Potential Mechanism of Huanglian Jiedu Decoction Regulating Iron Homeostasis in NLRP3/IFITM3/γ-secretase Pathway against AD Based on Network Pharmacology

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Abstract [**Objectives**] To explore the possible targets of Huanglian Jiedu Decoction in NLRP3/IFITM3/γ-secretase pathway through regulating iron homeostasis and the potential mechanism of anti-Alzheimer's disease (AD). [**Methods**] Firstly, the active components and related targets of Huanglian Jiedu Decoction were predicted in the database of Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), and the targets of AD were collected from Genecards, OMIM and MalaCards databases. Genes inhibiting iron homeostasis were obtained from the ferroptosis Database (FerrDB). Then, Huanglian Jiedu Decoction the interactive genes of the active component target, the AD target and the iron homeostasis target. Next, the protein-protein interaction (PPI) network of interactive genes was constructed, and the software Cytoscape 3.9.1 was used to visualize and screen out the key active components and target genes. Finally, Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed. [**Results**] A total of 51 Huanglian Jiedu Decoction components and 247 potential protein targets were identified, including 1942 AD targets, 369 iron homeostasis regulatory genes, and 18 intersection targets. Eleven key targets including CDKN2A, MAPK1, TGFβ1, MAPK14, TP53, EGFR, GSK3β, PTEN, HIF1α, HMOX1 and PRKCα were identified by PPI network analysis. [**Conclusions**] In the regulation of iron homeostasis in AD by Huanglian Jiedu Decoction, CDKN2A, MAPK1, TGFβ1, MAPK14, TP53, EGFR, GSK3β, PTEN, HIF1α, HMOX1 and PRKCα may be involved, involving ErbB signaling pathway, endocrine resistance signaling pathway, HIF-1 signaling pathway and so on.

Key words Huanglian Jiedu Decoction, Iron homeostasis, Action mechanism, Alzheimer's disease (AD), Network pharmacology

1 Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease and the most common type of dementia[1]. Its main clinical signs are memory impairment, apraxia, spatial memory impairment, executive dysfunction and neuropsychiatric symptoms[2]. In view of the pathogenesis mechanism of AD, the theory of "toxin impairing brain collaterals" has been put forward in traditional Chinese medicine. According to this theory, the pathogenesis of AD is "deficiency, blood stasis, turbidity and toxicity". Based on this theory, the heat-clearing and detoxifying method is safe and effective in the treatment of AD, and the commonly used prescription is recommended as Huanglian Jiedu Decoction[3]. Huanglian Jiedu Decoction can improve the oxidative stress caused by hypoxia, reduce neuroinflammation and increase the survival rate of neurons through its antioxidant effect[4]. Iron homeostasis is closely related to AD, and the accumulation of iron may lead to the aggravation of neuroinflammation, which accelerates the course of AD. Components in Huanglian Jiedu Decoction have good anti-inflammatory properties and can reduce inflammation. Inflammation is thought to be associated with iron homeostasis[5], so inhibition of inflammation by Huanglian Jiedu Decoction may be helpful in reducing iron accumulation[6-7]. However, the specific pathogenesis mechanism remains to be further studied. Some scholars have found that maintaining iron homeostasis in nerve cells can effectively slow down the course of AD[8]. At present, a variety of iron homeostasis inhibitors have been applied in clinic. Some active components of traditional Chinese medicine can also maintain iron homeostasis in nerve cells through the iron metabolism pathway, slow down the development of AD disease, and treat AD by maintaining iron homeostasis. Previous laboratory studies have shown that Huanglian Jiedu Decoction can slow down the development of AD disease. The physiological functions and underlying molecular mechanisms of active components of Coptidis Rhizoma, Scutellariae Radix, Phellodendri Chinensis Cortex, and Gardeniae Fructus (which are main components of Huanglian Jiedu Decoction at present) have been fully reported[9]. We inferred that the pharmacological mechanism of Huanglian Jiedu Decoction against

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AD may be to slow down the course of AD by maintaining iron homeostasis to inhibit inflammation. In this study, the network pharmacology method was used to explore the mechanism of Huanglian Jiedu Decoction regulating iron homeostasis and inhibiting inflammation to treat AD.

2 Data and methods

2.1 Screening of active components and targets of Huanglian Jiedu Decoction Taking Coptidis Rhizoma, Scutellariae Radix, Phellodendri Chinensis Cortex, and Gardeniae Fructus as search words, the active components were searched by TCM Pharmacology Database and Analysis Platform (TCMSP) (https://www.tcmsp-e.com/#/home), and the corresponding targets of each active component were obtained by setting the oral bioavailability (*OB*) ≥30% and the drug-like property (*DL*) ≥0.18. The UniProt database (https://www.uniprot.org) was used to limit the species as human, and the corresponding target genes were obtained, and the effective components with duplication and no target were eliminated, and the gene names of the targets obtained from the TCMSP database were standardized; the active components of some drugs were not found in TCMSP, and their targets were predicted using the SwissTarget Predicition platform (http://swisstargetprediction.ch), and the species name was set as "Homo sapiens". Download the Excel data sheet of the target of action, and retain the target of action with a comprehensive score ≥0.7. Finally, all the active components and action targets were merged and removed, and 52 Huanglian Jiedu Decoction active components and 247 action targets were obtained.

2.2 Disease targets of AD and iron homeostasis By GeneCards (https://www.genecards.org/), OMIM (https://www.omim.org/), MalaCards (https://www.malacards.org/) 3 databases were used to screen targets related to Alzheimer's disease, and "Alzheimer's disease" was searched. The results were sorted from high to low according to the score, and screened according to the median principle. The results were merged and the duplicates were removed, and 1 942 disease targets of AD were obtained. 379 targets related to iron homeostasis were screened from the FerrDB (HTTP://www.zhounan.org/ferrdb/) database.

2.3 Common genes of Huanglian Jiedu Decoction, AD and iron homeostasis The Huanglian Jiedu Decoction target genes, the AD target genes and the iron homeostasis genes are intersected by using an online website VENNY (https://bioinfogp.cnb.csic.es/tools/venny/), and the common targets of the three are screened out, Obtaining Huanglian Jiedu Decoction related target genes for regulating iron homeostasis and resisting AD, and making a Venn diagram.

2.4 Construction of "Traditional Chinese Medicine-Active Components-Intersection Target" network and screening of core components Based on the intersection targets of Huanglian Jiedu Decoction, AD and iron homeostasis, the CMM-component-target network was constructed by Cytoscape 3.9.1 software.

2.5 Construction of Protein-Protein Interaction (PPI) network and screening of key targets The intersection targets were imported into the STRING database (https://cn.string-db.org/), and the screening conditions were set to a comprehensive score of >0.4 and a hidden free target to obtain a PPI network diagram; the TSV format file was downloaded and imported into Cytoscape 3.9.1 software for drawing. With the help of Centiscape 2.2 plug-in, the core genes were screened, and the intersection targets greater than median of degree, closeness and betweenness were screened, and the top 15 intersection targets were selected as the key targets according to the value.

2.6 GO function and KEGG pathway enrichment analysis The DAVID database (https://david.ncifcrf.gov/) was used to analyze the pathway enrichment of the above potential targets by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG), and the mechanism and pathway of these potential targets were clarified. Homo sapiens was selected as the species, and the annotation "Official gene symbol" was selected for GO analysis of biological processes (BP) and KEGG pathway analysis. Analysis of go enrichment and KEGG pathway was performed using David online data, with $P < 0.05$ representing significance. On this basis, the corrected P values were arranged in order from small to large, and the top 20 were screened for GO and KEGG analysis. The GO and KEGG diagrams were plotted using the Weishengxin platform (http://www.bioinformatics.com.cn/).

3 Results and analysis

3.1 Acquisition of active component of Huanglian Jiedu Decoction and prediction of target In the TCMSP database, the main active components and targets of 4 kinds of traditional Chinese medicines in Huanglian Jiedu Decoction were searched by *OB* ≥30% and *DL*≥0.18, and 103 kinds of active components and 4 011 targets were obtained. 57 kinds of Huanglian Jiedu Decoction active components and 247 action targets were obtained by Swiss Target Predicition database prediction, Uniprot database standardization and TCMSP database retrieval results integration, de-duplication and merging.

3.2 AD disease targets A total of 1 924 disease targets were obtained by searching and screening in GeneCards, OMIM and MalaCards databases.

3.3 Screening of target genes and construction of TCM-component-target network After being downloaded and sorted from the FerrDB database, the genes related to inhibiting iron homeostasis are intersected with the Huanglian Jiedu Decoction target genes, the AD genes and the genes related to iron homeostasis to obtain 18 genes (Fig. 1), and meanwhile, the network of the active component-target of the traditional Chinese medicine is constructed (see Fig. 2). The basic information of the main active components is shown in Table 1.

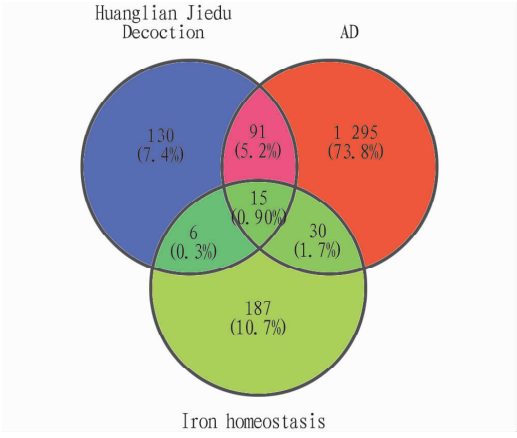
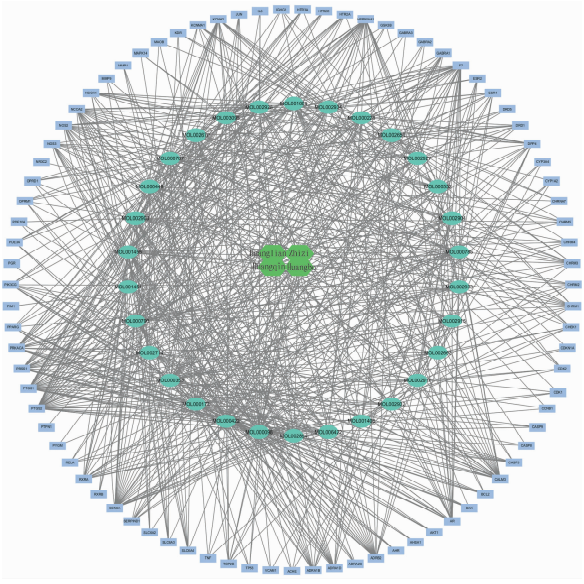


Fig. 1 Common genes of Huanglian Jiedu Decoction, AD and iron homeostasis



NOTE Green represents prescription components; cyan represents active component; blue represents the target.

Fig. 2 Traditional Chinese medicine active component-target network

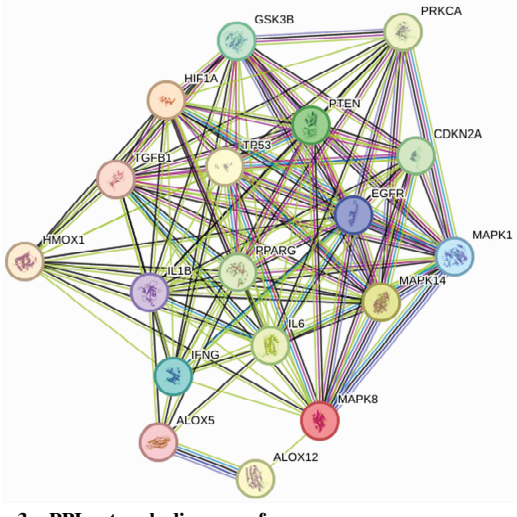


Fig. 3 PPI network diagram of common genes

3.4 Construction and analysis of cross-target protein-protein interaction (PPI) network

The PPI relationship network is obtained by STRING analysis, including 18 nodes and 101 edges (Fig. 3). The PPI network was imported into Cytoscape for visualization, and the plug-in Centiscape 2.2 was used to screen 11 genes through degree, closeness and betweenness (Fig. 4). They were protein kinase Cα (PRKCα), heme oxygenase 1 (HMOX1), hypoxia-inducible factor 1α (HIF1α), phosphatase gene (PTEN), glycogen synthase kinase 3β (GSK3β), epidermal growth factor receptor (EGFR), tumor protein p53 (TP53), Mitogen-activated protein kinase 14 (MAPK14), transforming growth factor β1 (TGFβ1), mitogen-activated protein kinase 1 (MAPK1), and cyclin-dependent kinase inhibitor 2A (CDKN2A) (Table 2).

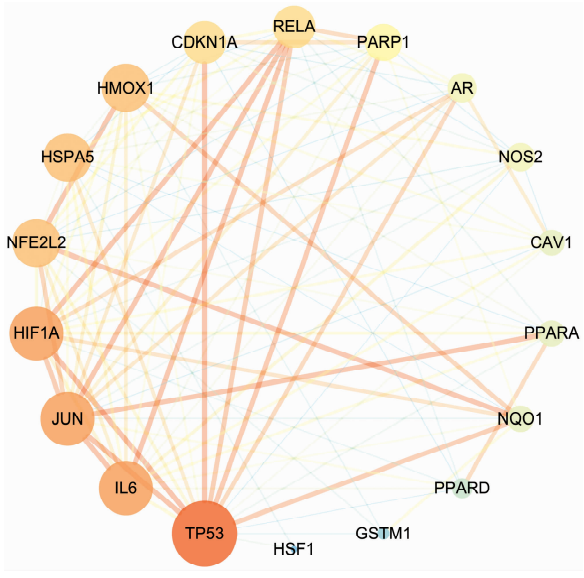


Fig. 4 PPI network of key targets

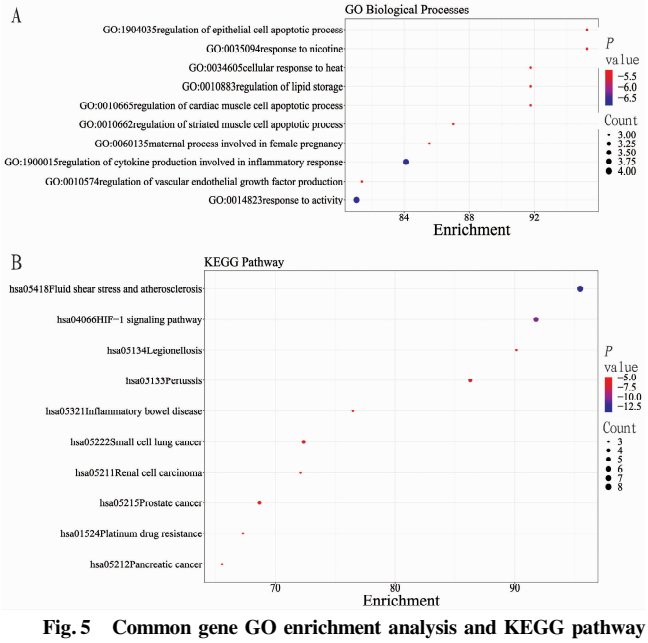


Fig. 5 Common gene GO enrichment analysis and KEGG pathway enrichment analysis

Table 1 Basic information of active components in active component-target network diagram

No.	MOI. ID	Name of active component	*OB*//%	*DL*
1	MOL002934	Neobaicalein	104.34	0.44
2	MOL002932	Panicolin	76.26	0.29
3	MOL000785	Palmatine	64.60	0.65
4	MOL000098	Quercetin	46.43	0.28
5	MOL002668	Worenine	45.83	0.87
6	MOL002897	Epiberberine	43.09	0.78
7	MOL000422	Kaempferol	41.88	0.24
8	MOL002928	Oroxylin a	41.37	0.23
9	MOL002662	Rutaecarpine	40.30	0.60
10	MOL001454	Berberine	36.86	0.78

Table 2 Basic parameters of key targets

Name	Average shortest path length	Degree centrality	Closeness	Between centrality
PRKCα	1.2	11.0	0.041 7	0
*HMOX*1	1.3	12.0	0.045 5	0.271
*HIF*1*α*	1.0	15.0	0.052 6	1.522
PTEN	1.0	15.0	0.052 6	1.522
GSK3β	1.0	14.0	0.047 6	0.897
EGFR	1.0	15.0	0.052 6	1.522
*TP*53	1.0	15.0	0.052 6	1.523
*MAPK*14	1.0	15.0	0.052 6	1.529
*TGFβ*1	1.0	15.0	0.052 6	1.522
*MAPK*1	1.1	14.0	0.050 0	0.989
CDKN2A	1.2	13.0	0.047 6	0.271

3.5 GO function and KEGG pathway enrichment analysis

Through go enrichment analysis, 174 BP items were included, and the top 10 BP items were selected to draw the go enrichment histogram (Fig. 5A). In the biological process (BP), it is mainly nuclear receptor activity, ligand-activated transcription factor activity, Transcriptional coregulator binding, and protein kinase inhibitor activity. In the KEGG pathway enrichment analysis, the involved pathways included the ErbB signaling pathway (ErbB signaling pathway). Endocrine resistance signaling pathway (Endocrine resistance signaling pathway) and HIF-1 signaling pathway, *etc.* The first 20 signaling pathways were selected to draw bubble diagram (Fig. 5B).

4 Discussion

In this study, the active components and targets of Huanglian Jiedu Decoction were screened out through the public database of network pharmacology. Studies have shown that Huanglian Jiedu Decoction regulate iron homeostasis to affect the morbidity process of AD[10], and Huanglian Jiedu Decoction has strong antioxidant properties, which can neutralize free radicals, reduce oxidative stress and inhibit neuroinflammation, so as to protect the cognitive function of Alzheimer's disease (AD) model mice[11]. Some studies have shown that Huanglian Jiedu Decoction can reduce AD-related plaque formation by interfering with the aggregation and deposition of β-amyloid[12].

Through the PPI protein network, we found that CDKN2A, MAPK1, TGFβ1, MAPK14, TP53, EGFR, GSK3β, PTEN, HIF1α, HMOX1, and PRKCα are the key genes for Huanglian Jiedu Decoction to regulate iron homeostasis in AD. Among them, CDKN2A maintains the balance of cellular iron metabolism by regulating cell cycle and activating p53 pathway[13]. MAPK1 and MAPK14 help to slow down the course of AD by inhibiting oxidative stress and maintaining iron homeostasis[14]. TGFβ1 is a driver of iron homeostasis, and inhibition of its expression can regulate iron homeostasis[15]. TP53 maintains iron homeostasis in cells by regulating iron metabolism-related genes such as FTH1 and FPN1 and by targeting DPP4[16]. EGFR promotes cell proliferation and survival by activating downstream signaling pathways (such as PI3K/Akt, MAPK), inhibits programmed cell death, and affects iron homeostasis, thereby affecting AD[17]. GSK3β is a serine/threonine-specific kinase with a dual role in neuronal survival and death. In neurodegenerative diseases such as AD, GSK3β increases the risk of neuronal death by promoting Tau phosphorylation[18]. PTEN is an important tumor suppressor gene that promotes apoptosis and inhibits cell proliferation by reducing PIP3 levels[19]. HIF1α inhibits iron homeostasis by increasing the expression of fatty acid-binding proteins[20]. HMOX1 is also a stress protein that catalyzes the conversion of heme to free ferrous iron, promoting mitochondrial dysfunction and iron aggregation in AD models[20]. PRKCα plays an important role in the activation, proliferation and differentiation of immune cells, regulates immune response and inflammation, reduces neuroinflammation, protects nerves, and slows down the course of AD[21].

The six key targets of ErbB and endocrine resistance signaling pathways, including CDKN2A, MAPK1, TGFβ1, MAPK14, TP53 and EGFR, may be the main pathways for Huanglian Jiedu Decoction to regulate iron homeostasis in AD. Erbβ signaling is mainly triggered by EGFR (epidermal growth factor receptor), which activates PI3K/Akt and MAPK signaling pathways to regulate cell apoptosis and metabolism[22-23]. Endocrine resistance signaling pathway involves a variety of hormones and their effects, such as insulin and GLP-1, which activate PI3K/Akt and MAPK signaling pathways through their receptors, affecting metabolism and inflammation[24]. Erbβ and endocrine resistance signaling pathways affect NLRP3 activity through PI3K/Akt and MAPK pathways, slowing down the course of AD[25]. The active component of Huanglian Jiedu Decoction plays a neuroprotective role by reducing neuroinflammation through the NLRP3-related pathway[26]. Studies have shown that the components of Huanglian Jiedu Decoction can effectively scavenge reactive oxygen species (ROS) *in vivo*, reduce oxidative stress and protect nerve cells[27]. Iron homeostasis, which is dependent on ROS accumulation, is an iron-dependent form of cellular homeostasis, especially in the accumulation of intracellular lipid peroxides[28]. NLRP3 plays an important role in the regulation of iron homeostasis, and the activation of NLRP3 is accompanied by the production of ROS, which can regulate a variety of cell signaling pathways, such as MAPK and PI3K/Akt pathways. Therefore, ROS generation may influence the NLRP3/IFITM3/γ-secretase pathway to regulate iron ho-

meostasis by promoting the activation of NLRP3[29-30]. Through these signaling pathways, ROS can enhance the sensitivity of cells to iron homeostasis and promote the release and accumulation of intracellular iron[5-31]. The excessive accumulation of iron will aggravate oxidative stress and form a vicious circle, affecting iron homeostasis[32]. Studies have shown that iron accumulation activates the MAPK pathway, which in turn activates NLRP3. Inhibition of MAPK can block the NLRP3/IFITM3/γ-secretase pathway, reduce neuroinflammation, maintain neuronal homeostasis, and slow down the course of AD. Mai *et al.* demonstrated that inhibition of MAPK signaling improves cognitive impairment and iron homeostasis in AD mice[33].

In conclusion, Huanglian Jiedu Decoction may act on core proteins such as CDKN2A, MAPK1, TGFβ1, MAPK14, TP53, EGFR, GSK3β, PTEN, HIF1α, HMOX1 and PRKCα. Regulation of MAPK signaling pathway inhibits NLRP3 activity and affects NLRP3/IFITM3/γ-secretase pathway, thus maintaining iron homeostasis in AD.

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