Research Article

Network Pharmacology and Molecular Docking-Based Strategy to Investigate the Multitarget Mechanisms of Shenqi Yizhi Granule on Alzheimer’s Disease

Linshuang Wang,1 Xiaoyu Xu,2,3 Zikang Wang,2 Qian Chen,2 Xiaodie Wei,4 Jingfan Xue,5 Zhanjun Zhang,6,7 Miao Wang,2,3 Yanping Li,2,3 Junying Zhang,1 and Dongfeng Wei1

1Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing 100700, China
2College of Traditional Chinese Medicine, Chongqing Medical University, Chongqing 400016, China
3Department of Rheumatology, Chongqing Hospital of Traditional Chinese Medicine, Chongqing 400021, China
4Xi’an Medical University, Xi’an 710000, China
5Huaiyin Normal University, Huai’an 223001, China
6State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing 100875, China
7BABRI Centre, Beijing Normal University, Beijing 100875, China

Correspondence should be addressed to Yanping Li; 840051779@qq.com, Junying Zhang; zhangjuny1985@163.com, and Dongfeng Wei; weidongfeng@aliyun.com

Received 24 February 2022; Accepted 13 April 2022; Published 30 April 2022

Academic Editor: Weidong Pan

Copyright © 2022 Linshuang Wang et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Traditional Chinese herbal medicine draws more attention to explore an effective therapeutic strategy for Alzheimer’s disease (AD). Shenqi Yizhi granule (SQYG), a Chinese herbal recipe, has been applied to ameliorate cognitive impairment in mild-to-moderate AD patients. However, the overall molecular mechanism of SQYG in treating AD has not been clarified. Objective. This study aimed to investigate the molecular mechanism of SQYG on AD using an integration strategy of network pharmacology and molecular docking. Methods. The active compounds of SQYG and common targets between SQYG and AD were screened from databases. The herb-compound network, compound-target network, and protein-protein interaction network were constructed. The enrichment analysis of common targets and molecular docking were performed. Results. 816 compounds and 307 common targets between SQYG and AD were screened. KEGG analysis revealed that common targets were mainly enriched in lipid metabolism, metal ion metabolism, IL-17 signaling pathway, GABA receptor signaling, and neuroactive ligand-receptor interaction. Molecular docking analysis showed high binding affinity between ginsenoside Rg1 and Aβ1–42, tanshinone IIA and BACE1, baikalin, and AchE. Conclusions. The therapeutic mechanisms of SQYG on AD were associated with regulating lipid metabolism, metal ion metabolism, IL-17 signaling pathway, and GABA receptor signaling. Ginsenoside Rg1, tanshinone IIA, baikalin, astragaloside IV, and folic acid may play an important role in AD treatment.

1. Introduction

Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by progressive loss of cognitive function, thought slowness, behavioral abnormalities, and irreversible weakness of daily living [1]. A total of 30 million AD patients worldwide have been recorded now. Without advances in effective therapeutics for dementia, the number of AD patients would rise to 100 million worldwide by 2050 [2]. Extracellular β-amyloid (Aβ) plaques and intraneuronal neurofibrillary tangles caused by phosphorylated tau proteins have been characterized as key pathologic features of AD [3]. In addition, a variety of factors contributed to the development of AD, including glucose metabolism,
mitochondrial dysfunction, synaptic transmission failure, oxidative stress, and cell apoptosis [4–7].

Although AD has been extensively studied for many years, its therapies are still lacking due to the complex pathology. Traditional Chinese medicine (TCM) has a long history of widely applications in Asia [8]. TCM showed remarkable efficacy in preventing and treating neurodegenerative illnesses based on its multicomponent and multitarget effects, which may bring novel therapy options for AD [9]. Shenqi Yizhi granule (SQYG) is a Chinese herbal recipe for AD treatment based on the theory of TCM. SQYG consists of Panax ginseng C.A. Mey, Astragalus membranaceus (Fisch.) Bunge, Scutellaria baicalensis Georgii, Salvia miltiorrhiza Bunge, and Alisma plantago-aquatica L. with a ratio of 2:4:3:3:2. The main active compounds of SQYG included ginsenoside Rb1, ginsenoside Rg1, ginsenoside Rd, baicalin, cryptotanshinone, and tanshinone IIA [10]. These active compounds have a wide range of activities, including neuron cells protection, synaptoprotective effect, antioxidation, promoting energy metabolism, anti-inflammation, lipid composition regulation, and metal ion homeostasis, which are all key points in AD therapy [11, 12]. SQYG has been used in clinical treatment of mild-to-moderate dementia in China, exerting a potent role in neuroprotection [13]. Previous studies have shown that SQYG ameliorated the cognitive impairments in APP/PS1 mice by inhibiting neuronal loss, soluble Aβ deposition, tau hyperphosphorylation, and inflammation [14]. The hippocampus of 5XFAD transgenic mice treated with SQYG presented fewer Aβ deposits and reduced Aβ$_{1–42}$ levels [10]. The neuroprotective mechanisms of SQYG on the hippocampus of 5XFAD mice were related to modulation of multiple pathological processes, including energy metabolism, stress response, cytoskeleton, synaptic transmission, signal transduction, and amino acid metabolism [15].

Network pharmacology, an approach capable of revealing the mechanisms of multiple drugs for diseases, makes the systematic study of herbal formulae achievable by interconnecting disease features, bioactive agents, and drug targets [16, 17]. Molecular docking is a computer simulation method for predicting the binding affinity of a small molecule ligand and a protein. Since the advantages in analyzing the complex interaction between herbal components and the targets of disease [18, 19], network pharmacology and molecular docking-based strategy were applicable to investigate the multitarget mechanisms of SQYG on AD and help uncover drug action mechanisms.

In the present study, the active compounds of SQYG and common targets between SQYG and AD were screened from databases. The network pharmacology was applied to construct a herb-compound network and compound-target network and analyze the key nodes based on active compounds and targets. Enrichment analysis was performed to classify cellular components, biological processes, molecular functions, and KEGG pathways. Molecular docking was employed to analyze the binding affinity between main compounds and key targets. This study aimed to elucidate the pharmacological mechanisms of SQYG on AD.

### 2. Materials and Methods

#### 2.1. Study Design

The active compounds of SQYG and common targets between SQYG and AD were screened from databases. The herb-compound network and compound-target network were constructed by the Cytoscape. The protein-protein interaction (PPI) network of common targets was constructed by the STRING. The Gene Ontology (GO) and KEGG enrichment analysis of common targets were performed by the SangerBox. The molecular docking was analyzed using the Autodock Vina and AutoDock. The schematic diagram of the study is shown in Figure 1.

#### 2.2. Screening the Active Compounds of SQYG

The active compounds of SQYG were collected from multiple databases, including the Traditional Chinese Medicine Systems Pharmacology database (TCMSP, https://tcmspw.com/tcmsp.php), Traditional Chinese Medicine Integrated Database (TCMID, http://www.megabionet.org/tcmid/), The Encyclopedia of Traditional Chinese Medicine (ETCM, http://www.tcmip.cn/ETCM/index.php/Home/), and Bioinformatics Analysis Tool for Molecular MechAanism of Traditional Chinese Medicine (BATMAN-TCM, http://bionet.ncpsb.org.cn/batman-tcm/) databases [18–21]. BATMAN-TCM was based on TCM ingredients’ target prediction and subsequent network pharmacology analyses.

#### 2.3. Screening the Targets of SQYG and AD

We hypothesize that the targets of SQYG intersect with the targets of AD were potential therapeutic targets of SQYG on AD. The protein targets retrieved from TCMSP databases were standardized using the UniProt Knowledgebase database (UniProt KB, http://www.uniprot.org/help/uniprotkb). The therapeutic targets for AD treatment were obtained from the DrugBank database (https://go.drugbank.com/), Therapeutic Target Database (TTD, http://db.idrlabnet/tdt/), ALZgene database (http://www.alzgene.org/), and DisGeNET database (https://www.disgenet.org/) [20, 21].

#### 2.4. Herb-Compound Network and Compound-Target Network Construction

The herb-compound network helps to probe deeper into the interactions between herbs and corresponding compounds. The compound-target network was constructed for understanding closer correspondence between compounds and potential targets. The herb-compound network and compound-target network were constructed by the Cytoscape. The “degree” calculated by linked edges can well reflect the significance of nodes. The degree of each node and compounds were analyzed by the CytoHubba plugin in Cytoscape [22].

#### 2.5. Gene Ontology (GO) and KEGG Enrichment Analysis

The enrichment analysis was performed by the SangerBox (http://sangerbox.com), which can classify cellular components, biological process, molecular function, and KEGG
2.6. Protein-Protein Interaction (PPI) Network Functional Enrichment Analysis. The STRING was applied to construct PPI networks using common targets between SQYG and AD [23]. Interactions with high confidence (interaction score >0.4) for PPI networks were employed for network visualization and analysis. The degree of each protein was calculated in the same manner. The protein subnetworks were constructed by the MultiContrast Delayed Enhancement (MCODE) [24].

2.7. Molecular Docking. The main compounds of SQYG and key protein targets were analyzed by molecular docking using the Autodock Vina and AutoDock [25]. The 3D structures of main compounds were obtained from the TCMSP database. The 3D structures of key protein targets were obtained from the RCSB Protein Data Bank (PDB) and AlphaFold (Table 1). The figures of the active binding site

drug targets were constructed by the MultiContrast Delayed Enhancement (MCODE) [24].

**Table 1: Candidate targets for molecular docking.**

| Gene symbol | Description                                | PDB ID | AlphaFold |
|-------------|--------------------------------------------|--------|-----------|
| INS         | Insulin                                    | 6B70   |           |
| ALB         | Albumin                                    | 1YSX   | P05231    |
| IL6         | Interleukin-6                              |        | P01375    |
| TNF         | Tumor necrosis factor                      |        |           |
| TP53        | Cellular tumor antigen p53                 | 3Q05   |           |
| IL1B        | Interleukin-1 beta                         | 4DEP   | P15692    |
| VEGFA       | Vascular endothelial growth factor-A       |        |           |
| APOE        | Apolipoprotein E                           | 1BZ4   |           |
| PPARG       | Peroxisome proliferator-activated receptor gamma | 1JPW |           |
| CTNNB1      | Catenin beta-1                             | 3E00   |           |

**Figure 1:** Schematic diagram of combining network pharmacology and molecular docking used in this study.
were generated with the PyMOL software [26]. Heatmaps were graphed according to the binding affinity between active compounds and key targets using Graph Pad Prism 5.0.

3. Results

3.1. Screened Active Compounds of SQYG. A total of 1436 compounds of SQYG were collected, including 365 compounds in ETCM, 330 compounds in BATMAN, 622 compounds in TCMD, and 148 compounds in TCMS database (Figure 2(a)). After removing duplicates, 816 compounds were collected, including 365 compounds in Panax ginseng C.A.Mey, 95 compounds in Astragalus mongholicus Bunge, 126 compounds in Scutellaria baicalensis Georgi, 237 compounds in Salvia miltiorrhiza Bunge, and 42 compounds in Alisma plantago-aquatica L (Table 2). The screened active compounds of each herb were listed and are ranked by degree in Supplementary Table 1.

3.2. Screened Common Targets between SQYG and AD. In order to screen the potential targets, the screened 816 compounds of SQYG were uploaded to TCMSP, BATMAN, and ETCM databases. 895 and 1727 target genes were collected from BATMAN and ETCM databases, respectively. 282 protein targets were collected from TCMSP database. After removing duplicates, a total of 2709 targets were obtained. A total of 856 AD-related targets were screened by retrieving DrugBank, TTD, ALZGene, and DisGeNET databases with a relevance score ≥ 0.3. There were 681, 66, 141, and 123 protein targets obtained from ALZGene, DrugBank, TTD, and DisGeNET databases, respectively. Overlap between targets of SQYG and AD, 307 targets of SQYG were found to be AD-related targets and presented by Venn diagrams (Figure 2(b)). These 307 common targets could be potential therapeutic targets for SQYG in AD treatment. Further bioinformatic analysis of these common targets were helpful in revealing the therapeutic mechanisms of SQYG on AD.

3.3. Herb-Compound Network and Compound-Target Network Analysis. To demonstrate the relationships between compounds and each herb, a herb-compound network was constructed. The common compounds in central circular area were presented in multiple herbs (Figure 2(c)). The active compounds and common targets were used to construct the compound-target network and the common targets were marked with blue in a center square region (Figure 2(d)). In both networks, herbs, compounds and targets were represented by nodes and linked with the edges.

3.4. Enrichment Analysis of Common Targets

3.4.1. Cellular Components Analysis. There were 42 GO terms enriched in cellular components. The main cellular components included integral components of the plasma membrane, synapse part, dendritic tree, neuronal cell body, transporter complex, membrane region, an intrinsic component of postsynaptic membrane, an intrinsic component of the presynaptic membrane, GABA receptor complex, and integral component of postsynaptic specialization membrane (Figure 3(a)).

3.4.2. Biological Process Analysis. There were 93 GO terms enriched in biological processes. The main biological process included circulatory system process, lipid localization, response to the metal ion, response to molecule of bacterial origin, hormone transport, response to the antibiotic, steroid metabolic process, G protein-coupled receptor signaling pathway, coupled to cyclic nucleotide second messenger, and ammonium transport (Figure 3(b)).

3.4.3. Molecular Function Analysis. There were 68 GO terms enriched in molecular functions. The bubble map provides a graphical representation of the highly enriched terms of molecular function (Figure 3(c)). The main molecular function included signaling receptor activity, protein dimerization activity, substrate-specific channel activity, chloride channel activity, transmitter-gated ion channel activity, carboxylic acid-binding, serotonin receptor activity, peptide binding, steroid hormone receptor activity, and acetylcholine binding. The involved proteins of each molecular function are listed in Supplementary Table 2.

3.4.4. KEGG Pathway Analysis. There were 119 pathways obtained from KEGG enrichment analysis. The top 10 enriched pathways are shown in Figure 3(d) and Supplementary Table 3, including RAGE receptor binding, arachidonic acid-binding, Toll-like receptor 4 binding, icosanoid binding, icosatetraenoic acid binding, Toll-like receptor binding, long-chain fatty acid binding, organic acid-binding, microtubule binding, and fatty acid derivative binding.

3.5. PPI Network Analysis of Common Targets. The PPI network consists of 307 nodes and 4780 edges, with an average node degree of 31.1 (Figure 4(a)). The key protein targets with high degree are shown in Figure 4(b)). The PPI network contained 3 clusters, including module 1 (MCODE score = 43.382) (Figure 4(c)), module 2 (MCODE score = 20) (Figure 4(d)), and module 3 (MCODE score = 6.67) (Figure 4(e)). The details of each cluster are shown in Table 3. The clusters 1, 2, and 3 were related to the IL-17 signaling pathway, GABA receptor signaling, neuroactive ligand-receptor interaction, respectively.

3.6. Molecular Docking Analysis. The main compounds of SQYG are shown in Figure 5(a). These compounds and key targets were selected for molecular docking analysis. The drug-target binding affinity and interaction between main compounds and key targets were indicated in heat map and interaction network, respectively (Figure 5(b)-5(c)). The molecular docking results of INS-folic acid and IL1B-folic acid are shown in Figures 5(d)-5(e) as representative...
results. Aβ\textsubscript{1–42}, BACE1, and AchE were commonly recognized as the classical therapeutic targets in AD. The drug-target binding affinity and the best-scored docked position between these therapeutic targets and 3 representative compounds (ginsenoside Rg1, baicalin, and tanshinone IIA) are indicated in Figures 6(a)-6(b).

**Table 2:** Number of compounds from five herbs of SQYG after removing duplicates.

| Herbs                          | BATMAN | ETCM | TCMD | TCMSP | Total |
|-------------------------------|--------|------|------|-------|-------|
| Panax ginseng C. A. Mey       | 155    | 157  | 293  | 22    | 365   |
| Astragalus membranaceus (fisch.) bunge | 35    | 27   | 70   | 20    | 95    |
| Scutellaria baicalensis georgi | 65    | 54   | 92   | 36    | 126   |
| Salvia miltiorrhiza bunge     | 75    | 96   | 166  | 65    | 237   |
| Alisma plantago-aquatica linn | 21    | 31   | 33   | 10    | 42    |
| Total                         | 330    | 336  | 622  | 148   | 816   |
Figure 3: Continued.
4. Discussion

TCM has been used in clinical practice for several thousand years. TCM-based new drug development for treating complex diseases is promising. However, it is difficult to reveal molecular mechanisms of the Chinese herbal prescription due to the diverse ingredients and their complex interaction with the human body [27]. Modern pharmacological research methods including network pharmacology, bioinformatics, and molecular docking contributed to understanding the “multicomponent, multitarget, and multipathway” of TCM, and provided valuable clues for subsequent experimental validation. SQYG has been applied to ameliorate cognitive impairment in mild-to-moderate AD patients. However, the underlying therapeutic mechanisms remain incompletely understood.

In this study, network pharmacology, bioinformatics, and molecular docking network were applied to investigate the underlying pharmacological mechanisms of SQYG on AD. The main compounds of SQYG included gamma-sitosterol, β-sitosterol, suffruticoside A, choline, cetylic acid, stigmasterol, hexadecanoic acid, 3-hydroxycoumarin, baicalin, ginsenoside Rb1, ginsenoside Rg1, ginsenoside Re, danshenol A, salvianolic acid B, danshenol B, astragaloside IV, 3 beta-hydroxytanshinone IIA, and isoastragaloside I. The PPI network results indicated that INS, ALB, IL6, TNF, TP53, IL1B, VEGFA, APOE, CTNNB1, and PPAR were key targets of SQYG on AD. The compounds (ginsenoside Rg1, baicalin, and tanshinone IIA) were detected by high-performance liquid chromatography (HPLC) in previous research. They were also screened by network pharmacology from TCM database. So, they were selected for further molecular docking with classical AD targets.

GO enrichment analysis was used to explore the distribution of the overall proteins and grasp the correlation between proteins and biological function in a whole [28–30]. In this study, GO enrichment analysis was applied to classify cellular components, biological process, molecular function, and KEGG pathway of the common protein targets between SQYG and AD. The results indicated that the common protein targets have multiple biological functions, including lipid localization, response to the metal ion of biological process, synapse part, neuronal cell body, GABA receptor complex of biological process, transmitter-gated ion channel activity, peptide binding, and acetylcholine binding of molecular function.

**Figure 3**: Enrichment analysis results of common targets. The GO enrichment results of cellular component (a) and biological process (b). (c) Bubble map of molecular function analysis. (d) Directed acyclic graph (DAG) of the KEGG pathway. The darker the blue, the higher the degree of enrichment.
Figure 4: PPI network construction and subnetwork analysis. (a) PPI network of common protein targets of SQYG. (b) Bar plot of the key protein targets. The y-axis represents the number of neighboring proteins of the protein target. The x-axis represents the protein target. (c) Cluster 1 and its core protein targets. (d) Cluster 2 and its core protein targets. (e) Cluster 3 and its core protein targets.

Table 3: Clustering analysis results of PPI network. 3 subnetworks were identified, and the details of each subnetwork were listed.

| Cluster | Targets                                                                 | Count | Score  |
|---------|-------------------------------------------------------------------------|-------|--------|
| 1       | AGTR1, AGT, GSK3B, SIRT1, MPO, CCL2, APOE, CRP, IL1B, ICAM1, APP, PPARG, ALB, NOS3, SOD2, LEP, CAV1, MMP9, IL10, IL6, INS, TNF, IL4, PPARA, MAPK14, NR3C1, TP53, CASP3, NFE2L2, HSP90AA1, CTNNB1, NOS2, PTGS2, CDK2A, IKKKB, RELA, ESRI, NFKBIA, HIF1A, VEGFA, CXCL10, ACE, CCL5, HMOX1, CASP8, TGFB1, SERPINE1, IFNG, CAT, REN, SMAD3, MMP1, FOS, MMP3, IGF1, PLG | 56    | 43.382 |
| 2       | GABRB2, GABRB1, GABRB3, GABRA6, GLRB, GABRA2, GABRQ, GLRA3, GABRA3, GABRA4, GABRE, GABRG1, GLRA1, GABRG2, GABRP, GABRA1, GABRG3, GLRA2, GABRA5 | 20    | 20     |
| 3       | SLC6A4, GRIN2D, GRIN2G, GSTM1, GRIN1, COMT, DRD4, CHRM3, CHRM2, HTR3A, GSTP1, CHRM1, CHRM5, MAOB, GRIN3B, TPH1, GRIN3A, GRIN2B, GRIA1 | 19    | 6.667  |
Figure 5: Continued.
There were a lot of metabolic, regulatory, and signal transduction pathways in the organism. KEGG pathway enrichment analysis allowed us to identify important biochemical-metabolic pathways and signal transduction pathways in which the key proteins were involved [31]. In this study, the IL-17 signaling pathway, GABA receptor signaling, neuroactive ligand-receptor interaction, RAGE receptor binding, Toll-like receptor binding, and long-chain fatty acid binding were the main pathways where SQYG regulates for therapeutic effects. These key proteins, biological functions, and signaling pathways collectively revealed the therapeutic mechanisms of SQYG on AD. The putative schematic model of pharmacological mechanisms of SQYG ameliorating cognitive impairment of AD is shown in Figure 7. The key targets and compounds are discussed in detail below.
The transcription factor TP53, commonly known as p53, can initiate apoptosis. Hypoxia, DNA damage, oncogene activation, microtubule destruction, and oxidative damage all caused an increase in the p53 expression [32]. Overexpression of p53 caused apoptosis in cultured rat hippocampal pyramidal neurons [33]. TP53 induced neuronal apoptosis via transcription-associated molecular pathways that regulate apoptosis-dependent targets [34]. The mitophagy were downregulated by TP53 [35]. It is worth noting that p53 expression levels in cerebral gray matter...
were positive correlated with Aβ in PS/APP mice [36]. Corresponding to that, dexametomidine was against Aβ by suppressing the TP53 expression [37].

Interleukin-1 beta (IL1B) is ubiquitously distributed in the hippocampus and hypothalamus [38]. IL1Bs were mainly released in the brain by microglia and astrocytes, which have critical roles in the immune response. These signaling molecules mediated neuronal proliferation, differentiation, and apoptosis and induced late long-term potentiation [39]. Neuroinflammation plays a critical role in the pathophysiology of AD and is partly characterized by increased pro-inflammatory cytokines such as IL1B [40]. Moreover, IL1B levels were elevated in the brain and serum of patients with AD [41].

The peroxisome proliferator-activated receptor-γ (PPARγ) is a member of the PPAR family. The activation of PPARγ controlled the multiple pathways involved in inflammation and lipid metabolism. In addition, the vital role of PPARγ agonists in neuroprotection has been extensively studied in neurodegeneration, such as in Aβ-induced AD. Also, in the light of the present evidence, the neuroprotective effects shown by agonists of PPARγ were related to the capability of decreasing Aβ levels [42]. Overall, PPARγ has a wide spectrum of functions in nerve inflammation [43], energy metabolism, cerebrovascular protection [44], and reducing oxidative stress [45], which may significantly improve AD-induced cognitive impairment.

Baicalin has been shown to have anti-inflammation and neuroprotective effects. Baicalin effectively improved Aβ-induced learning and memory deficit, hippocampus injury, and neuron apoptosis. The neuroprotective mechanisms were related to preventing the decrease of Aβ-induced mitochondrial membrane potential, cytochrome c release, and caspase-9/-3 activation [46]. Besides, baicalin alleviated microglia-induced neuroinflammation by inhibiting NLRP3 inflammasome activation and the TLR4/NFκB signaling pathway. Baicalin has been shown to effectively reduce the number of activated microglia and pro-inflammatory cytokines in Aβ-stimulated BV2 microglial cells [47].

Folic acid deficiency is linked to cognitive deterioration and AD [48]. The folic acid levels in serum and cerebrospinal fluid of AD patients were decreased [49–52]. Randomized clinical trials have shown that folate supplementation can enhance cognition and social function in older people with neuropsychiatric disorders [52, 53]. The APP, PS1, and Aβ protein levels in APP/PS1 mice hippocampus were found to be elevated due to the lack of folate [54]. Moreover, folic acid could reduce the deposition of Aβ42 by decreasing the mRNA and protein expressions of β-secretase and γ-secretase complex catalytic component in the APP/PS1 mice brain [55].

Dauricine is a bisbenzylisoquinoline alkaloid derivative extracted from the rootstock of Menispermum dauricum DC. Dauricine alleviated cognitive deficits in 3×Tg-AD mice by lowering Aβ plaques and hyperphosphorylated tau and raising hippocampus ATP levels. After dauricine administration, Aco2, Ndufs1, Cox5a, and SDHB involved in the mitochondrial energy metabolism were significantly increased, while the expression level of synapse-related proteins such as Syn1 and Syn2 were upregulated [56]. Dauricine regulated the proteins levels of Nrf2 and Kelch-like ECH-associated protein 1 (Keap1) that is necessary for the activation of Nrf2 in APPsw cells [57]. Overall, dauricine is beneficial to inhibit inflammatory reaction and apoptosis.

However, there were still limitations in the present study. The screened active compounds of SQYG lack analytical chemistry identification. Moreover, the key targets and potential pathways screened by enrichment analysis require experimental validation.

5. Conclusion

In conclusion, the present study screened 816 active compounds and 307 common targets of SQYG on AD and constructed compound-target network and PPI network using network pharmacology analysis. SQYG alleviated cognitive impairment of AD by regulating lipid metabolism, metal ion metabolism, IL-17 signaling pathway, GABA receptor signaling, and neuroactive ligand-receptor interaction. The molecular mechanisms of SQYG improving the cognitive function were associated with high binding affinity between ginsenoside Rg1 and Aβ1-42, tanshinone IIA and BACE1, and baicalin and AchE. This study provides insights into pharmacological mechanisms of SQYG in ameliorating the cognitive impairment of AD.

Data Availability

The data of this study are accessible upon an appropriate request from the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Linhuang Wang and Xiaoyu Xu authors have contributed equally to this work.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (grant number: 82174210 and 81603488), the Open Research Fund of the State Key Laboratory of Cognitive Neuroscience and Learning (grant number: CNLZD1504), the Scientific and technological innovation project of China Academy of Chinese Medical Sciences (grant number: CI2021B003), the State Key Program of National Natural Science Foundation of China (grant number: 81430100), National Key Research and Development Project of China (grant number: 2018YFC1315203), the Youth Program of National Natural Science Foundation of China (grant number: 81803965), and the Fundamental Research Funds for the Central Public Welfare Research Institutes (grant number: ZZ13-YQ-073).
**Supplementary Materials**

Table S1: The screened active compounds of five herbs of SQYG. Table S2: Top 10 terms of molecular function of common targets. Table S3: Top 10 terms of KEGG pathway of common targets. *(Supplementary Materials)*

**References**

[1] "Molecular map of the human blood-brain barrier reveals links to Alzheimer’s disease," *Nature*, 2022.

[2] Z. Breijyeh and R. Karaman, "Comprehensive review on Alzheimer’s disease: causes and treatment," *Molecules*, vol. 25, no. 24, p. 5789, 2020.

[3] G. Bjorklund, J. Aaseth, M. Dadar, and S. Chirumbolo, "Molecular targets in Alzheimer’s disease," *Molecular Neurobiology*, vol. 56, no. 10, pp. 7032–7044, 2019.

[4] D. A. Butterfield and B. Halliwell, "Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease," *Nature Reviews Neuroscience*, vol. 20, no. 3, pp. 148–160, 2019.

[5] L. Guo, J. Tian, and H. Du, "Mitochondrial dysfunction and synaptic transmission failure in Alzheimer’s disease," *Journal of Alzheimer’s Disease*, vol. 57, no. 4, pp. 1071–1086, 2017.

[6] V. R. Lo Vasco, "The phosphoinositide signal transduction pathway in the pathogenesis of Alzheimer’s disease," *Current Alzheimer Research*, vol. 15, no. 4, pp. 355–362, 2018.

[7] T. Rush, J. Martinez-Hernandez, M. Dollmeyer et al., "Synaptotoxicity in Alzheimer’s disease involved a dysregulation of actin cytoskeleton dynamics through cofilin 1 phosphorylation," *Journal of Neuroscience*, vol. 38, no. 48, pp. 10349–10361, 2018.

[8] S. Li, Z. Wu, and W. Le, “Traditional Chinese medicine for dementia,” *Alzheimer’s and Dementia*, vol. 17, no. 6, pp. 1066–1071, 2021.

[9] C. Tang, Y. Ye, Y. Feng, and R. J. Quinn, “TCM, brain function and drug space,” *Natural Product Reports*, vol. 33, no. 1, pp. 6–25, 2016.

[10] P. Li, Q. Wu, X. Li, B. Hu, W. Wen, and S. Xu, "Shenqi Yizhi Granule attenuates Aβ1–42 induced cognitive dysfunction via inhibiting JAK2/STAT3 activated astrocyte reactivity," *Experimental Gerontology*, vol. 151, Article ID 111400, 2021.

[11] L. Nie, J. Xia, H. Li et al., “Ginsenoside Rg1 ameliorates behavioral abnormalities and modulates the hippocampal proteomic change in triple transgenic mice of Alzheimer’s disease,” *Oxidative Medicine and Cellular Longevity*, vol. 2017, Article ID 6473506, 17 pages, 2017.

[12] S. G. Sreenivasmurthy, J. Y. Liu, J. X. Song et al., "Neurogenic traditional Chinese medicine as a promising strategy for the treatment of Alzheimer’s disease,” *International Journal of Molecular Sciences*, vol. 18, no. 2, p. 272, 2017.

[13] W. Yujiao, Y. Hao, S. Juan, J. Shan, W. Fei, and X. Daojun, “Clinical research of treating alzheimer disease with Shenqi xingnao granule,” *Clinical Journal of Traditional Chinese Medicine*, vol. 29, no. 05, pp. 699–703, 2017.

[14] H. An, D. Wei, Y. Qian, N. Li, and X. Wang, "SQYZ granules, a traditional Chinese herbal, attenuate cognitive deficits in AD transgenic mice by modulating on multiple pathogenesis processes," *American Journal of Translational Research*, vol. 10, no. 11, pp. 3857–3875, 2018.

[15] J. Ren, D. Wei, H. An, J. Zhang, and Z. Zhang, "Shenqi Yizhi granules protect hippocampus of AD transgenic mice by modulating on multiple pathological processes," *Journal of Ethnopharmacology*, vol. 263, Article ID 112869, 2020.

[16] Y. Wang, H. Yang, L. Chen, M. Jafari, and J. Tang, "Network-based modeling of herb combinations in traditional Chinese medicine," *Briefings in Bioinformatics*, vol. 22, no. 5, 2021.

[17] J. Wang, M. Zhang, S. Sun et al., "Network pharmacology-based prediction of catalpol and mechanisms against stroke," *Evidence-Based Complementary and Alternative Medicine*, vol. 2021, Article ID 2541316, 14 pages, 2021.

[18] H. M. An, D. R. Huang, H. Yang et al., "Comprehensive chemical profiling of Jia-Wei-Qi-Fu-Yin and its network pharmacology-based analysis on Alzheimer’s disease,” *Journal of Pharmaceutical and Biomedical Analysis*, vol. 189, Article ID 113467, 2020.

[19] X. C. Pang, J. S. F. Kang, J. S. Fang et al., "Network pharmacology-based analysis of Chinese herbal Naodesheng formula for application to Alzheimer’s disease,” *Chinese Journal of Natural Medicines*, vol. 16, no. 1, pp. 53–62, 2018.

[20] J. Pinero, J. M. Ramirez-Anguita, J. Sauch-Pitaroch et al., "The DisGeNET knowledge platform for disease genomics: 2019 update," *Nucleic Acids Research*, vol. 48, no. D1, pp. D845–D855, 2020.

[21] Y. Wang, S. Zhang, F. Li et al., "Therapeutic target database 2020: enriched resource for facilitating research and early development of targeted therapeutics," *Nucleic Acids Research*, vol. 48, no. D1, pp. D1031–D1041, 2020.

[22] C. H. Chin, S. H. Chen, H. H. Wu, C. W. Ho, M. T. Ko, and C. Y. Lin, "cytoHubba: identifying hub objects and sub-networks from complex interactome," *BMC Systems Biology*, vol. 8, no. S4, p. S11, 2014.

[23] A. Jia, L. Xu, and Y. Wang, "Venn diagrams in bio-informatics," *Briefings in Bioinformatics*, vol. 22, no. 5, 2021.

[24] W. P. Bandettini, P. Kellman, C. Mancini et al., "Multi-Contrast Delayed Enhancement (MCODE) improves detection of subendocardial myocardial infarction by late gadolinium enhancement cardiovascular magnetic resonance: a clinical validation study," *Journal of Cardiovascular Magnetic Resonance*, vol. 14, no. 1, p. 83, 2012.

[25] O. Trott and A. J. Olson, “AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading,” *Journal of Computational Chemistry*, vol. 31, no. 2, pp. 455–461, 2010.

[26] S. K. Burley, H. M. Berman, G. J. Kleywegt, J. L. Markley, H. Nakamura, and S. Velankar, "Protein Data Bank (PDB): the single global macromolecular structure archive,” *Methods in Molecular Biology*, vol. 1607, pp. 627–641, 2017.

[27] Z. Liu, F. Guo, Y. Wang et al., "BATMAN-TCM: a bio-informatics analysis Tool for molecular mechanAism of traditional Chinese medicine," *Scientific Reports*, vol. 6, no. 1, Article ID 21146, 2016.

[28] B. Park, B. K. Kang, A. R. Kim et al., "Particulate matter exposure and the changes in immune biomarkers: effects of bioeom-go on the nasal mucosa of patients with allergic rhinitis and a particulate matter-treated mouse model," *Molecular Sciences*, vol. 6, no. 1, Article ID 21146, 2016.

[29] C. T. Tcheutshoua, D. C. Bilanda, P. D. D. Dzeufet et al., "Preventive potential of the aqueous extract of the mixture of bidens pilosa (asteraceae) and cymbopogon citratus (poaceae) aerial parts on hypertension induced by a chronic salt and alcohol consumption on the rats," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 4259669, 8 pages, 2022.

[30] Z. Long, W. Xiang, J. Li, T. Yang, and G. Yu, “Exploring the mechanism of resveratrol in reducing the soft tissue damage of osteoarthritis based on network pharmacology and
experimental pharmacology,” Evidence-Based Complementary and Alternative Medicine, vol. 2021, Article ID 9931957, 13 pages, 2021.

[31] Y. Alhaiti, Y. Cui, X. Tuerhong et al., “Therapeutic effects of naringin in rheumatoid arthritis: network pharmacology and experimental validation,” Frontiers in Pharmacology, vol. 12, Article ID 672054, 2021.

[32] C. Lanni, M. Racchi, S. Stanga et al., “Unfolded p53 in blood as a predictive signature signature of the transition from mild cognitive impairment to Alzheimer’s disease,” Journal of Alzheimer’s Disease, vol. 20, no. 1, pp. 97–104, 2010.

[33] Z. Liu, D. R. Hurst, X. Qu et al., “Re-expression of DIRAS3 and p53 induces apoptosis and impaired autophagy in head and neck squamous cell carcinoma,” Military Medical Research, vol. 7, no. 1, p. 48, 2020.

[34] M. Jazvinscak Jembrek, N. Slade, P. R. Hof, and G. Simic, “FT_he role of inflam-mation and microglial activation in the pathophysiology of Alzheimer’s disease patients and healthy controls,” Antioxidants and Redox Signaling, vol. 17, no. 2, pp. 195–204, 2012.

[35] F. Checler, T. Goiran, and C. Alves da Costa, “Nuclear TP53: a new regulator of the kynurenine pathway affecting human hippocampal neurogenesis,” Neuro-psychopharmacology, vol. 37, no. 4, pp. 939–949, 2012.

[36] G. Lopez-Castejon and D. Brough, “Understanding the mechanism of IL-1β secretion,” Cytokine & Growth Factor Reviews, vol. 22, no. 4, pp. 189–195, 2011.

[37] J. G. Walker, P. J. Batterham, A. J. Mackinnon et al., “Oral folic acid and vitamin B12 supplementation to prevent cognitive decline in community-dwelling older adults with depressive symptoms the beyond Ageing Project: a randomized controlled trial,” The Journal Of Prevention of Alzheimer’s Disease, vol. 8, no. 3, pp. 1–8, 2021.

[38] M. J. Serot, D. Christmann, T. Dubost, M. C. Béné, and G. C. Faure, “CSF-folate levels are decreased in late-onset AD patients,” Journal of Neural Transmission, vol. 108, no. 1, pp. 93–99, 2001.

[39] H. Chen, S. Liu, B. Ge et al., “Effects of folic acid and vitamin B12 supplementation on cognitive impairment and inflammation in patients with Alzheimer’s disease: a randomized, single-blinded, placebo-controlled trial,” The Journal Of Prevention of Alzheimer’s Disease, vol. 8, no. 1, pp. 194–203, 2012.

[40] G. Li, H. Liu, M. Yu et al., “Folic acid administration inhibits amyloid beta-peptide accumulation in APP/PS1 transgenic mice,” Journal of Nutritional Biochemistry, vol. 26, no. 8, pp. 883–891, 2015.

[41] T. Tian, D. Bai, W. Li, G. W. Huang, and H. Liu, “Effects of folic acid on secretases involved in abeta deposition in APP/ PS1 mice,” Nutrients, vol. 8, no. 9, 2016.

[42] C. Chen, P. Liu, J. Wang et al., “Dauricine attenuates spatial memory impairment and alzheimer-like pathologies by enhancing mitochondrial function in a mouse model of Alzheimers disease,” Frontiers in Cell and Developmental Biology, vol. 8, Article ID 624339, 2021.

[43] L. Wang, Z. Pu, M. Li, K. Wang, L. Deng, and W. Chen, “Antioxidative and antiapoptosis: neuroprotective effects of dauricine in Alzheimers disease models,” Life Sciences, vol. 243, Article ID 117237, 2020.