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Exploring the mechanism of action of dried tangerine peel in treating Alzheimer's disease based on network pharmacology and molecular docking.

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Abstract

The objective of this study was to elucidate the mechanism by which Citri Reticulatae Pericarpium (CRP) treated Alzheimer's disease (AD) using network pharmacology and molecular docking. Initially, a screening process identified 98 target compounds and 628 related component targets within CRP. Additionally, 2483 AD targets were retrieved from disease databases. Subsequently, an overlapping targets map was constructed, integrating CRP and AD targets, followed by the creation of a protein-protein interaction network map to identify 66 targets closely associated with the treatment of AD using CRP. These targets were identified through topological attribute analysis. To gain further insights, GO function and KEGG pathway enrichment analyses were conducted on the 66 identified targets. The results revealed enrichment in various biological pathways, including the relaxin signaling pathway, calcium signaling pathway, HIF-1 signaling pathway, and IL-17 signaling pathway. Finally, molecular docking verification was performed on the targets and active components of CRP. Active components, such as flavanone, tangeretin, flavonol, carvacrol, and perillaldehyde, were found to form hydrogen bonds with targets, with binding energies below 0 kg/mol. This study utilized network pharmacology and molecular docking methods to systematically elucidate the mechanism by which CRP treats AD. The findings provided a theoretical foundation for future research and clinical investigations

Keywords: Citric reticulate pericarpium; Alzheimer's disease; Network pharmacology; Molecular docking

1. Introduction

Alzheimer's disease (AD) is an irreversible degenerative disease of the central nervous system that commonly affects the elderly population. It is a major cause of morbidity and mortality among aging individuals. The prevalence of AD is continuously increasing, and its progression is often slow and concealed. The initial stage is characterized by mild memory difficulties, which gradually worsen, leading to functional loss. The key features of AD include memory loss and progressive cognitive dysfunction [1]The exact pathogenesis of Alzheimer's disease is unclear, the underlying pathogenesis is complex, there are currently no broadly effective therapies[2]. Drugs approved by FDA for treating AD, such as Cholinesterase inhibitor, merely targeting the symptoms so as to improve a patient's cognitive outcome, in removing the root of AD pathogenesis was unhelpful [3] It may also cause adverse reactions such as nausea, vomiting, and diarrhea to the patient [4]

The symptoms of AD bear a resemblance to the traditional Chinese medicine (TCM) concepts of 'unwieldiness', 'good forgetfulness', 'dementia', and 'senile dementia' [5]. TCM has made certain progress in the treatment of AD in recent years[6]. AD is a complex disease related to multiple factors, chemical drugs of single target or single pathogenic pathway is difficult to obtain great effect. The multi-target and multi-link treatment characteristics of TCM have advantages in treating AD[7].

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Citri Reticulatae Pericarpium (CRP) refers to the mature pericarp of Citrus reticulate Blanco and its cultivated varieties. CRP exhibits pungent, bitter, and warm properties and belongs to the spleen and lung meridians. It is known for its functions in regulating qi, harmonizing the middle, drying dampness, and resolving phlegm. Modern pharmacological studies have demonstrated that CRP possesses various pharmacological effects, including relieving asthma[8], exhibiting anti-inflammatory[9], antioxidant properties [[10,11], alleviating cough and anti-cancer effects[12]. In the clinical treatment of AD with TCM, CRP used for treating AD of turbid phlegm type.

Currently, the precise mechanism of action of CRP in AD treatment remains unclear. CRP contains a complex mixture of active components, making it challenging to conduct individual component analysis. Additionally, there may be synergistic interactions among the components of CRP, which contribute to its therapeutic effects or reduce toxic reactions. Network pharmacology has emerged as a novel approach for investigating the mechanisms of drug components in disease treatment. This method enables a comprehensive analysis of biological system networks, revealing the relationships between drugs, targets, and diseases within the network. It provides insights into the synergistic effects of TCM components, illustrating how they act on multiple targets at different levels. Network pharmacology promotes the study of TCM's synergistic effects and unveils the intricate connections between drugs and diseases[13]. In this study, we employed network pharmacology and molecular docking approaches to explore the targets of CRP in AD treatment and investigate the underlying mechanisms by which CRP exerted its therapeutic effects.

2. Material and methods

2.1. Screening the main active ingredients of CRP

HERB database (http://herb.ac.cn/) was used to retrieve all the active components of CRP, compounds structures were obtained from PubChem database (http://pubchem.ncbi.nlm.nih.gov), and the SwissTiarget Prediction database (www.swiss targetprediction.cn) was used to predict the target of active components of CRP so as to establish the targets database of active components of CRP, which is convenient for subsequent network pharmacology research.

2.2. Screening of targets related to AD

In the Gene Cards database (https://www.genecards.org), Drug bank database (https://www.drugbank.ca/), OMIM database (https://www.omim.org/), and TTD database (http://bidd.nus.edu.sg/group/cjttd/), the targets of AD were searched, and the targets database of AD was established.

2.3. Construction of overlapping targets of CRP-AD

The Venn (2.1 Online software, https://bioinfogp.cnb. csic.es/tools/venny/index.html) diagram was plotted to obtain the overlapping targets data of CRP and AD. The interaction between the related targets of AD and the potential targets of CRP in the treatment of AD was studied.

2.4. Construction of protein-protein interaction (PPI) network model

The overlapping targets data of CRP-AD were imported into the String platform (11.5 software, https://cn.string.db.org), and 'Homo sapiens (human)' was used as the research species. The confidence level was set to 'medium confidence (0.400)', and the PPI network was constructed, namely the 'CRP-target-AD' network.

2.5. Screening key targets

Cytoscape (3.9.1 software,https://Cytoscape.org) was used to analyze the topological properties of the PPI network diagram. Centi ScaPe 2.2 Menu was used to calculate the closeness centrality (CC), betweenness centrality (BC), and degree centrality (DC) of the whole network. The mean values of closeness, betweenness, and degree were selected as 'threshold'. The possible mechanism of action of key targets in PPI networks was studied by using targets that were greater than the mean values of closeness, betweenness, and degree.

2.6. GO function and KEGG pathway enrichment analyses of key targets

To perform further analysis on the key targets, they were input into the Metascape database (https://metascape.org/gp/index.htm), with the species set as 'Homo sapiens (66)' for the analysis. GO function and KEGG pathway enrichment analyses were conducted on these key targets to gain additional insights.

2.7. Molecular docking

The target protein structure was retrieved from the PDB database (https://www.rcsb.org), while the 3D structure SDF format images of the active ingredients of CRP were obtained from the PubChem database. Molecular docking between the target protein and CRP was performed using Autodock tools (https://autodock.scripps.edu). The docking results were visualized using PyMOL software, the study flowchart as shown in Figure 1.

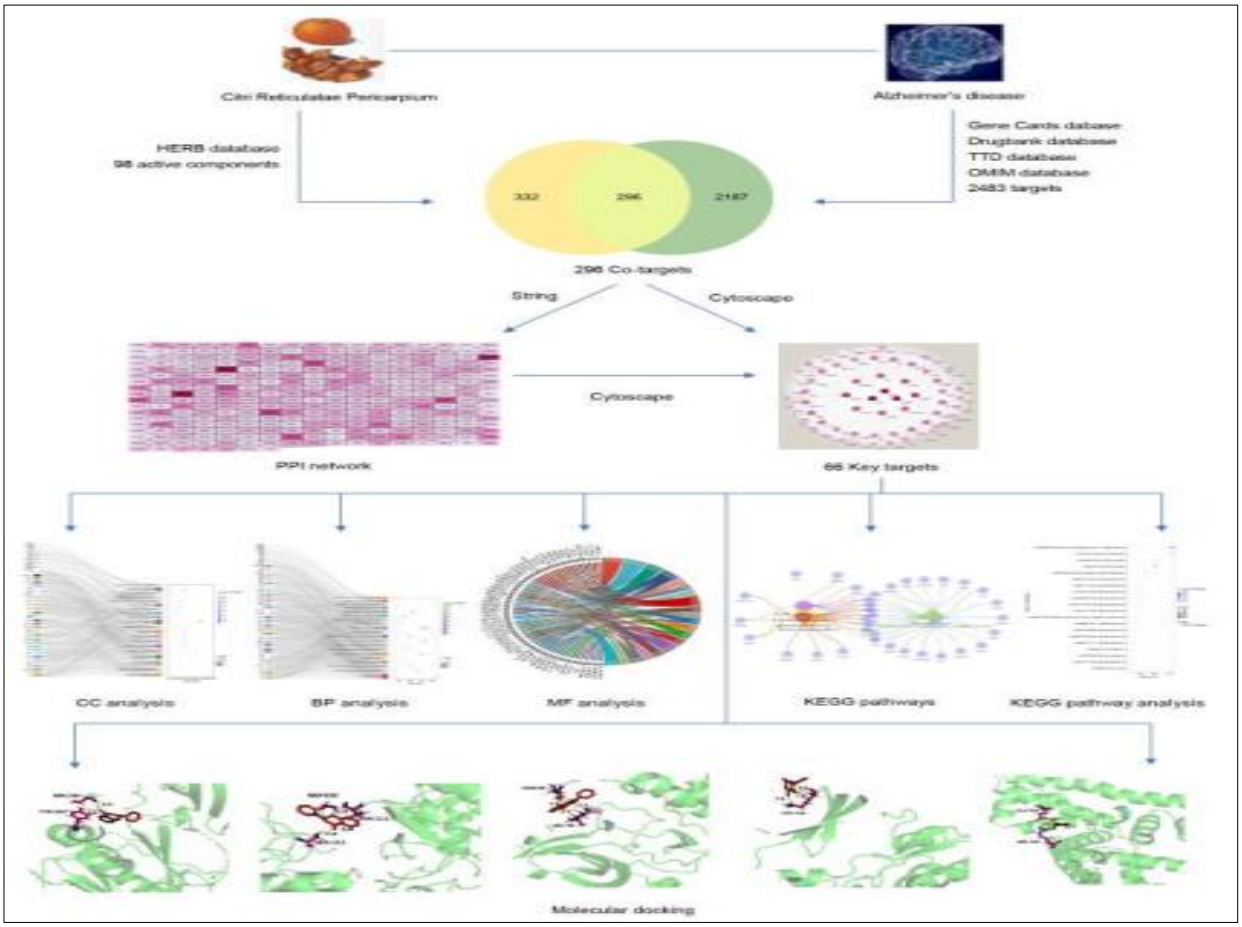


Figure 1 Study flow chart Results and discussion

3. Results

3.1. Componetargets information of CRP

From the HERB database, a total of 150 active ingredients present in CRP were retrieved. To predict the targets of these active ingredients, the SwissTarget Prediction database was utilized. Excluding those active ingredients without targets or with unidentifiable targets, a final set of 98 active ingredients and 628 related targets were obtained.

3.2. Gene targets information related to AD

Gene Cards, Drugbank, TTD, and OMIM databases were used to query the targets of AD. Among them, 10 704 targets related to AD were retrieved from the Gene Cards database. According to the 'Score' value of AD and gene targets, the gene targets with 'Score > = 10.45' were selected to obtain 1848 gene targets related to AD, and 146 were retrieved from the Drugbank database. The OMIM database was used to retrieve 543 targets, and the TTD database was used to retrieve 148 targets. Finally, 2483 targets were obtained.

3.3. Targets information of overlapping active components of AD and CRP

A total of 628 targets related to active ingredients of CRP and 2483 targets related to AD were crossed, and the Venn diagram was drawn. Moreover, 296 targets were common targets, as shown in Figure 2.

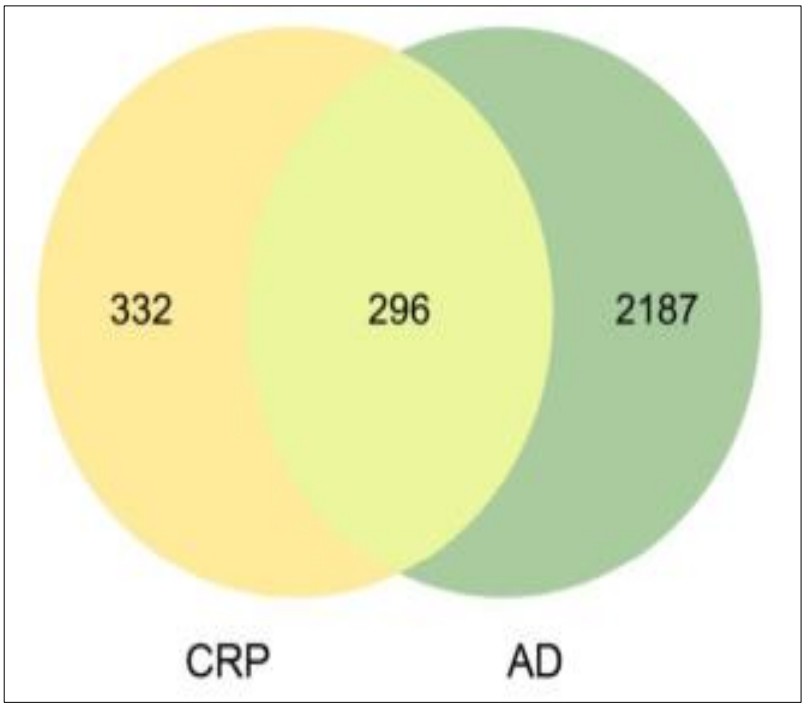


Figure 2 Venn Diagram of CRP-AD

To investigate the interaction among the targets of the active ingredients in vivo and identify potential targets, a total of 296 targets were input into the String platform for PPI network analysis. The resulting PPI network diagram, as shown in Figure 3, revealed interactions among 296 target proteins, resulting in a total of 4034 PPIs. The average number of nodes in the network was 27.3. The PPI network diagram demonstrated the interconnectedness of the target proteins related to the active ingredients of CRP, indicating various synergistic anti-AD effects.

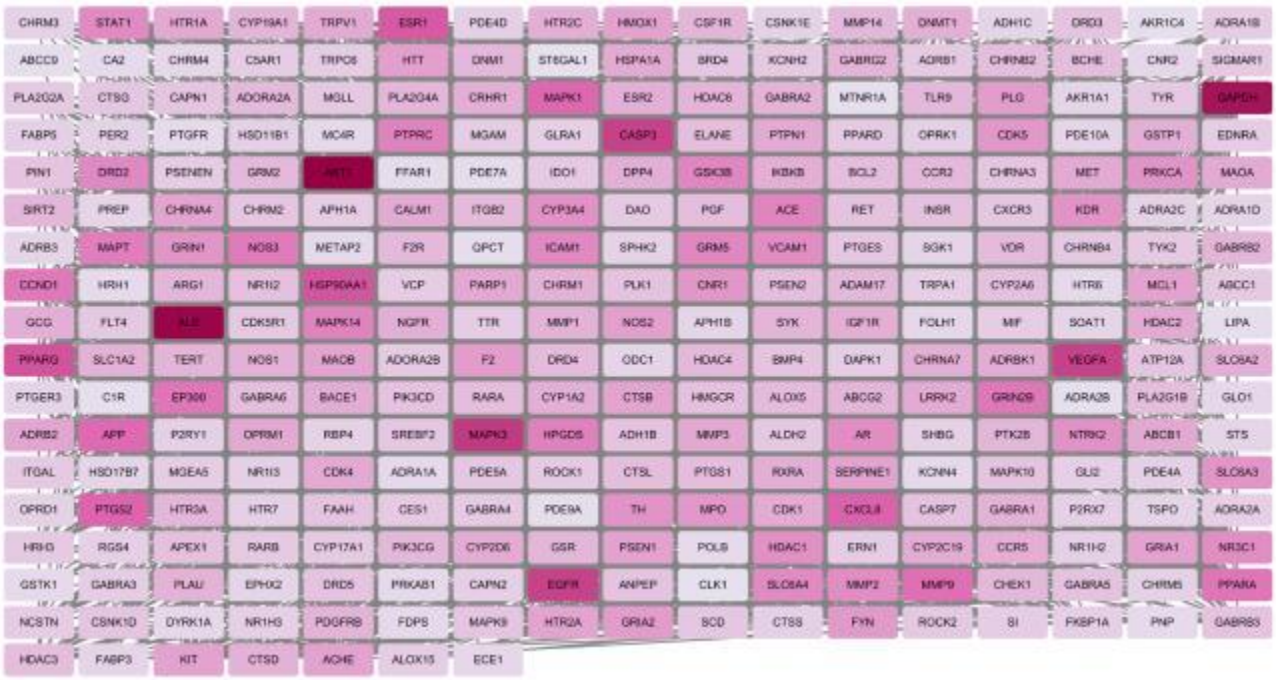


Figure 3 PPI Network diagram of the target proteins

Cytoscape 3.9.1 software was utilized to calculate the PPI network diagram and perform network topology analysis. The number of neighbors of the PPI network was found to be 27.257, with a network heterogeneity of 0.834, and a network

density of 0.092. Among the target proteins, 66 proteins exhibited degree values, betweenness, and tightness values exceeding the average, indicating that these 66 target proteins held a crucial position in the PPI network. Therefore, they were likely to be key targets of CRP against AD. Figure 4a presents the top 20 target proteins ranked by degree value, targets information as shown in Table 1. These targets are primarily involved in various functions, including metabolic regulation, apoptosis inhibition, cell division and proliferation promotion, enhancement of cell stress tolerance, neuronal protection, impact on spatial memory and synaptic plasticity, regulation of mitosis, participation in cell growth, angiogenesis regulation, vascular endothelial cell protection, cell adhesion regulation, direct or indirect involvement in tissue model reconstruction, and combating oxidative stress.

Table 1 Top 20 key targets information

Target	Full name	Uniprot ID	Target	Full name	Uniprot ID
AKT1	RAC-alpha serine/threonine-protein kinase	P31749	ALB	Albumin	P02768
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase	P04406	MAPK3	Mitogen-activated protein kinase 3	P27361
EGFR	Epidermal growth factor receptor	P00533	CASP3	Caspase-3	P42574
VEGFA	Vascular endothelial growth factor A	P15692	PPARG	Peroxisome proliferator-activated receptor gamma	P37231
HSP90AA1	Heat shock protein HSP 90-alpha	P07900	ESR1	Estrogen receptor	P03372
CXCL8	Interleukin-8	P10145	PTGS2	Prostaglandin G/H synthase 2	P35354
MAPK1	Mitogen-activated protein kinase 1	P28482	APP	Amyloid-beta precursor protein	P05067
GRM5	Metabotropic glutamate receptor 5	P41594	GRIN2B	Glutamate ionotropic receptor NMDA type subunit 2B	A0A8D9PHB2
NOS3	Nitric oxide synthase, endothelial	P29474	MAPT	Microtubule-associated protein tau	P10636
ACE	Angiotensin-converting enzyme	P12821	PPARA	Peroxisome proliferator-activated receptor alpha	Q07869

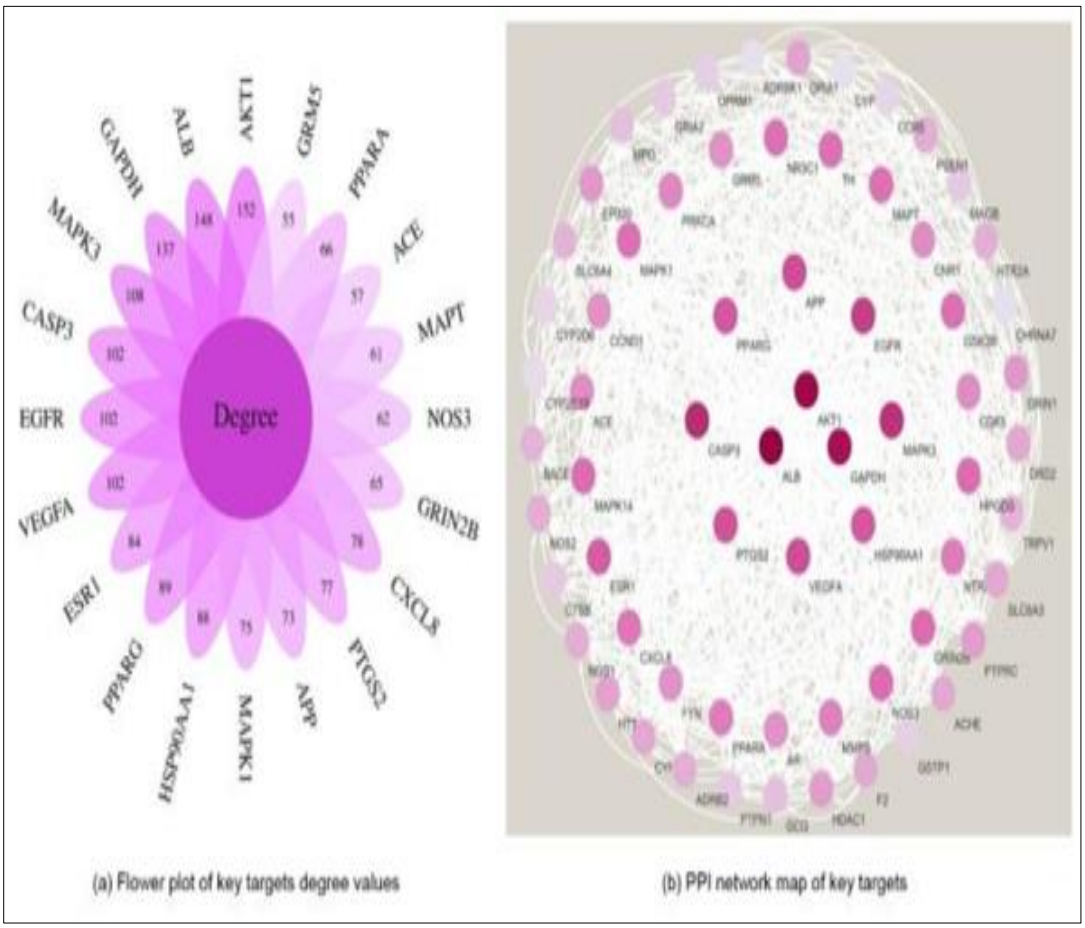


Figure 4 The key targets degree values and PPInetwork

PPI network diagram of key targets, 66 target protein interactions, produced 853 PPI edges, number of neighbors is 25.848; Clustering coefficient is 0.605, network density is 0.398, network heterogeneity is 0.391 (Fig. 4b).

3.4. GO function and KEGG pathway enrichment analyses of the key targets

The key targets underwent GO function and KEGG pathway enrichment analyses using the Metascape database. The GO function enrichment analysis included molecular function, biological process, and cellular components.

In the GO biological process analysis, a total of 253 enriched items were obtained. The top 20 items were selected based on the P-value and included behavioral, cellular response to nitrogen compound, cellular response to organonitrogen compound, learning or memory, cognition, etc. The top 20 items and genes enriched on items as shown in Figure 5a.

For the GO cellular component analysis, a total of 95 enriched items were obtained. The top 20 items based on the P-value were membrane raft, membrane microdomain, postsynapse, dendrite, etc. (Fig. 5b).

In the GO molecular function analysis, 130 enriched entries were identified. The top 20 entries based on the P-value were kinase binding, amyloid-beta binding, heme binding, tetrahydrobiopterin binding, tetrapyrrole binding, neurotransmitter receptor activity, etc., as shown in Figure 5c and supplement.

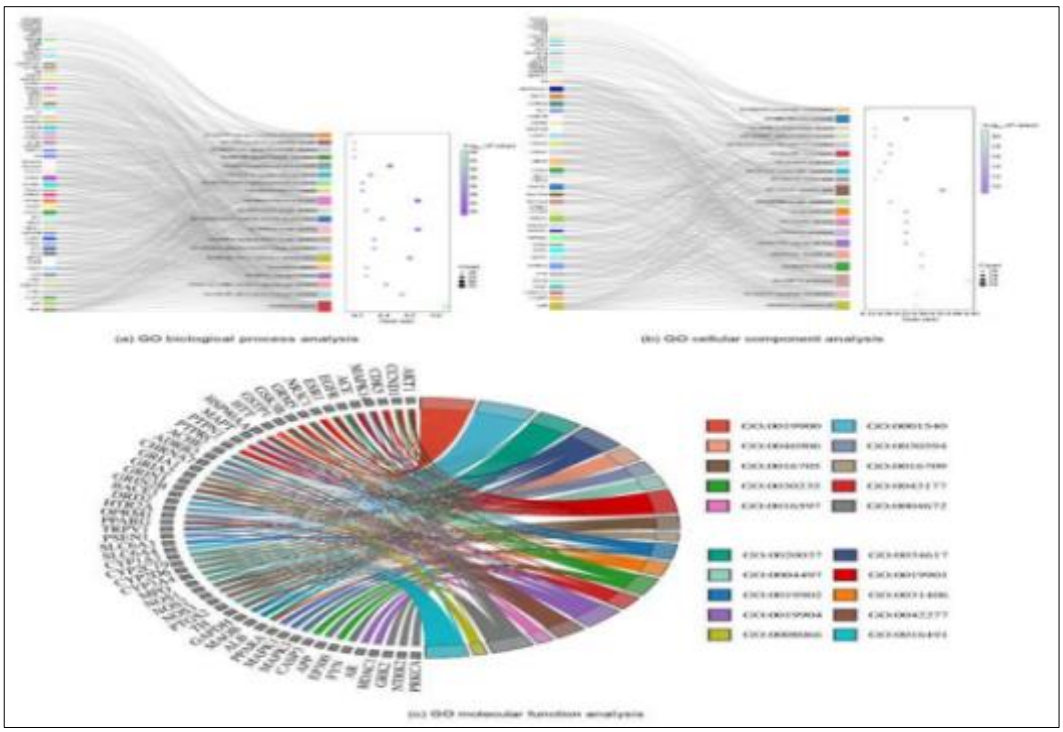


Figure 5 GO functional enrichment analysis

The KEGG pathway enrichment analysis resulted in a total of 160 entries. Exclude cancer, hepatitis, influenza and other pathways, 94 pathways have been linked directly or indirectly to AD. Based on the P-value, the top 20 enriched pathways were identified. These pathways included neurodegenerative diseases, AD, neuroactive ligand-receptor interaction, relaxin signaling pathway, dopaminergic synapse, AGE-RAGE signaling pathway in diabetic complications, long-term potentiation, HIF-1 signaling pathway, cAMP signaling pathway, calcium signaling pathway, IL-17 signaling pathway, VEGF signaling pathway, endocrine resistance, estrogen signaling pathway, etc (Fig. 6).

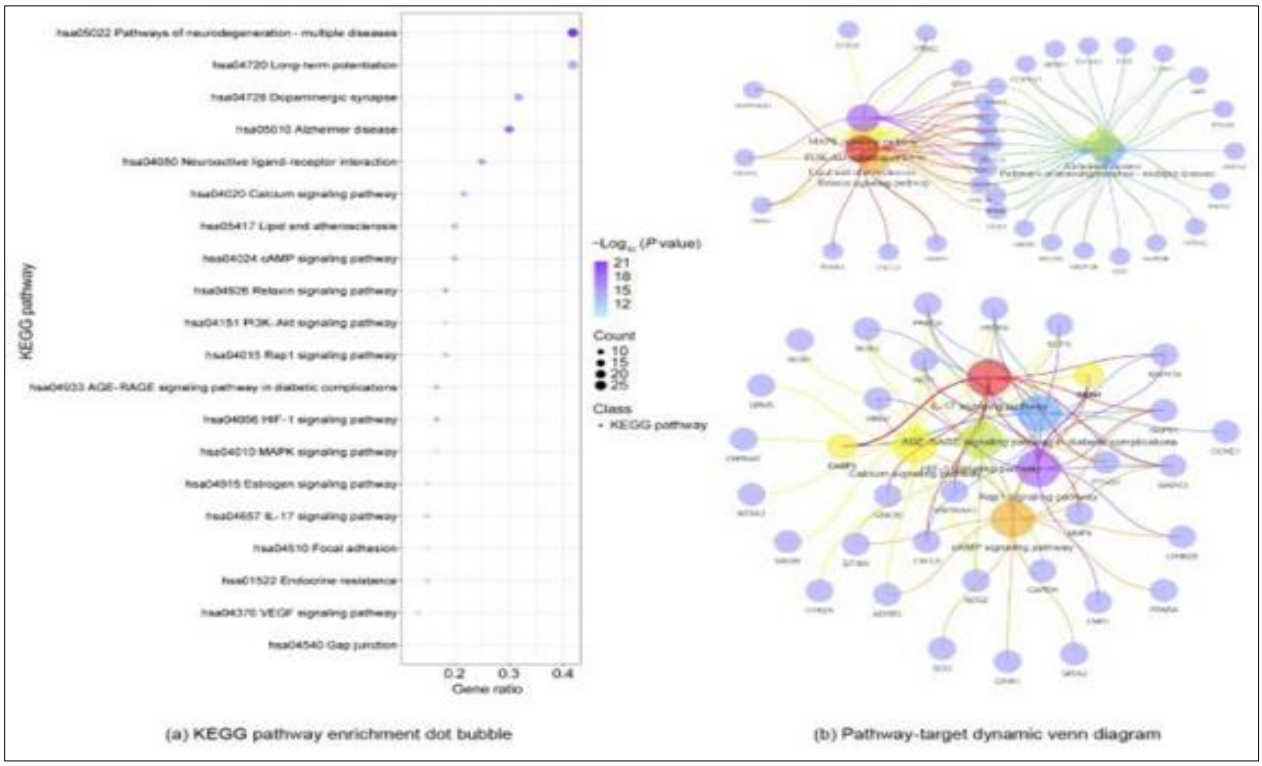


Figure 6 KEGG pathway enrichment analysis

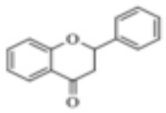
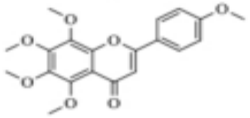
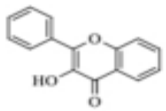
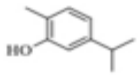
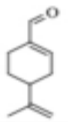
3.5. Molecular docking

Molecular docking was conducted between the first five key targets (AKT1, ALB, GAPDH, MAPK3, EGFR) and the active ingredients (flavanone, tangeretin, flavonol, carvacrol, perillaldehyde) of CRP-AD. The binding energy, which represents the energy released when particles combine from a free state into a composite particle, was calculated. A smaller binding energy indicates a more stable molecular structure. The docking results revealed that the binding energies of the ligands and receptors were all less than 0.00 kJ/mol, as shown in Tables 2 and 3, indicating favorable binding interactions. Additionally, hydrogen bonding was observed between the ligands and receptors, further supporting the stability of the molecular complexes, as depicted in Figure 7.

Table 2 The binding energy of molecular docking between key targets and corresponding active components of CRP

Receptor	Ligand	Binding energy (kJ/mol)
AKT1	Flavanone	−6.83
AKT1	Tangeretin	−4.58
AKT1	Flavonol	−5.68
ALB	Carvacrol	−4.85
GAPDH	Flavanone	−6.97
MAPK3	Perillaldehyde	−5.26
EGFR	Tangeretin	−4.38
EGFR	Flavonol	−5.63

Table 3 Active components and structure of CRP

HERB ID	Chemical name	Molecular formula	CAS ID	PubChem ID	Molecular structure
HBIN026527	Flavanone	$C_{15}H_{12}O_2$	487-26-3	10251	
HBIN045469	Tangeretin	$C_{20}H_{20}O_7$	481-53-8	68077	
HBIN026565	Flavonol	$C_{15}H_{10}O_3$	577-85-5	11349	
HBIN038398	Carvacrol	$C_{10}H_{14}O$	499-75-2	10364	
HBIN039229	Perillaldehyde	$C_{10}H_{14}O$	2111-75-3	16441	

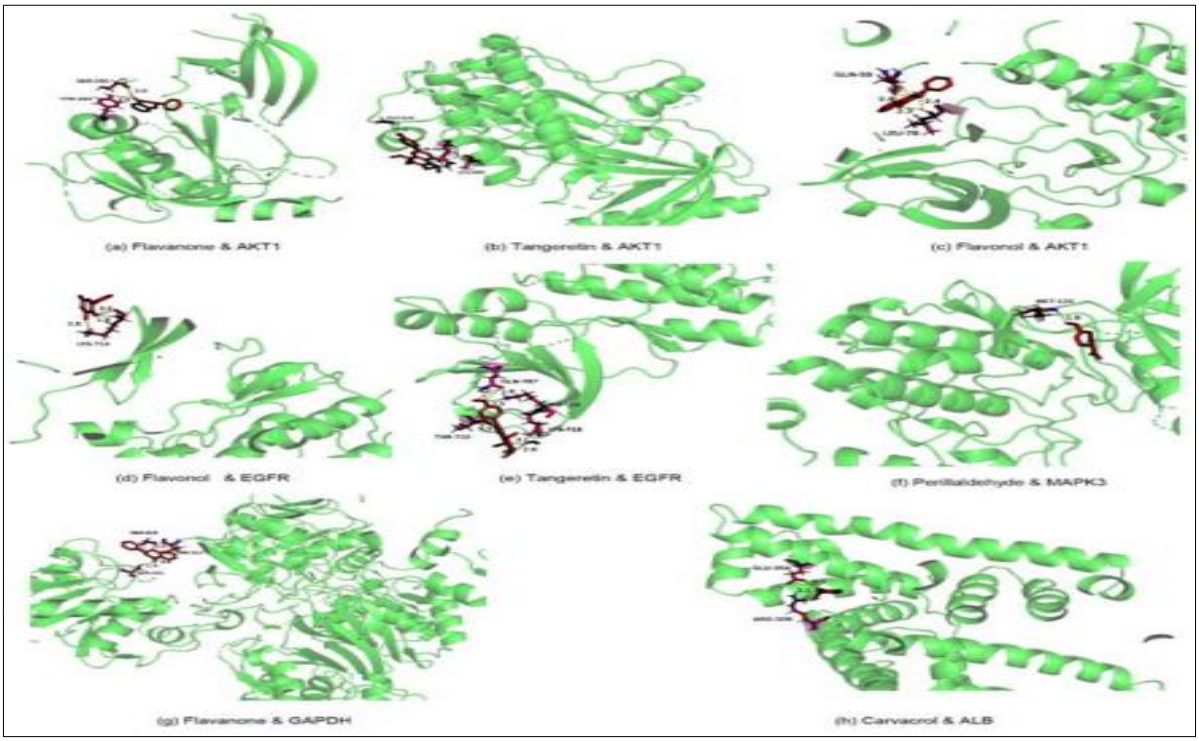


Figure 7 Molecular docking. figure results

4. Discussion

In this study, network pharmacology was utilized to investigate the active components, targets, biological information, and signaling pathways associated with CRP in the treatment of AD. Among the 150 active components identified from the HERB database, 98 were found to have 296 targets. These active components primarily included flavonoids, alkaloids, and volatile oils. Flavonoids, for instance, have been reported to possess anti-aggregation and neuroprotective effects against

amyloid β, a toxic protein involved in AD[14], have potent inhibitory activities against AChE and BChE[15,16]. Nobiletin and tangeretin have been shown to decrease the abnormal accumulation of neurotoxic amyloid β, restore N-methyl-D-aspartate (NMDA) receptor function, suppress tau protein hyperphosphorylation, and enhance neuropeptide levels [17]. While carvacrol possesses antioxidative stress, anti-inflammatory, and antibacterial effects [18].

Based on the topological analysis of the PPI network diagram, 66 key targets were identified from the initial 296 targets. One of the key targets, Akt1, is a cell survival kinase that plays a role in the Akt1/mTOR signaling pathway. Oxidation of Akt1 caused by reactive oxygen species generated by deposited beta-amyloid protein (Aβ) can impair mTOR signaling and lead to reduced activity-dependent protein translation. Overexpression of Akt1 can rescue ROS-mediated Akt1 oxidation, suggesting that promoting the Akt1/mTOR signaling pathway may be a potential therapeutic target for AD [19]. ALB, which encodes blood proteins, has been found to undergo oxidative damage in the early stages of neurodegenerative diseases [20]. GAPDH forms stable aggregates with extracellular amyloid-β (Aβ), extracellular GAPDH compromises Aβ clearance and accelerates neurodegeneration [21]. EGFR, epidermal growth factor receptors, hyperactivation of EGFR has been implicated in many neurodegenerative disorders, including AD, EGFR inhibitors as burgeoning therapeutic strategies for AD [22]. VEGFA can promote neural stem cell proliferation and survival, and exhibit neurotrophic and protective effects on neurons and glial cells [23]. The GluN2B subunit encoded by GRIN2B is involved in brain development, synaptic plasticity, cell migration, and differentiation, and plays a role in learning and memory [24]. Mutations in the APP gene, which is central to the amyloid hypothesis in AD, are associated with AD. Upregulation of APP promotes Aβ production and contributes to the development of AD [25,26].

These targets are closely related to AD, and the treatment of AD with CRP may involve the regulation of these targets. By modulating nerves, protecting neurons, influencing spatial memory and synaptic plasticity, and promoting cell differentiation and proliferation, CRP may exert its therapeutic effects against AD. The molecular docking results indicate that the active components of CRP bind stably to the target proteins with a binding energy of less than 0 kJ/mol. GO biological process analysis reveals that CRP may regulate behavioral responses, kinase activity, and cognitive behavior and affect learning and memory functions in the treatment of AD. KEGG pathway enrichment analysis suggests that CRP may influence the occurrence and progression of AD through multiple pathways, including the relaxin signaling pathway, calcium signaling pathway, HIF-1 signaling pathway, and IL-17 signaling pathway.

The HIF-1 signaling pathway encompassed 10 genes. HIF can regulate hypoxia, metabolic damage, and oxidative stress, Alzheimer's disease may result from inadequate engagement of adaptive signaling pathways that culminate in HIF activation [27]. In the Relaxin signaling pathway, 11 genes were enriched. Relaxin, through Gs protein mediation, can increase cAMP levels in tissue cells and activate protein kinase A (PKA). Cognitive dysfunction in AD may be associated with impaired PI3K/Akt insulin signaling cascade pathway caused by insulin resistance induced by type II diabetes. Impairment of the PI3K/Akt signaling pathway leads to brain energy metabolism disorders, Aβ deposition, hyperphosphorylation of Tau protein, and the development and progression of AD cognitive dysfunction [28]. In the IL-17 signaling pathway, nine genes were enriched. Studies have found that IL-17 produced by Th17 cells that plays a crucial role in inflammation [29].

The calcium signaling pathway contained 12 enriched genes. Intracellular calcium homeostasis plays a crucial role in learning and memory functions [30]. The dysregulation of intracellular calcium homeostasis is considered to be associated with Aβ neurotoxicity [31], by reducing the activity of Ca2+ signaling, have proved successful in alleviating the symptoms of some of these neural diseases [32].

Using network pharmacology, we established a molecular biological network of the active components of CRP and their targets in AD. The findings demonstrated that CRP exhibited potential therapeutic effects for AD through neural regulation, neuroprotection, apoptosis modulation, anti-inflammatory activity, and antioxidant properties. These results established CRP as a promising candidate for the treatment and prevention of AD, providing a solid theoretical foundation. However, further research is required to validate the specific mechanisms involved.

5. Conclusion

This study successfully elucidated the mechanisms by which Citri Reticulatae Pericarpium (CRP) treats Alzheimer's disease (AD) using network pharmacology and molecular docking. By identifying 66 key targets through overlapping target maps and protein-protein interaction networks, and further analyzing these targets via GO function and KEGG pathway enrichment, the study highlighted the involvement of crucial biological pathways, including the relaxin, calcium, HIF-1, and IL-17 signaling pathways. Molecular docking further confirmed the strong interactions between CRP's active components and these targets, suggesting a potential therapeutic effect of CRP on AD. These findings provide a valuable theoretical foundation for future research and clinical applications, offering a promising pathway for

the development of novel treatments for AD, ultimately benefiting society by contributing to the fight against this debilitating disease.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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