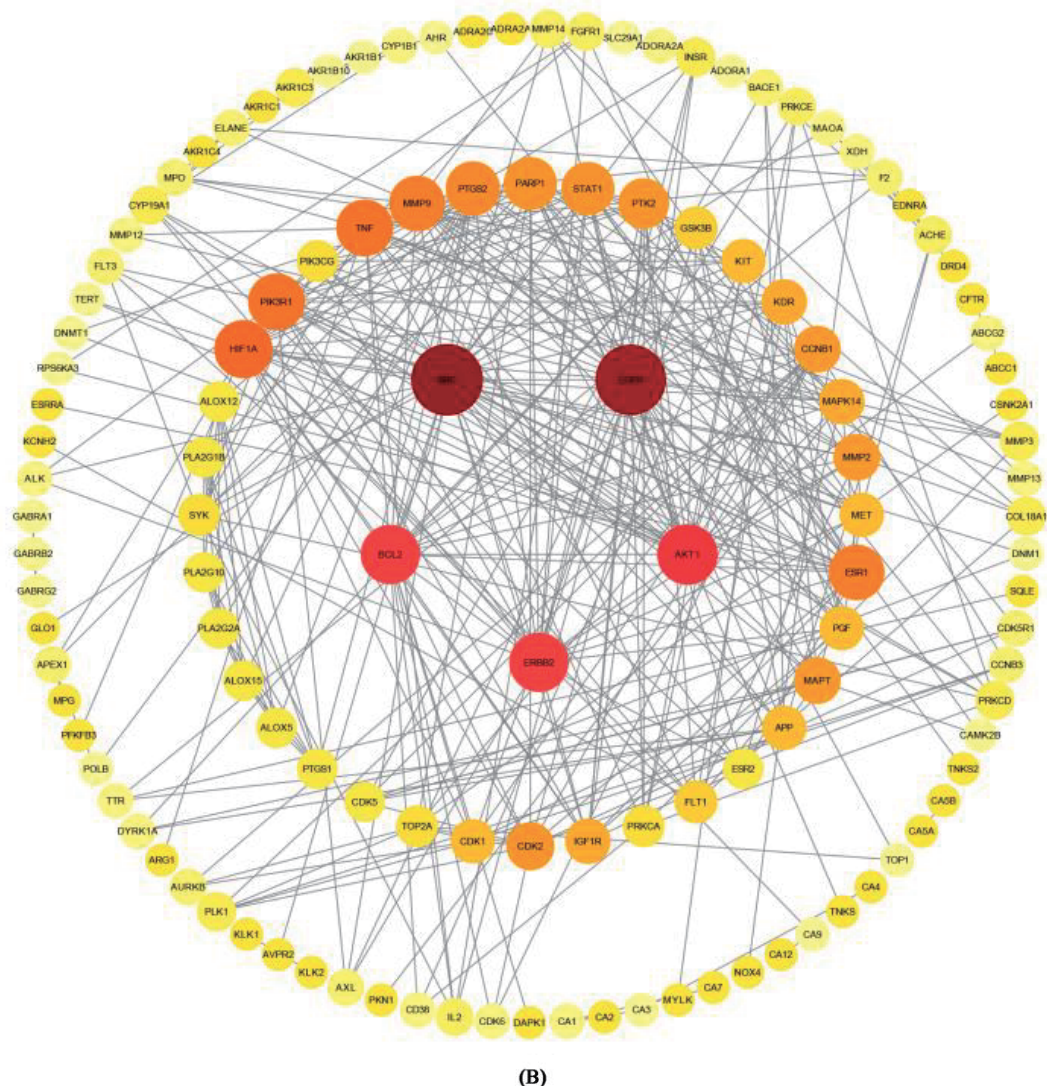


Fig. 3 PPI protein interaction network diagram (A) and “component-target” Venn diagram (B)

3.5 KEGG enrichment analysis

Based on DAVID database analysis, a total of 136 pathways were obtained from 147 potential targets for flavonoid compounds in *Crataegus pinnatifida* fruit to improve AD through coenrichment, and the first 20 pathways with relatively small *P* value were selected for visual analysis through the bioinformatics online mapping platform, as shown in Fig. 4, where the X axis was the FDR value. The results showed that the larger the $-\log_{10}(P \text{ value})$ was, the smaller the *P* value would be, and the more significant the effect of

this pathway would be. Based on the bubble chart, the dots changed from green to red, and the *P* value was gradually smaller. The pathway represented by the red dot indicated that the pathway might play a significant role in the improvement of AD. The higher the enrichment degree of target genes in the pathway was. The value of Count indicated the number of genes enriched in this pathway. The larger Count was, the more genes were enriched in this pathway. The KEGG enrichment results indicated that Pathways in cancer, PI3K/Akt signaling pathway and Proteoglycans in cancer were the main enrichment pathways.

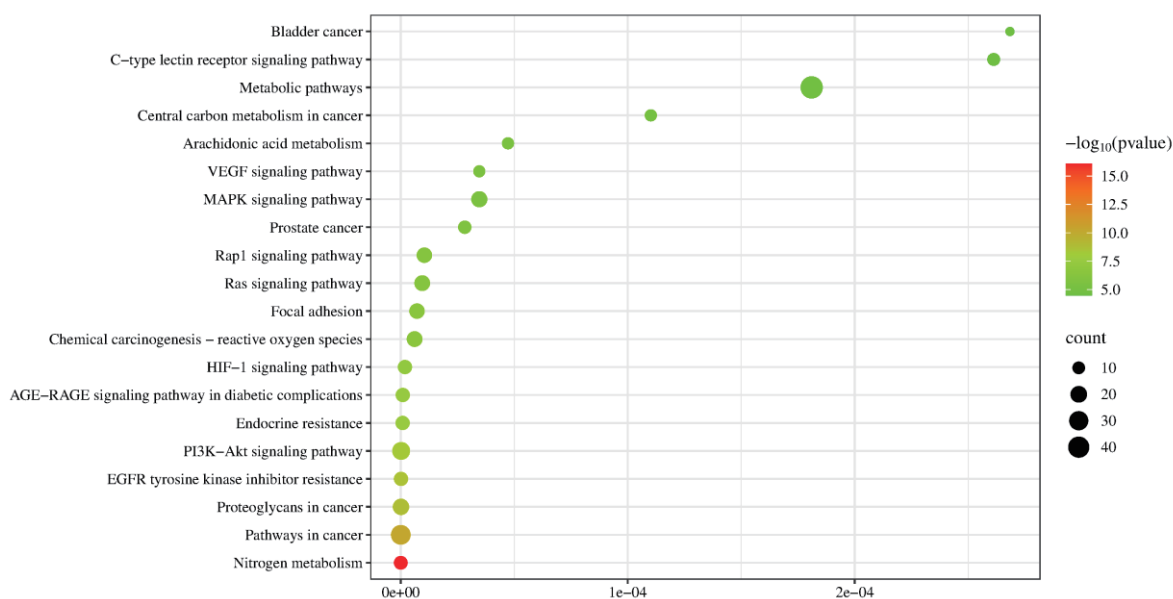


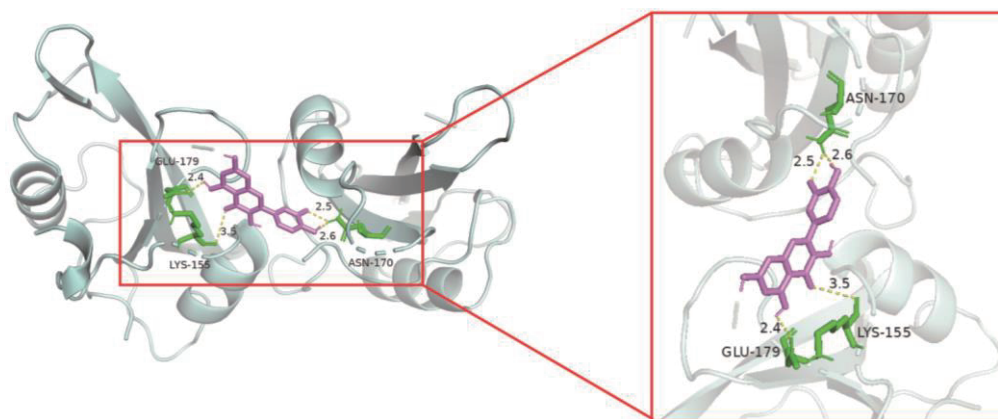
Fig. 4 KEGG pathway enrichment analysis

3.6 Molecular docking verification

Molecular docking was performed on the main active ingredient in the network, quercetin, and the first two genes with moderate PPI network values. The molecular docking energies of -6.6 kcal/mol and -8.0 kcal/mol were obtained by molecular docking of SRC and EGFR, two key targets of *Crataegus pinnatifida* fruit, with quercetin, one of the main active components for the treatment of AD. Studies have shown that a fraction of docking affinity below -5.0 kcal/mol is a criterion for indicating a strong binding

energy between a compound and its target gene. The docking results showed that the flavonoid active components in *Crataegus pinnatifida* fruit had a certain regulatory effect on the key targets for the treatment of AD. The docking results were processed by PyMOL software and the molecular docking pattern was obtained (Fig. 5). The green part was the amino acid residue connected with hydrogen bonds, with the numbers beside it as the amino acid name, the yellow part as the hydrogen bonds, and the numbers beside it as the hydrogen bond length.

Quercetin-SRC



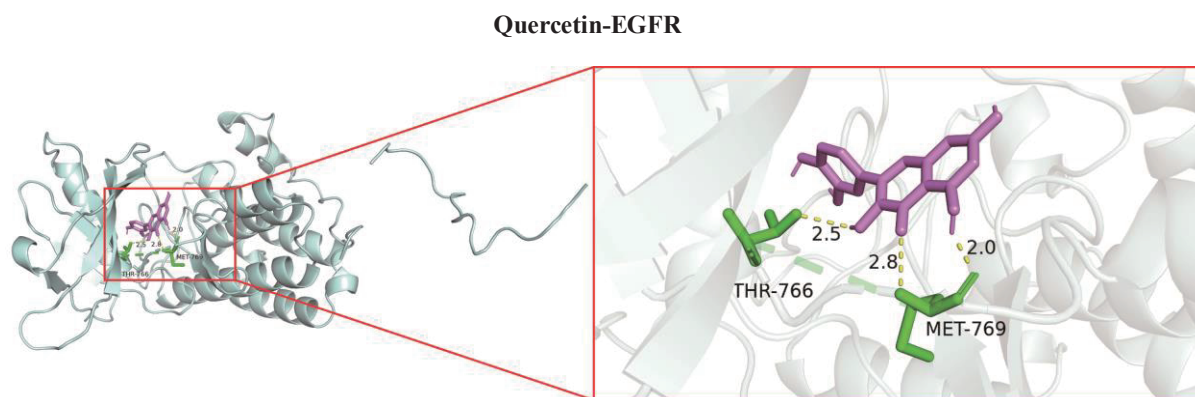


Fig. 5 Molecular docking and visualization of docking results

4 Discussion

AD is a progressive neurodegenerative disease, with a complex etiology and a lack of radical treatment. The cognitive decline and decline in quality of life caused by the disease are becoming increasingly serious. The flavonoids in *Crataegus pinnatifida* fruit can effectively inhibit the deposition of $A\beta$ and neuronal damage related to AD. Its natural origin and multi-target mechanism allow it to demonstrate unique advantages in improving cognitive function and delaying disease progression. In this study, eight flavonoid active components and 160 corresponding targets in *Crataegus pinnatifida* fruit were preliminarily screened, and the degree value of quercetin was the highest. It can demonstrate a significant neuroprotective effect through a variety of mechanisms, such as anti-oxidation, anti-inflammation, inhibition of $A\beta$ deposition and multi-target synergy [13]. Quercetin-activated AMPK has been shown to reduce oxidative stress and inhibit the release of inflammatory factors [14]. These effects help quercetin to reduce neuroinflammation and play a neuroprotective role. In addition, Abeer Alghamdi et al. demonstrated that quercetin could inhibit $A\beta$ aggregation and reduce $A\beta$ plaques formation [15], thereby slowing the progression of AD. It has also been found that quercetin can simultaneously regulate multiple signaling pathways, such as PI3K/Akt and MAPK/ERK pathways [16], more comprehensively improve the pathological state of AD.

A total of 147 potential targets for improved AD

were screened, and two core targets were identified as SRC and EGFR after PPI protein interaction analysis. SRC is a nonreceptor tyrosine kinase that participates in the regulation of various cellular signaling pathways and plays an important role in the occurrence and development of AD. The research by Mastroeni D et al. shows that the expression of SRC in multiple brain regions of AD patients is upregulated, such as the middle temporal gyrus and the hippocampus, and the expression of SRC in excitatory neurons increased significantly, suggesting that SRC is involved in the pathological process of AD [17]. Furthermore, $A\beta$ in AD can activate SRC, leading to the activation of microglia and the secretion of pro-inflammatory factors, triggering neuroinflammation and affecting the survival and function of neurons [18]. The abnormal activation of SRC may also lead to hyperphosphorylation of tau protein, thereby forming neurofibrillary tangles, which is one of the important pathological features of AD [19].

EGFR is a transmembrane receptor tyrosine kinase that participates in cell proliferation, differentiation, division, and survival [20]. In the context of AD, abnormal activation of EGFR signaling pathway is closely related to neuroinflammation and neuronal damage. Studies have found that $A\beta$ deposition can stimulate EGFR in both astrocytes and neurons. The hyperphosphorylation of EGFR, activation of astrocytes, and subsequent production of pro-inflammatory cytokines all exacerbate neuroinflammation [21]. In addition, EGFR inhibitors can significantly reduce glial cell activation and

the accumulation of A β plaques, and also promote axonal regeneration after neurodegeneration^[22]. The upregulation of EGFR and human epidermal growth factor receptor-2 (HER-2) is tightly contributed to amyloid plaque formation in AD. By inhibiting HER-2 to activate autophagy, it reduces the Amyloid Precursor Protein (APP) C-terminal and A β levels in AD^[23]. Excessive activation of EGFR can inhibit the function of NMDA receptors, damage synaptic plasticity, and lead to memory disorders. Abnormal EGFR signaling can also cause oxidative stress, further exacerbating neuronal apoptosis^[24].

Through KEGG enrichment analysis, it was screened that the flavonoid compounds in *Crataegus pinnatifida* fruit could improve AD by acting on the signaling pathways such as pathways in cancer, PI3K/Akt signaling pathway, and Proteoglycans in cancer, in addition, all three pathways have EGFR. Molecular docking results showed that the two core targets SRC, EGFR and key active components had good binding activity, and the scores of quercetin and EGFR were the lowest, indicating that the compound could play an important role in the treatment of AD, thus further validating the results of network pharmacology.

5 Conclusion

In this study, the active components of *Crataegus pinnatifida* fruit flavonoids were collected through the database and literature. Based on network pharmacology and molecular docking technology, the potential mechanism of *Crataegus pinnatifida* fruit flavonoids to improve AD was revealed. The binding activity of key components and core targets were verified, which provided a research direction for further exploration of the mechanism of *Crataegus pinnatifida* fruit flavonoids to improve AD. Additionally, this research offered a theoretical support for the development of *Crataegus pinnatifida* fruit health food aimed at ameliorating AD.

Acknowledgements

This research was supported by National

Natural Science Foundation of China (No. 82374333, No.82173961), LiaoNing Revitalization Talents Program (XLYC2203200), SPU Excellent Youth Program (YQ202310), SPU Youth Career Development plan (ZQN202211), Key Laboratory of polysaccharide bioactivity evaluation of TCM of Liaoning Province-Liaoning Distinguished Professor Project for Ying Jia (2017), High-level innovation and entrepreneurship team of Liaoning Province (XLYC2008029), Liaoning Provincial Department of Education Fund (LJ212410163006, LJ212410163018), Postgraduate Education and Teaching Reform Research Project of Liaoning Province in 2024 (LNYJG2024251).

References

- [1] Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease [J]. *Lancet*, 2021, 397(10284): 1577-1590.
- [2] Twarowski B, Herbet M. Inflammatory Processes in Alzheimer's Disease-Pathomechanism, Diagnosis and Treatment: A Review [J]. *Int J Mol Sci*, 2023, 24(7): 6518.
- [3] Dai ZJ, Lin QX, Li T, et al. Disrupted structural and functional brain networks in Alzheimer's disease [J]. *Neurobiol Aging*, 2019, 75: 71-82.
- [4] Passeri E, Elkhoury K, Morsink M, et al. Alzheimer's Disease: Treatment Strategies and Their Limitations [J]. *Int J Mol Sci*, 2022, 23(22): 13954.
- [5] Lee J, Cho E, Kwon H, et al. The fruit of *Crataegus pinnatifida* ameliorates memory deficits in β -amyloid protein-induced Alzheimer's disease mouse model [J]. *J Ethnopharmacol*, 2019, 243: 112107.
- [6] Al Amin M, Dehbia Z, Nafady MH, et al. Flavonoids and Alzheimer's disease: reviewing the evidence for neuroprotective potential [J]. *Mol Cell Biochem*, 2025, 480(1): 43-73.
- [7] Zhang JX, Hao JY, Liu R, et al. Hawthorn flavonoid ameliorates cognitive deficit in mice with Alzheimer's disease by increasing the levels of Bifidobacteriales in gut microbiota and docosapentaenoic acid in serum metabolites [J]. *Food Funct*, 2022, 13(23): 12371-12382.
- [8] Zhao L, Zhang H, Li N, et al. Network pharmacology, a promising approach to reveal the pharmacology

- mechanism of Chinese medicine formula [J]. *J Ethnopharmacol*, 2023, 309: 116306.
- [9] Cui T, Li JZ, Kayahara H, et al. Quantification of the polyphenols and triterpene acids in chinese hawthorn fruit by high-performance liquid chromatography [J]. *J Agric Food Chem*, 2006, 54(13): 4574-4581.
- [10] Yang QM, Huan R, Meng DF, et al. Progress in the study of anti-tumor effects and mechanisms of vitexin [J]. *Pharmacol Rep*, 2025, 77(1): 124-134.
- [11] Bernatoniene J, Masteikova R, Majiene D, et al. Free radical-scavenging activities of *Crataegus monogyna* extracts [J]. *Medicina (Kaunas)*, 2008, 44(9): 706-712.
- [12] Jurikova T, Sochor J, Rop O, et al. Polyphenolic profile and biological activity of Chinese hawthorn (*Crataegus pinnatifida* BUNGE) fruits [J]. *Molecules*, 2012, 17(12): 14490-14509.
- [13] Chiang MC, Tsai TY, Wang CJ. The Potential Benefits of Quercetin for Brain Health: A Review of Anti-Inflammatory and Neuroprotective Mechanisms [J]. *Int J Mol Sci*, 2023, 24(7): 6328.
- [14] Sang A, Wang Y, Wang S, et al. Quercetin attenuates sepsis-induced acute lung injury via suppressing oxidative stress-mediated ER stress through activation of SIRT1/AMPK pathways [J]. *Cell Signal*, 2022, 96: 110363.
- [15] Alghamdi A, Birch DJS, Vyshemirsky V, et al. Impact of the Flavonoid Quercetin on β -Amyloid Aggregation Revealed by Intrinsic Fluorescence [J]. *J Phys Chem B*, 2022, 126(38): 7229-7237.
- [16] Ghafouri-Fard S, Shoorei H, Sasi AK, et al. The impact of the phytotherapeutic agent quercetin on expression of genes and activity of signaling pathways [J]. *Biomed Pharmacother*, 2021, 141: 111847.
- [17] Mastroeni D, Chan CK, Morshed N, et al. Upregulation of the Proto-Oncogene Src Kinase in Alzheimer's Disease: From Molecular Interactions to Therapeutic Potential [J]. *bioRxiv*, 2024: 579336.
- [18] Portugal CC, Almeida TO, Socodato R, et al. Src family kinases (SFKs): critical regulators of microglial homeostatic functions and neurodegeneration in Parkinson's and Alzheimer's diseases [J]. *Febs j*, 2022, 289(24): 7760-7775.
- [19] Dhawan G, Combs CK. Inhibition of Src kinase activity attenuates amyloid associated microgliosis in a murine model of Alzheimer's disease [J]. *J Neuroinflammation*, 2012, 9: 117.
- [20] Sabbah DA, Hajjo R, Sweidan K. Review on Epidermal Growth Factor Receptor (EGFR) Structure, Signaling Pathways, Interactions, and Recent Updates of EGFR Inhibitors [J]. *Curr Top Med Chem*, 2020, 20(10): 815-834.
- [21] Mansour HM, Fawzy HM, El-Khatib AS, et al. Repurposed anti-cancer epidermal growth factor receptor inhibitors: mechanisms of neuroprotective effects in Alzheimer's disease [J]. *Neural Regeneration Research*, 2022, 17(9): 1913-1918.
- [22] Choi HJ, Jeong YJ, Kim J, et al. EGFR is a potential dual molecular target for cancer and Alzheimer's disease [J]. *Front Pharmacol*, 2023, 14: 1238639.
- [23] Mansour HM, Fawzy HM, El-Khatib AS, et al. Potential Repositioning of Anti-cancer EGFR Inhibitors in Alzheimer's Disease: Current Perspectives and Challenging Prospects [J]. *Neuroscience*, 2021, 469: 191-196.
- [24] Tavassoly O, Sato T, Tavassoly I. Inhibition of Brain Epidermal Growth Factor Receptor Activation: A Novel Target in Neurodegenerative Diseases and Brain Injuries [J]. *Mol Pharmacol*, 2020, 98(1): 13-22.