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Drug Combination Therapy 2023;5(1):1. https://doi.org/10.53388/DCT20230001

Exploring the mechanism of Guizhi decoction's "Jun-Chen-Zuo-Shi" in treating plant nervous disorders based on weighted network pharmacology and molecular docking techniques

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Author contributions

Xiao-Bin Ye and Qing-Song Liu conceived this study, carried out this study, and drafted the manuscript. Qing-Song Liu and Mi Jing designed the study, collected and analyzed the data. Qing-Song Liu directed the R software drawing and reviewed the article critically. Mi Jing helped accomplish the conception and design of the study. Xiao-Bin Ye and Qing-Song Liu were responsible for this manuscript and reviewed the article critically. All authors read and approved the final manuscript.

Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This study was supported by College Student Research Practice Innovation Project of Chengdu University of Chinese Medicine 2022-2023 (ky-2023002); Graduate Research Innovation Practice Project 2021 (CXZD2021007).

Peer review information

Drug Combination Therapy thanks Yu-Xi Huang and other reviewers for their contribution to the peer review of this paper.

Abbreviations

TCMSP, The Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform; GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Citation

Ye XB, Jing M, Liu QS. Exploring the mechanism of Guizhi decoction's "Jun-Chen-Zuo-Shi" in treating plant nervous disorders based on weighted network pharmacology and molecular docking techniques. *Drug Comb Ther*. 2023;5(1):1. doi: 10.53388/DCT20230001.

Executive editor: Shan-Shan He.

Received: 03 February 2023; **Accepted:** 16 February 2023;

Available online: 22 February 2023.

Abstract

Objective: To explore the mechanism of Guizhi decoction's "Jun-Chen-Zuo-Shi" in treating plant nervous disorders based on network pharmacology and molecular docking methods. **Methods**: The main active ingredients of Guizhi decoction were screened from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), and plant nervous disorder-related targets were screened from the Gene Cards database, OMIM database, and PharmGKB database. The intersection of the two was obtained. The intersection targets were used to draw a protein interaction network and a "Traditional Chinese Medicine-active ingredient-target" network using the STRING database and Cytoscape 3.9.1. The nodes in the "Traditional Chinese Medicine-active ingredient-target" network were weighted according to the "Jun-Chen-Zuo-Shi" principle. Kyoto Encyclopedia of Genes and Genomes, and gene ontology enrichment analysis were performed on the intersection targets. Molecular docking was used to verify the affinity between core targets and key ingredients. **Results**: A total of 225 effective components of Guizhi decoction were screened, among which 127 components could bind to 160 common targets and play a therapeutic role. The common targets were mainly enriched in 2785 gene ontology entries and 189 Kyoto Encyclopedia of Genes and Genomes pathways. Molecular docking confirmed that core targets could spontaneously bind to key ingredients. **Conclusion**: The key targets for the treatment of plant nervous disorders by Guizhi decoction are MAPK1, TP53, RB1, STAT3, MAPK3, MAPK14, etc., which reflect the characteristics of the synergistic mechanism of traditional Chinese medicine with multiple components, targets, and pathways through the regulation of inflammatory signal pathways and oxidative stress processes.

Keywords: network pharmacology; molecular docking; Guizhi decoction; plant nervous disorders; weighted network

Introduction

Vegetative system dysfunction, also known as autonomic dysfunction, is a non-organic disorder caused by dysregulation of the vegetative nervous system, leading to psychological or neurosensory abnormalities that are characterized by prominent subjective symptoms and insignificant objective signs [1]. The external manifestations of autonomic dysfunction are diverse, including not only cardiovascular symptoms , gastrointestinal symptoms, malfunction of sweat glands and temperature control, urinary system symptoms, abnormal pupils, but also sleep and breathing disorders [2, 3]. Traditional Chinese medicine, which combines the four diagnostic methods and syndrome differentiation, has unique characteristics in the treatment of "vegetative system dysfunction" and has the advantages of high safety and good efficacy.

Guizhi decoction originated from the first prescription in the classic of traditional Chinese medicine, Shang Han Lun, and is the ancestor of the prescription. It consists of Guizhi (cinnamon twig), Baishao (white peony root), Shengjiang (fresh ginger), Dazao (Chinese date), and Gancao (honey-fried licorice root). It is a representative prescription that regulates the yin and yang, nourishes the body's defensive and nutritive aspects, and strengthens the body to expel pathogenic factors. Guizhi is the chief herb, and Baishao is the deputy herb. They work together to regulate the body's defensive and nutritive aspects. Ginger and dates help to strengthen the spleen and stomach and promote the circulation of qi and blood. Licorice is an envoy herb that harmonizes the other herbs. In recent years, multiple studies have shown that Guizhi decoction can inhibit excessive sympathetic nerve proliferation by reducing the overexpression of nerve growth factors, increase the activity of the vagus nerve by increasing the expression of ciliary neurotrophic factor, and significantly improve the regulation of autonomic nervous function and the tension of the vagus nerve [4].

The systemic and holistic features of network pharmacology have been widely applied to better explain the system and holistic views of traditional Chinese medicine. However, the simple presentation of the relationship between drugs and targets neglects the crucial aspect of compatibility in Chinese medicine prescriptions, which reduces the reliability of prediction results to some extent. Therefore, this study uses the techniques of network pharmacology and the compatibility theory of traditional Chinese medicine to explore the effective active ingredients and targets of Guizhi decoction in treating vegetative system dysfunction, and employs molecular docking technology to verify the potential mechanism of action of Guizhi decoction in treating vegetative system dysfunction, providing a reference for future related research.

Materials and methods

Screening of effective components and targets of Guizhi decoction

The Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) was used to search for the effective components of each herb in Guizhi decoction, including Guizhi, Baishao, Shengjiang, Dazao, and Gancao. The screening criteria were based on an oral bioavailability ≥ 30% and a drug-likeness ≥ 0.18 [5–7]. This resulted in obtaining the binding targets and effective components of all drugs. UniProt database (https://www.uniprot.org/) was used for validation and after removing duplicates, a total of 322 component targets were obtained.

Screening of targets associated to autonomic neurological disorders

"Vegetative system dysfunction" was used as a screening term to search for disease-related targets in human gene databases (Gene Cards database, https://www.genecards.org/), the Human Mendelian Genetics Database (OMIM database, https://omim.org/), and the Pharmacogenomics and Pharmacogenetics Database (PharmGKB database, https://www.pharmgkb.org/) [8–10]. The targets obtained from each database were combined and used as the target database for the disease. The drug targets and disease targets were intersected, and a Venn diagram was drawn using the R language.

Construction of a "Chinese medicine-ingredient-target-disease" weighted network

Using Cytoscape 3.9.1 software, we constructed a "Chinese medicine-ingredient-target-disease" network for Guizhi decoction in the treatment of vegetative system dysfunction, and obtained the degree values through topological analysis. Considering the compatibility of Guizhi decoction, we carried out a weighted analysis on the "Chinese medicine-ingredient-target-disease" network. According to the reference literature, the specific operation is as follows: the weight of the "Jun Yao" is 2, the weight of the "Chen Yao" is 1, the weight of the "Zuo Yao" is 0.6, and the weight of the "Shi Yao" is 0.4 [11]. The weighted score is obtained by multiplying the number of corresponding degree values in the network by the weight value. If it is a common component of multiple drugs, it is assigned the highest weight.

Construction and visualization analysis of protein-protein interaction network

We selected the STRING database (https://string-db.org/) to construct a protein-protein interaction network, with the species set to "homo sapiens" and the comprehensive score of protein interactions > 0.9. The resulting network was analyzed and visualized using the CytoScape 3.9.1 software, and the "Analyze Network" tool in the software was used to perform topological analysis on the network diagram, and the main target points were selected based on the degree values.

Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis

Using R 4.2.0 software, we performed GO and KEGG pathway enrichment analysis on the intersecting targets [12, 13]. This yielded detailed information on biological processes, molecular functions, cellular components, and pathway analysis [14–16].

Molecular docking of active ingredients and target molecules

We selected the 3D structure model of the target protein from the RCSB PDB database (https://www.rcsb.org/) and searched for and saved the main active ingredients as ligand small molecules in the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). After importing the structure files into PyMol 2.4.0 and Auto Dock Tools software for processing and modification, molecular docking was performed. Finally, PyMol 2.4.0 software was used for visualization and further modification.

Results

Screening of active ingredients in Guizhi decoction and obtaining related target proteins

Using the TCMSP database and searching with oral bioavailability ≥ 30% and drug-likeness ≥ 0.18, the active ingredient composition of Guizhi decoction was obtained, including 7 active ingredients in Guizhi, 13 in Baishao, 5 in Shengjiang, and 29 in Dazao, and 92 in Gancao. Finally, a total of 127 active ingredients in Guizhi decoction were obtained, and after standardization, correction, and deduplication using the UniProt database, 225 target proteins were obtained.

Obtaining target proteins related to plant nervous system disorders

A search was performed in the GeneCards, OMIM, and PharmGKB databases, resulting in 1495, 116, and 2259 related target proteins, respectively. After integration and deduplication of disease targets from these three databases, a total of 3576 disease-related target proteins were obtained. The intersection of the 225 active ingredient targets in Guizhi decoction and the 3576 disease targets related to

plant nervous system disorders resulted in 160 intersection targets, as shown in Figure 1.

Construction of the "Chinese medicine-component-target" network for the treatment of vegetative system dysfunction with Guizhi decoction

The "Chinese medicine-component-target-disease" network was constructed using Cytoscape 3.9.1 software, as shown in Figure 2. The rectangular nodes represent disease-related targets, the spherical nodes represent active ingredients in the medicine, and the thickness of the edges represents the weight of the connections. The key effective components of Guizhi decoction for repairing vegetative system dysfunction were identified as quercetin, isorhamnetin, β-sitosterol, medicarpin, and other components. The weighted network analysis is shown in Figure 3. The key active ingredients in Guizhi decoction for the treatment of vegetative system dysfunction after weighting are quercetin, kaempferol, β-sitosterol, taxifolin, and other components, with the top 20 active ingredients listed in Table 1.

Protein interaction network analysis

The protein interaction network was constructed using CytoScape 3.9.1 software, as shown in Figure 4. The size and color depth of the nodes represent the degree of interaction, making it easier to identify the interactions between various proteins. The top 20 degree values of the target network node characteristics can be found in Table 2, which predicts the potential core target of Guizhi decoction in the treatment of plant nerve disorders, including HSP90AA1, TP53, MAPK3, AKT1, and MAPK1.

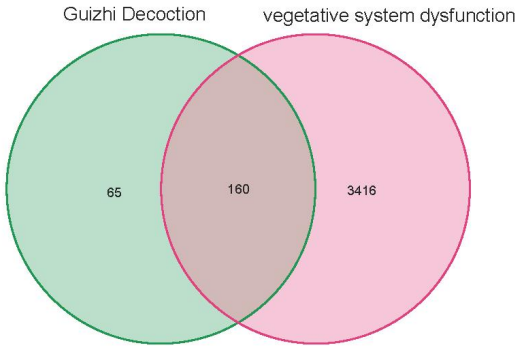

Figure 1 Venn diagram of active ingredients of Guizhi decoction and targets related to vegetative nerve disorders

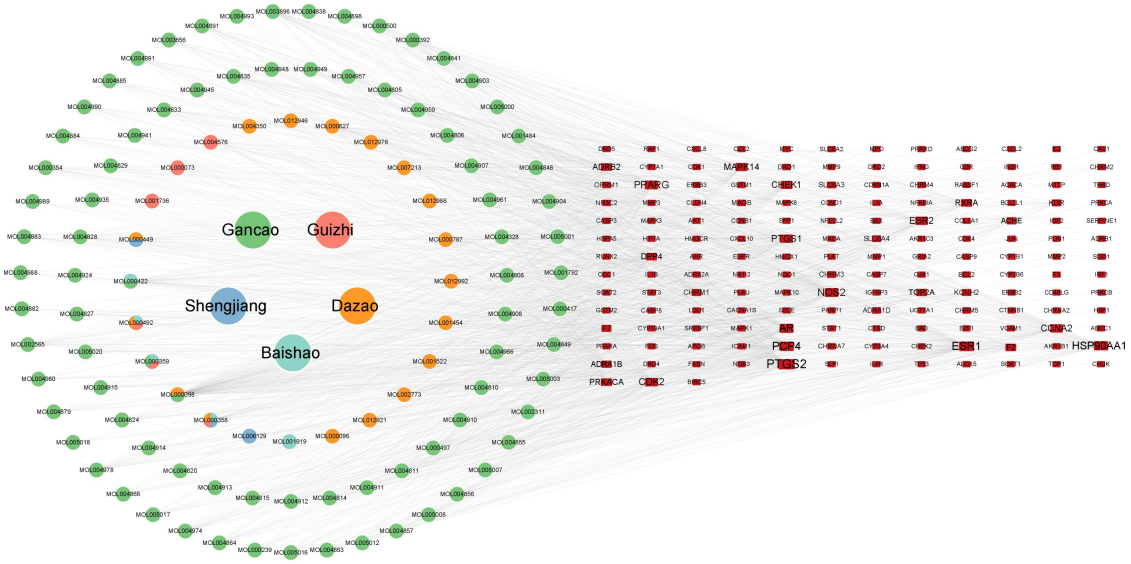

Figure 2 Unweighted network diagram of "Guizhi decoction-ingredients-targets"

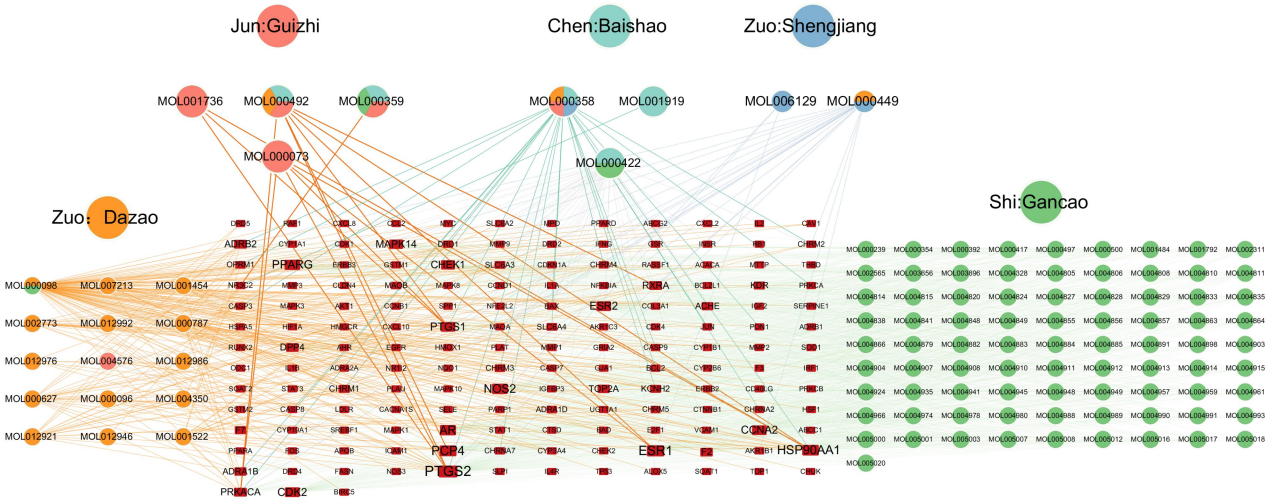

Figure 3 Weighted network diagram of "Guizhi decoction-ingredients-targets"

Table 1 Main active ingredients of Guizhi decoction

ID	Active ingredient	Degree value	Post-weighted score	Source of drugs
MOL000098	quercetin	103	41.2	Dazao, Gancao
MOL000422	kaempferol	41	24.6	Baishao, Gancao
MOL000358	beta-sitosterol	24	24	Guizhi, Baishao, Shengjiang, Dazao
MOL004576	taxifolin	8	16	Guizhi
MOL000492	(+)-catechin	7	14	Guizhi, Baishao, Dazao
MOL000627	Stepholidine	21	12.6	Dazao
MOL000787	Fumarine	21	12.6	Dazao
MOL003896	7-Methoxy-2-methyl isoflavone	31	12.4	Gancao
MOL007213	nuciferin	19	11.4	Dazao
MOL012921	stepharine	19	11.4	Dazao
MOL000449	Stigmasterol	19	11.4	Shengjiang, Dazao
MOL002565	Medicarpin	26	10.4	Gancao
MOL004328	naringenin	26	10.4	Gancao
MOL001522	(S)-Coclaurine	17	10.2	Dazao
MOL002773	beta-carotene	17	10.2	Dazao
MOL000392	formononetin	25	10	Gancao
MOL000073	ent-Epicatechin	5	10	Guizhi
MOL000497	licochalcone a	23	9.2	Gancao
MOL000354	isorhamnetin	22	8.8	Gancao
MOL000500	Vestitol	22	8.8	Gancao

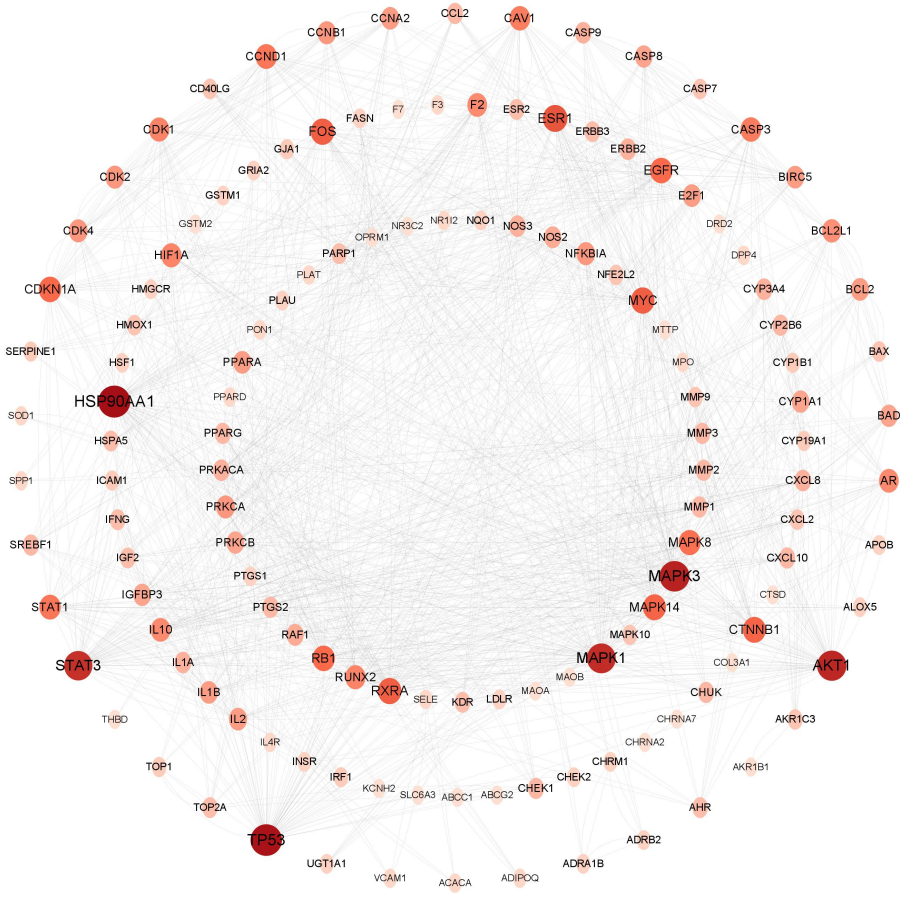

Figure 4 PPI network of Guizhi decoction and its targets in vegetative nervous disorders. PPI, Protein-protein interaction.

Table 2 Node characteristic parameters of the main target network of Guizhi decoction in the treatment of vegetative system dysfunction

Ranking	Target spot	Point degree centrality	Intermediary centrality	Close to centrality
1	HSP90AA1	74	1781.8082	76.3167
2	TP53	72	1885.4204	75.4333
3	MAPK3	66	1356.0178	76.9333
4	AKT1	64	1120.1341	74.5167
5	MAPK1	62	1231.8665	75.6000
6	STAT3	60	1899.4458	72.9000
7	ESR1	46	1151.8882	69.9833
8	FOS	42	725.6141	67.3000
9	MYC	42	272.1131	69.1833
10	RXRA	42	2071.6227	67.3333
11	CTNNB1	40	677.4686	66.6000
12	MAPK14	40	908.4564	67.1333
13	EGFR	38	406.0019	66.8000
14	CDKN1A	38	167.9599	64.4333
15	RB1	38	219.5084	65.6000
16	MAPK8	36	293.7718	64.6833
17	CCND1	34	122.2366	62.4667
18	STAT1	34	377.9849	65.7333
19	CAV1	32	418.5275	63.1833
20	CASP3	32	673.1848	63.7500

GO enrichment analysis results

After completing the GO enrichment step, a total of 2785 GO functional entries (adjusted $P < 0.05$) were enriched, of which 2474 were related to biological processes, including key steps such as response to xenobiotic stimulus, response to nutrient levels, and response to oxidative stress; 99 entries were related to cellular components, mainly membrane region, membrane microdomain, and transcription regulator complex; and 212 entries were related to molecular functions, mainly DNA-binding transcription factor binding, RNA polymerase II-specific DNA-binding transcription factor binding, and transcription coregulator binding. This suggests that the active ingredients in Guizhi decoction may play a role in the treatment of plant neurosis through the biological reactions mentioned above, as shown in Figure 5.

KEGG enrichment analysis results

The KEGG signaling analysis identified 189 pathways involved in the signaling pathways, including disease, inflammatory signaling pathways, viral infection pathways, immune signaling pathways, metabolic steps, and others. Further analysis of the KEGG pathway enrichment results revealed the top 30 pathways (adjust. $P < 0.05$), as shown in Figure 6. Inflammatory signaling pathways such as the TNF signaling pathway and IL-17 signaling pathway play an important role in the treatment of plant nerve disorders with Guizhi decoction.

Molecular docking results

After weighted network analysis, the important components of Guizhi decoction were found to be quercetin, β-sitosterol, and pinusol. The core target proteins were MAPK1, TP53, RB1, STAT3, MAPK3, MAPK14, and MYC. Molecular docking was performed on these target proteins, and the tendency for them to react with each other increases as the energy carried when the ligand and receptor bind to each other decreases and the conformation tends to be stable. This study used a binding energy threshold of ≤ –5.0 kJ/mol for selection. The binding energies of HSP90AA1, AKT1, and quercetin, β-sitosterol, and pinusol were all greater than –5.0 kJ/mol, indicating low reaction tendency, unstable conformation, and weak binding force [17]. The results of molecular docking are shown in Table 3. PyMOL software was used to visualize the docking of TP53, STAT3, MAPK3 with quercetin, β-sitosterol, and pinusol, as shown in Figure 7.

Discussion

The mainstream view in western medicine is that the subcortical autonomic nervous system is controlled by the hypothalamus, which integrates sympathetic and parasympathetic nerves to maintain a relatively stable internal environment in the body. Autonomic nervous system disorders can lead to dysregulation of endocrine, glucose and lipid metabolism, body temperature regulation, mood and sleep mechanisms, and non-organic neurological disorders with somatic symptoms, which are a type of emotional disorder known as “Xu Lao” in traditional Chinese medicine. The name of “Xu Lao” was first seen in Zhang Zhongjing’s “Jin Kui Yao Lue” [18]. It is mostly caused by the decline of organ function and the long-term loss of yin and yang qi and blood, with the pathogenesis summarized as the internal deficiency of yin and yang imbalance and the external weakness of the defense system. In treatment, the focus is not on immediate efficacy, but rather on the overall concept, with the goal of treating the deficiency of the five internal organs, nourishing the spleen and kidney, harmonizing yin and yang, nourishing body fluids and blood, and promoting the positive while eliminating the negative.

Harmonizing the defensive and nourishing systems can be used to improve the imbalance of sympathetic nervous system dominance [19]. Guizhi decoction is not designed specifically for exterior-releasing, but can release exterior while nourishing the defensive system and invigorating the defensive qi, while also benefiting the spleen and liver, and nourishing qi and blood. The efficacy of Guizhi is to promote sweat gland secretion, warm the meridians, assist yang in transforming qi, and relieve muscle tension, while Baishao mainly nourishes blood and consolidates yin, relieves pain and soothes the liver, regulates the defensive and nourishing systems, astringes yin and blood, and harmonizes yin and yang. The combination of these two herbs can harmonize yin, yang, qi, blood, and the defensive and nourishing systems. Baishao and Gancao sour

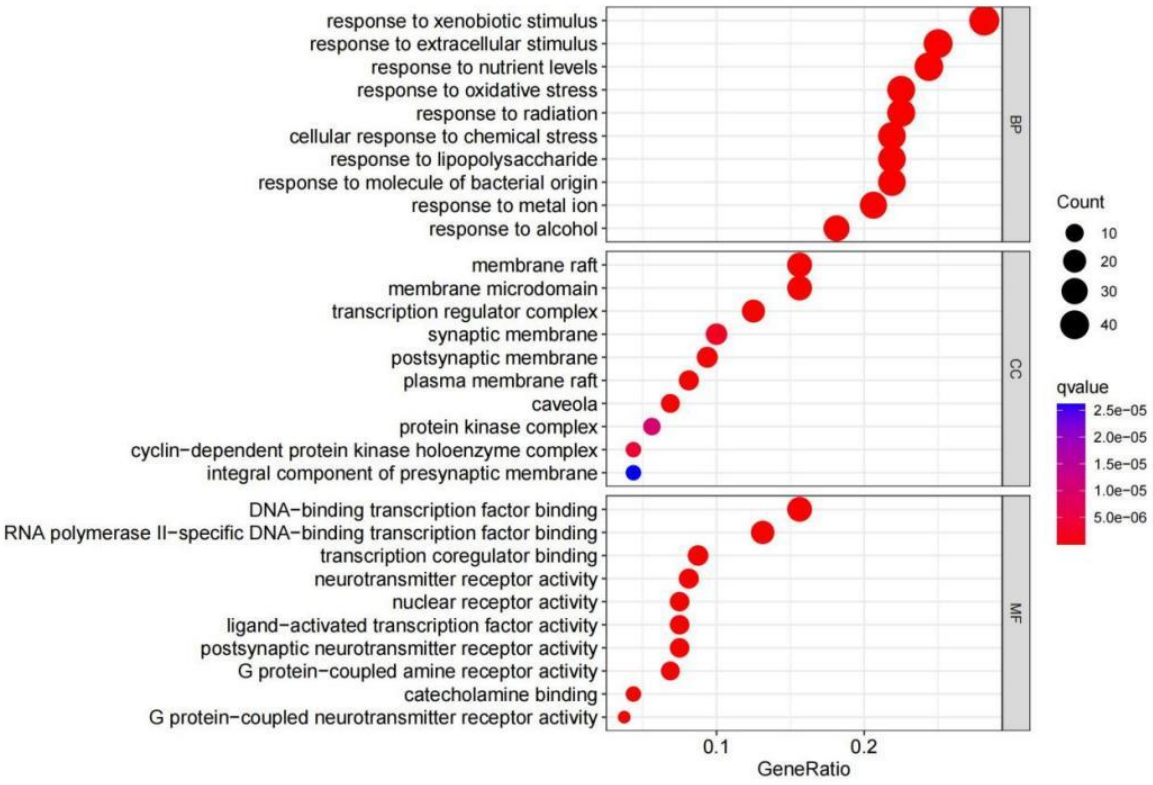

Figure 5 Bubble plot of GO enrichment for targets repaired by Guizhi decoction in plant nerve disorder. GO, gene ontology.

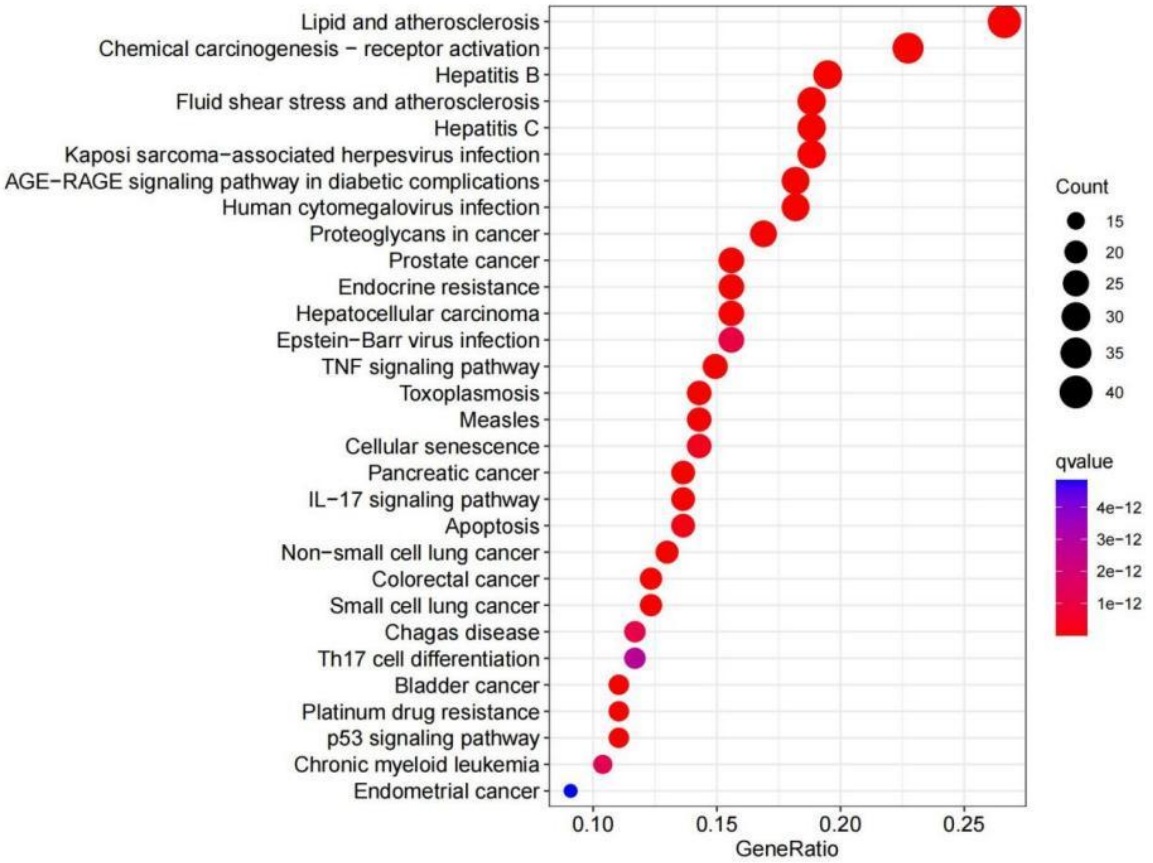

Figure 6 Bubble chart of KEGG enrichment analysis results of targets for treating plant nervous system disorders in Guizhi decoction. KEGG, Kyoto Encyclopedia of Genes and Genomes.

Table 3 Molecular docking results of core active compounds and core protein targets of Guizhi decoction

Target protein	Binding energy/KJ·mol^{-1}		
	Quercetin	Beta-sitosterol	Taxifolin
TP53	–8.3	–8.5	–8.7
MAPK3	–9.8	–7.1	–7.6
MAPK1	–7.8	–6.9	–6.7
STAT3	–7.7	–8.1	–7.2
MYC	–6.2	–5.6	–6.0
RB1	–8.2	–6.6	–7.7
MAPK14	–9.0	–6.6	–6.6

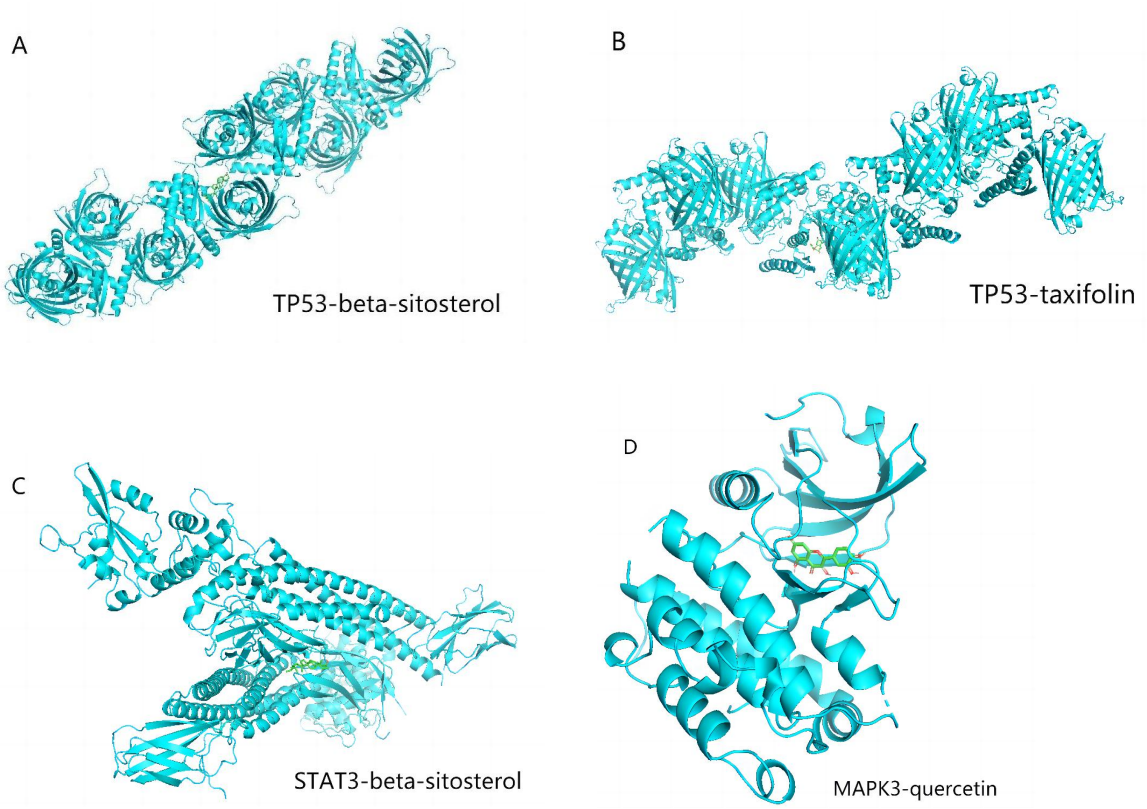

Figure 7 Molecular docking mode of core active compounds and core protein targets of Guizhi decoction. A, beta-sitosterol-TP53; B, taxifolin-TP53; C, STAT3-beta-sitosterol; D, MAPK3-quercetin.

and sweetly supplement yin, one to reach the defensive system, and the other to harmonize spleen yang, while the spleen yang moves and nourishes the defensive yin. Gancao has the function of replenishing qi and regulating the middle, which has a synergistic effect with Guizhi. The two herbs can warm the heart yang and supplement qi deficiency. Shengjiang is warm and soothing to the stomach and can also assist Guizhi in releasing the exterior and promoting sweating. Dazao is sweet and mild, nourishing the middle and supplementing qi, and can promote the nourishing effect of Baishao. The Guizhi decoction formula combines sweet supplementation and bitter purging, sour restraining, and acrid dispersing, which integrates yin and yang, cultivates qi and blood, and harmonizes the defensive and nourishing systems, so that the heart can be nourished and the spirit can be returned [20]. Therefore, Guizhi decoction is an important formula for treating autonomic nervous system disorders. Studies have shown that Guizhi decoction can reverse myocardial collagen remodeling, inhibit inflammatory factors and abnormal sympathetic nervous system remodeling, improve sympathetic nervous system function dominance, and maintain autonomic nervous system balance [21]. Therefore, the mechanism of action of Guizhi decoction in treating autonomic nervous system disorders has great research value.

The key active components of Guizhi decoction for treating vegetative nervous disorders are quercetin, naringenin, β-sitosterol, taxifolin, and catechin, as identified by a weighted network analysis. Quercetin inhibits neuronal oxidative stress and inflammation, and can also modulate sleep-wake cycles through activating GABA receptors and enhancing sedative effects by regulating the serotonin system [22]. Naringenin can reduce inflammation and oxidative stress by affecting Ca^{2+} transport proteins, and has neuroprotective effects by inhibiting smooth muscle cell proliferation, migration, and α-glucosidase activity [23]. β-sitosterol and catechin have anti-inflammatory, antioxidant, and neuroprotective effects [24]. Furthermore, taxifolin has been shown to protect against oxidative neuronal damage in the rat cortex [25]. These results indicate that the therapeutic effects of Guizhi decoction for treating vegetative nervous disorders are the result of the combined actions of multiple

compounds, highlighting the characteristic of multi-component formulations in traditional Chinese medicine.

By analyzing the GO biological enrichment results, it can be found that Guizhi decoction has a specific effect on the response to oxidative stress. Studies have shown that pathological changes such as energy metabolism disorders, disruption of the balance between the sympathetic and parasympathetic nervous systems caused by oxidative stress and mitochondrial dysfunction can lead to vegetative nerve disorders [26]. KEGG enrichment pathways show that inflammation signals such as TNF signaling pathway and IL-17 signaling pathway play an important role in repairing vegetative nerve disorders in Guizhi decoction. TNF is a potential biomarker reflecting the degree of nerve damage and inflammatory response, and IL-17 and its signaling pathways are related to the development of central nervous system diseases and nerve damage [27]. Inflammatory reactions can worsen vegetative nerve disorders [28]. Therefore, it is believed that Guizhi decoction may act on vegetative nerve disorders through inflammatory reactions and oxidative stress.

The final results of molecular docking show that β-sitosterol and pinosylvin have a high affinity with TP53, STAT3, and MAPK family. Studies have found that TP53 and AKT1 induce cell differentiation and apoptosis, regulate the cell cycle, and participate in the inflammatory response process by regulating miRNA expression. TP53 is a tumor suppressor that plays multiple roles in controlling cell cycle checkpoints, apoptosis, and DNA repair [29]. Abnormal TP53 gene expression may lead to the occurrence of malignant tumors. Malignant tumor cells can form or induce the formation of certain cell products, which can cause systemic organ damage, and the nervous system is the most commonly affected system, and autonomic nervous dysfunction is also one of its pathological symptoms [30]. The MAPK signaling pathway is undoubtedly a critical pathway involved in inflammation, immune responses, and cell apoptosis and plays an indispensable role in repairing many types of pathological physiological steps in cells. MAPK1 is the core kinase in the MAPK signaling pathway and undoubtedly plays a vital role in synaptic plasticity, neural activity, and connectivity [31]. It is speculated that Guizhi decoction may intervene in the plant nerve disorder through the above targets, but further experimental verification is needed.

Traditional Chinese medicine's "differentiation and treatment" and "Jun-Chen-Zuo-Shi" embody the idea of network pharmacology's "multi-component, multi-target, and system regulation". However, the current network pharmacology is a static network and cannot reflect the traditional Chinese medicine theories such as drug formulation, the compatibility of Jun-Chen-Zuo-Shi, medication decoction methods and time, which may lead to homogenization in the selection of key components in the disease-specific network [32]. This study combined the theory of Jun-Chen-Zuo-Shi in traditional Chinese medicine to weight the drug-component-disease-target network, aiming to reduce the homogenization effect. After weighting, the key active components for treating plant nerve disorders with Guizhi decoction were identified as quercetin, naringenin, β-sitosterol, pinocembrin, and catechin, with TP53, STAT3, and MAPK as the main targets. The mechanism of action mainly involves oxidative stress, inflammatory pathways, and other aspects, fully reflecting the characteristics of multi-component-multi-target-multi-pathway synergistic effects. This provides a reference for further research on the mechanism of Guizhi decoction's "Jun-Chen-Zuo-Shi" in treating plant nerve disorders.

However, this study still has certain limitations. Firstly, the data in network pharmacology comes from existing databases, and the accuracy and completeness of the data directly determine the reliability of the results. In the future, we can use computer virtual docking and text mining to further verify the database targets. Secondly, the screening of effective components in this study only considers their activity, without considering the issue of the blood-brain barrier. In addition, the evaluation methods for molecular docking in the field of Chinese medicine have limitations, and molecules with high scores may not necessarily be the best ligands. In future research, further animal experiments are needed to verify the weighted network.

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