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Active Components and Mechanism of Dihuang Yinzi in Treatment of Vascular Dementia Based on Network Pharmacology and Molecular Docking Technology

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Abstract: The objective this study aims to look into the active ingredients and mechanism of Dihuang Yinzi in the treatment of vascular dementia (VaD) using network pharmacology and molecular docking technology. Methods Based on network pharmacology, screening of the chemical composition and its role of Dihuang Yinzi targets, disease targets, intersection targets, and other related information, and then based on bioinformatics technology, the key pathways related annotation, the active components of Dihuang Yinzi intervention vascular dementia and the underlying mechanisms, and then will get key components and key targets for molecular docking. Results According to network pharmacology, the active ingredients of Dihuang Yinzi in the treatment of VaD were Stigmasterol, beta-sitosterol, Erianin, and others. Dihuang Yinzi's signaling pathways in the treatment of VaD primarily include lipid and atherosclerosis, the PI3K-Akt signaling pathway, the TNF signaling pathway, apoptosis, and so on. Stable structures can be formed by docking key targets with key component molecules. Conclusion Dihuang Yinzi works by using several components, multiple targets, and multiple pathways to cure and prevent VaD.

1. Introduction

A type of dementia known as vascular dementia is brought on by brain damage brought on by many cerebrovascular lesions. Advanced neurocognitive dysfunction, including memory, cognition, and behavior, is the major characteristic of this category of clinical syndromes [1]. According to reports, less than 0.0395% of senior Chinese adults over 65 have dementia, with VaD accounting for 68.5% of those cases and coming in first place [2]. Cerebrovascular disease patients are becoming more numerous and younger in recent years, which not only poses a major risk to their own health but also places a heavy strain on families and society. As a result, VaD therapy and

prevention are crucial.

The only form of dementia that is now preventable is VAD [3], and early intervention can stop it from progressing further. Western medicine has not made significant strides in treating vascular dementia, focusing instead on preventing the development of cerebrovascular disorders. According to the literature on traditional Chinese medicine, VaD falls within the categories of "dementia," "staycation disease," "forgetting disease," and other ailments [4]. The cause of VaD is a deficiency in kidney essence and an interaction between blood stasis and phlegm that causes veins to get blocked [5]. Dihuang Yinzi comes from Saint Francis's General Record. It is used to treat deficiency, failure, and turbation-related constipation syndrome. It causes Kaiqiao, phlegm, kidney-yin, and kidney-yang. Dihuang Yinzi has been proven in recent research to have some protective and healing effects on nervous system damage [6], which can significantly alleviate cognitive dysfunction in VaD patients. Using network pharmacology and molecular docking technologies, this study aims to investigate the potential mechanism of dihuang Yinzi in the treatment of vascular dementia.

2. Methods

2.1. Active Ingredient Screening and Target Prediction

TCMSP[7] was used to retrieve the active ingredients of ripe Rehmannia officinalis, Fructus officinalis, Schisandra schisandra, Calamus calamus, Poria cocos, Cistanciola, cinnamon, Aconite and Morberda officinalis. The screening conditions were OB≥ 30%, BBB≥ -0.3 and DL≥ 0.18.The chemical constituents of Dendrobium, Ophiopogonis and Polygonum were retrieved from the Chinese Knowledge Resource Database (CNKI, http://www.cnki.net/), and the effective constituents were screened by Swiss ADME platform (http://www.swissadme.ch/). The screening conditions were as follows: Gastrointestinal absorption was High, BBB permeant was yes, and Drug likeness was 5 Yes. In order to find appropriate targets, the chosen active ingredients were paired with TCMSP and Swiss Target Prediction, and the target gene names were matched using the UniProt database (https://www.uniprot.org/).

2.2. Disease Target Acquisition

VaD-related disease targets were retrieved from Gene Cards (https://www.genecards.org), OMIM (https://www.omim.org), and a database retrieval service called "vascular dementia" (http://db.idrblab.net/ttd/). The targets retrieved from the three databases were then combined and deduplicated, and the verified human target gene names were matched using the UniProt database.

2.3. Acquisition of Drug-Disease Intersection Targets

Using microscopic letter platform (http://www.bioinformatics.com.cn/) to Dihuang Yinzi drug targets for diseases associated with VaD targets, respectively, take intersection, we obtain Dihuang Yinzi active ingredients directly related to the disease targets.

2.4. Network creation for disease, medication, component, and target

Cytoscape3.8.0 was used to construct the disease-drug-drug-component-target network with disease, rehmandii Yinzi, prescription drugs, drug active components, and their related targets as nodes, and the relationships among nodes as edges, and the core components were selected according to degree value.

2.5. Building a Protein Interaction Network (Ppi) and Identifying the Main Vad Therapeutic Targets with Dihuang Yinzi

To create the drug-disease intersection -target-protein interaction (PPI) network, the aforementioned intersection targets were imported into the STRING database (https://string-db.org/), where the confidence level was set to >0.95. The PPI network was then topologically analyzed to screen potential targets.

2.6. GO and KEGG Pathway Enrichment Analysis

R 4.0.2 software was used to install the relevant integrated package. According to $P \leq 0.05$ and $q \leq 0.05$, GO and KEGG enrichment analysis results were calculated.

2.7. Molecular Docking

The top 8 main components in the disease-drug-ingredient-target network and the top 8 core targets in the PPI network were selected. In order to obtain the three-dimensional structure, the PDB database (http://www.wwpdb.org/), the PubChem database (https://pubchem.ncbi.nlm.nih.gov), and Vina molecular docking, respectively, the best combination is visualized using Pymol.

3. Results

3.1. Drug Active Ingredients and Corresponding Targets

After weight removal, 100 of Dihuang Yinzi's active components were retrieved and screened using TCMSP and CNKI. 776 drug targets were found using the TCMSP and SwissADME platforms after the weight was removed.

3.2. Disease Targets

Gene Cards database yielded 4625 VaD-related targets, and filtering yielded 2313 VaD targets with correlations above the median. One TTD database and 37 OMIM databases are available. The validated human targets were matched using the UniProt database using the combined and deweighted targets. The collection includes 2322 VaD disease targets.

3.3. Drug-Disease Intersection Targets

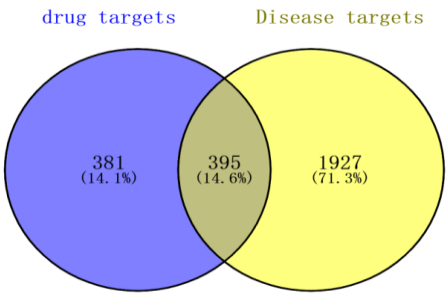


Figure 1: Drug-disease intersection targets.

Figure 1 illustrates the intersection of pharmacological targets and illness targets to find the 395 intersection targets specifically connected to VaD for Dihuang Yinzi.

3.4. Disease - Drug - Ingredient - Target Network

Using Cytoscape3.8.0 to construct disease, drug, ingredients and target networks, the top 8 of degrees can be divided into : Stigmasterol,beta-sitosterol,Erianin,Moscatilin,Chrysotoxine,orchinol, 1, 2, 3, 6, 7-pentamethoxyxanthone, Myfadol, as shown in Figure 2.

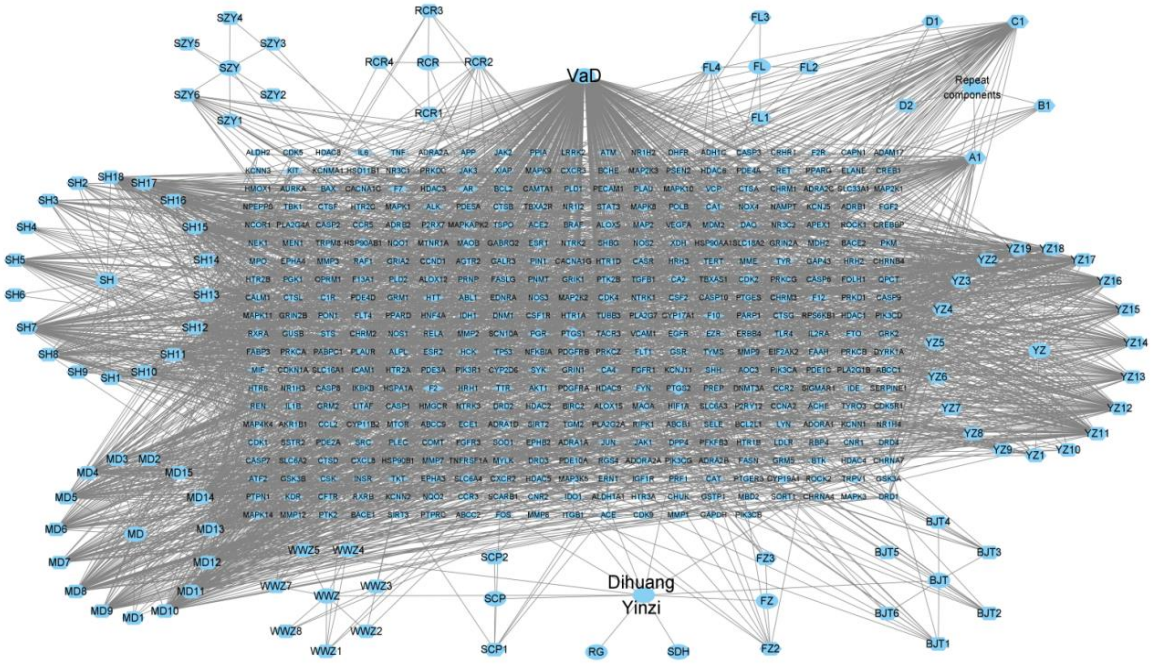


Figure 2: Disease - Drug - ingredient - target network.

3.5. Construction of Protein Interaction Network (PPI) and Screening of Core Targets for Dihuang Yinzitreatment of VaD

The intersection targets of drugs and VaD were, respectively, imported into STRING database to construct PPI network. The network was analyzed by CytoNCA plug-in and the values of BC, CC, DC, EC, LAC, and NC were all defined to be greater than or equal to the 4x the median number to obtain the PPI core network, and the network node was the key target. The top 8 are STAT3, JUN, ESR1, SRC, MAPK3, CREBBP, TP53 and HIF1A, as shown in Figure 3.

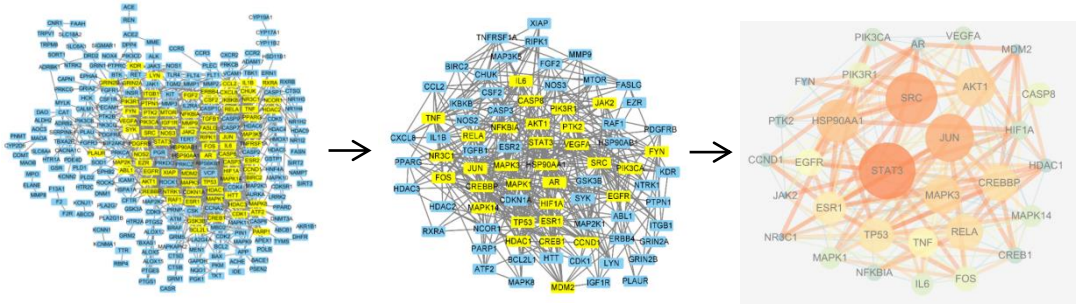


Figure 3: PPI.

3.6. GO and KEGG Enrichment Analysis Results

Core target GO enrichment Core target analysis results, including 3253 biological processes (BP), mainly involved in positive regulation of MAPK cascade, positive regulation of kinase activity, response to lipopolysaccharide etc. There were 184 Cellularcomponent (CC), mainly involving

membrane raft, membrane microdomain, neuronal cell body,etc.320 Molecularfunction (MF), mainly involving protein serine/threonine/tyrosine kinase activity, protein tyrosine kinase activity, neurotransmitter receptor activity, etc. as shown in Figure 4.

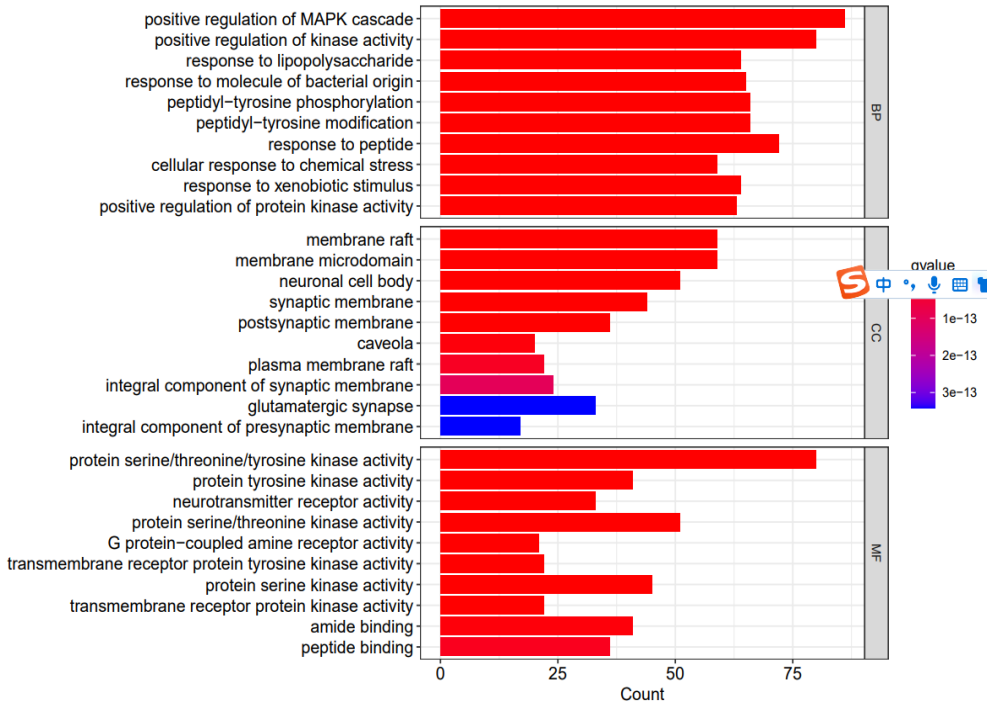


Figure 4: GO enrichment analysis.

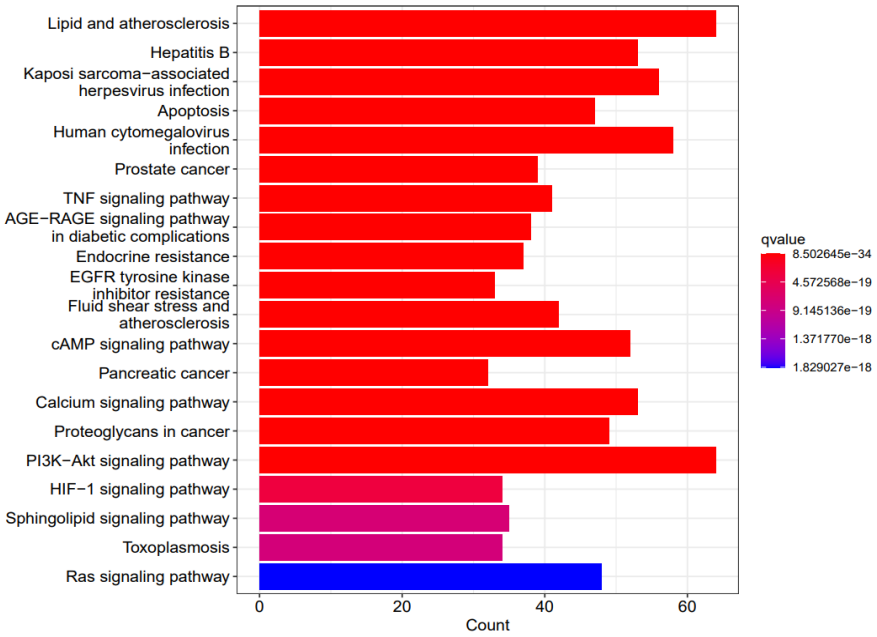
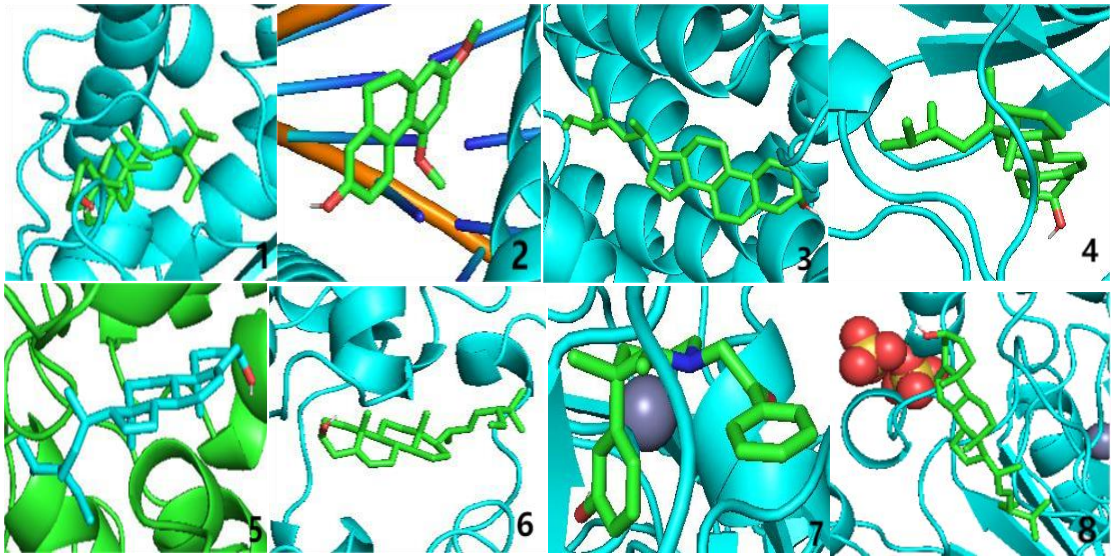


Figure 5: KEGG enrichment analysis.

The core target KEGG enrichment analysis showed 188 enrichment pathways (P< 0.05). The first 20 pathways were determined according to the number of enrichment factors and showed to be Lipid and Atherosclerosis, Apoptosis, TNF signaling pathway, AGE-RAGE signaling pathway in diabetic complications, Fluid shear stress and atherosclerosis, PI3K-Akt signaling pathway, as shown in Figure 5.

3.7. Molecular Docking Results

For molecular docking, the top 8 important targets and constituents were chosen. The conformation of ligand and receptor binding is more stable and contact is more likely the lower energy. Figure 6 displays the essential elements and important targets that had the best docking outcomes.



1:beta-sitosterol—STAT3;2:orchinol—JUN;3:Stigmasterol—ESR1;4:beta-sitosterol—SRC;5:beta-sitosterol—MAPK3;6:Stigmasterol—CREBBP;7:Myfadol—TP53;8:Stigmasterol—HIF1A

Figure 6: Molecular docking.

4. Discussion

Vascular dementia, the second leading cause of dementia after Alzheimer's disease, is getting increasingly prevalent as the population ages [8]. The most prevalent clinical signs and symptoms of cerebrovascular illness include neurological dysfunction, increased cognitive decline, memory, language, and social impairment. Studies have revealed that apoptosis, necrosis, inflammation, and autophagy are important variables in vascular dementia [9], despite the fact that the pathophysiology of VaD is still unknown. VaD is classified as "dementia" and "stupidity" in traditional Chinese medicine, and its primary etiology is "kidney deficiency and pulp deficiency" [10]. The benefits of traditional Chinese medicine in the treatment of vascular dementia have steadily gained attention in recent years. In this article, network pharmacology and molecular docking were used to analyze and validate Rehmannia Yinzi, a commonly prescribed medication for the clinical treatment of VaD.

The active components and target of Rehmannia Yinzhi were analyzed by the network pharmacology. The key targets of this prescription for VaD treatment were STAT3, JUN, ESR1, SRC, MAPK3, etc. The active components were Stigmasterol, beta-sitosterol, Erianin, Moscatilin,

Chrysotoxine etc. Zhou Zhiyuan et al. [11] showed that stigmasterol has anti-inflammatory, antioxidant, and improved learning and memory.Chen Yuan-kun [12] et al. showed that beta-sitosterol has anti-inflammatory, antioxidant and anti-atherosclerosis effects. Maolin belongs to the class of dibenzyl compounds, which have anti-apoptotic and neuroprotective effects [13]. Golden yellow toxin has neuroprotective effects and may be related to the regulation of NF-κB through mitochondrial protection [14]. KEGG analysis showed that Rehmannia rehmannii was mainly processed by PI3K-Akt signaling pathway, MAPK signaling pathway, Lipid and

atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, Fluid shear stress and atherosclerosis, TNF signaling pathway, Apoptosis on VaD.

The PI3K-Akt signaling pathway is closely related to the pathogenesis and progression of VaD. PI3K can regulate cell proliferation and apoptosis [15]. Phosphorylation of Akt and the binding of antiapoptotic factors Bcl-2 and Bcl-xl can reduce cell death, maintain cell survival, and protect the nervous system [16]. Apoptosis is one of the main forms of neuronal damage during ischemia and hypoxia, and the brain is very sensitive to ischemia and hypoxia. Studies have shown that MAPK signaling pathway and PI3K-Akt signaling pathway are the main pathways related to apoptosis after cerebral ischemia [17]. Studies have shown that down-regulating the content of TNF-α in hippocampus can effectively reduce inflammation and reduce brain injury [18]. Dihuang Yinzi may downregulate the content of TNF-α through the TNF signaling pathway, thus achieving the therapeutic effect of reducing brain injury. Atherosclerosis and abnormal lipid metabolism are risk factors for vascular dementia, and studies have shown that age-rage signaling pathways, lipid and atherosclerosis pathways, fluid shear stress, and atherosclerosis pathways are closely related to atherosclerosis. In conclusion, Dihuang Yinzican use several components, multiple targets, and multiple pathways to treat and prevent VaD.

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