Accepted Manuscript

Submission Date: 2024-10-20
Accepted Date: 2025-01-07
Accepted Manuscript online: 2025-01-08

Planta Medica

Application of Network Pharmacology in the Treatment of Neurodegenerative Diseases with Traditional Chinese Medicine

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DOI: 10.1055/a-2512-8928

Please cite this article as: Chen Q, Chen G, Wang Q. Application of Network Pharmacology in the Treatment of Neurodegenerative Diseases with Traditional Chinese Medicine. Planta Medica 2025. doi: 10.1055/a-2512-8928

Conflict of Interest: The authors declare that they have no conflict of interest.

This study was supported by the Natural Science Foundation of Hubei Province, 2023AFB677, 2024AFB578, the Intramural Research Program of Liyuan Hospital, Tongji Medical College, Huazhong University of Science and Technology, 2023LYYYGZRP0003, 2023LYYYSZRP0001

Abstract:
In recent years, the incidence of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis, has shown a steadily rising trend, which has posed a major challenge to the global public health. Traditional Chinese Medicine (TCM), with its multi-component and multi-target characteristics, offers a promising approach for the treatment of neurodegenerative diseases. However, it is difficult to comprehensively elucidate the complex mechanisms underlying TCM formulations. As an emerging systems biology approach, network pharmacology has provided a crucial tool for uncovering the multi-target mechanisms of TCM through high-throughput technologies, molecular docking, and network analysis. This paper reviews the advancements in the application of network pharmacology in treating neurodegenerative diseases with TCM, analyzes the current status of relevant databases and technological methods, discusses the limitations in the research, and proposes future directions to promote the modernization of TCM and the development of precision medicine.
Keywords: Neurodegenerative diseases, Traditional Chinese Medicine, Network pharmacology, Therapeutic targets

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Application of Network Pharmacology in the Treatment of Neurodegenerative Diseases with Traditional Chinese Medicine

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Abstract

In recent years, the incidence of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), has exhibited a steadily rising trend, which has posed a major challenge to the global public health. Traditional Chinese Medicine (TCM), with its multi-component and multi-target characteristics, offers a promising approach to treating neurodegenerative diseases. However, comprehensively elucidating the complex mechanisms underlying TCM formulations remains challenging. As an emerging systems biology method, network pharmacology has provided a vital tool for revealing the multi-target mechanisms of TCM through high-throughput technologies, molecular docking, and network analysis. This paper reviews the advancements in the application of network pharmacology in treating neurodegenerative diseases using TCM, analyzes the current status of relevant databases and technological methods, discusses the limitations, and proposes future directions to promote the modernization of TCM and the development of precision medicine.

Keywords: Neurodegenerative diseases, Traditional Chinese Medicine, Network pharmacology, Therapeutic targets

Introduction

Network pharmacology is an emerging discipline initially proposed by the British pharmacologist Andrew L. Hopkins in 2007[1]. This discipline integrates systems biology, network biology, computational simulation, and chemoinformatics to construct a "drug–component–target–disease" network model, aiming to reveal the multidimensional therapeutic mechanisms of complex diseases. Network pharmacology enhances the multi-target and multi-pathway analysis, which is particularly well-suited to research on traditional Chinese medicine (TCM), aligning with the multi-component and multi-pathway therapeutic characteristics of TCM, and compensating for the limitations of traditional single-target pharmacological research[2][3].

Neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS)[4]. These diseases can gradually result in the degeneration of the central nervous system functions, which is manifested as declines in memory, motor control, and cognitive ability[5][6]. For example, AD is identified as the leading cause of dementia in the elderly, while PD is primarily characterized by motor dysfunction[7]. Current treatments mainly focus on slowing down disease progression with medication, while their efficacy is limited and can not cure any of these diseases[8]. For instance, AD treatments mainly focus on slowing down cognitive decline, but their long-term effects remain uncertain, and side effects are common[9]. Emerging therapies such as stem cell therapy and gene therapy have aroused wide attention; meanwhile, lifestyle factors including diet, exercise, and sleep are increasingly recognized for their roles in preventing and managing these diseases[10][11]. With global population aging, the incidence of neurodegenerative diseases is significantly rising, especially in developed countries[12][13]. Although the current treatments can delay disease progression to some extent, the complexity of these diseases presents major clinical challenges. Therefore, the search for more effective treatments has become an urgent priority. The multi-target and

multi-pathway analysis methods of network pharmacology provide novel possibilities for studying neurodegenerative diseases. Numerous effective components and formulations in TCM have already been illustrated through network pharmacology to show their mechanisms of action in treating these diseases [14]. The relationship between digestive diseases and network pharmacology is shown in Figure 1.

Commonly Used Network Pharmacology Databases

The Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP)

TCMSP is a systems pharmacology database developed for TCM research, integrating chemical information, biological activities, targets, and pharmacokinetic parameters of TCM components[16]. Covering 499 herbal medicines, 29,384 compounds, and 3,311 targets, it is widely used for screening multi-component, multi-target drugs and exploring mechanisms of action[17,18]. TCMSP offers tools for identifying potential effective components and predicting their absorption, distribution, metabolism, and excretion (ADME) properties[19,20]. For example, active components in *Scrophularia ningpoensis* were found to modulate 40 targets related to β-amyloid and tau proteins in AD[20]. Effective components in Suanzaoren Decoction were identified to modulate pathways associated with insulin resistance and inflammation, improving AD-related diabetes symptoms[22]. Data from TCMSP also revealed that BM25 (Ershiwuwei Shancorawan) exhibited neuroprotection and anti-inflammatory activities by regulating multiple targets, reducing β-amyloid and tau protein accumulation, and delaying cognitive decline in AD[23]. In addition, TCMSP was used for analyzing the mechanisms of Jianpi Huatan Quyu Decoction in treating chronic heart failure, exhibiting its cardiovascular protection and anti-inflammatory effects by regulating several pathways[24].

The Kyoto Encyclopedia of Genes and Genomes (KEGG) database

KEGG is an integrative bioinformatics database encompassing gene, protein, disease, and metabolism data. Through investigating signal transduction and metabolic pathways, KEGG helps researchers reveal drug mechanisms in complex diseases. In addition, it is widely used in network pharmacology to investigate how TCM components regulate sophisticated pathways. KEGG analysis suggested that active components of *Asparagus officinalis* mitigated fluorosis-induced oxidative stress and inflammation, protecting brain cells through antioxidative and anti-inflammatory mechanisms[25]. Mahboob et al. employed KEGG to identify AD-related genes and pathways, highlighting their roles in apoptosis, neuroinflammation, and oxidative damage[26]. These findings demonstrate the critical role of KEGG in clarifying mechanisms underlying neurodegenerative diseases.

The Search Tool for Interactions of Chemicals (STITCH) database

STITCH integrates interaction data between genes, proteins, and chemicals, including over 2.6 million proteins and 30,000 small molecules from 1,133 species[27]. Through the combination of computational predictions, experimental validation, and literature-based associations, STITCH provides compound-target interaction networks, helping researchers explore multi-target mechanisms of chemicals. This database is widely used in drug discovery and target screening, allowing researchers to predict compound effects in multi-target diseases by examining interactions with multiple protein targets. STITCH identified AD-related differentially expressed genes (DEGs) and several key pathways through enrichment analysis[28]. Olatunde, et al. employed STITCH to construct protein-compound networks, showing multi-target, multi-component mechanisms of TCM in treating complex diseases including diabetes and cancer[29]. STITCH offers APIs and interactive network views for investigating protein-chemical interactions in biological processes[30]. These studies emphasize the value of STITCH in illuminating the multi-target mechanisms of TCM.

The Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database

STRING is a database concentrates on protein-protein interactions, integrating experimental verification and predictive data to provide insights into functional and physical relationships between proteins. It has been widely applied to explore drug targets and construct protein regulatory networks. Using STRING, researchers can identify direct and indirect protein interactions and examine their potential impacts on disease development, making it especially significant for research on multi-target disease mechanisms. In network pharmacology research, STRING is usually used for analyzing interaction networks between effective TCM components and disease-related proteins. By constructing multi-target protein interaction networks, STRING contributes to uncovering the multidimensional regulatory mechanisms of TCM in complex disorders, further elucidating the associated TCM mechanisms and potential therapeutic targets. For example, in a study on *Andrographis paniculata* for the treatment of AD, the authors utilized both STITCH and STRING databases to construct protein-compound interaction networks, identifying key AD-related pathways including NF-κB and PI3K-Akt. Experimental verification showed that effective compounds from *Andrographis paniculata* significantly lowered inflammatory proteins including PTGS2 (COX2) and BACE1, consequently suppressing the progression of AD[31]. This study underscores the importance of STRING in unveiling the multi-target mechanisms of TCM.

PubChem

PubChem is a public chemical information database established by the U.S. National Institutes of Health. It integrates chemical structures, biological functions, properties, and pharmacological effects, covering millions of compounds and experimental bioactivity data. As one of the largest open-access chemical databases, PubChem exerts an essential role in drug discovery, compound screening, and bioactivity analysis, especially for drug development and repositioning. In network pharmacology, PubChem is widely used to obtain detailed chemical information and analyze interactions with disease-related genes or proteins in combination with other databases. In addition, it enables large-scale compound screening

and evaluation of their therapeutic potential. For example, in an AD study, PubChem was used to screen AD-related compounds, and network pharmacology revealed compound-target gene interactions, exhibiting their role in reducing neuroinflammation and mitigating neural injury[32]. Similarly, PubChem was used to identify ALS-related compounds and investigate their impacts on ALS pathology[33]. These studies underscore PubChem's importance in comprehending complex disease mechanisms.

ChEMBL

ChEMBL, developed by the European Bioinformatics Institute, concentrates on bioactive compounds and offers extensive data on drugs and their targets[34]. With millions of bioactivity data entries for small molecules, it is widely used for drug discovery and target prediction, enabling researchers to explore drug-target interactions and screen potential drug candidates. In network pharmacology, ChEMBL provides bioactivity data for compounds and protein targets, supporting the analysis of interactions between small molecules or TCM components and disease-related genes. This helps uncover multi-target TCM mechanisms and advances network pharmacology-based drug development. ChEMBL also promotes research on neurodegenerative diseases by exploring multi-target compound bioactivity, particularly through datasets of animal disease models and phenotypic endpoints for translational medicine research[35].

Application of Network Pharmacology in TCM Research

Network Pharmacology Research Techniques

Network pharmacology combines the updated approaches like high-throughput technology, molecular docking and systems biology to assist researchers in analyzing the multi-target, multi-pathway TCM mechanisms. Among them, high-throughput technology can process a variety of samples concurrently, rapidly producing massive biological data, like protein interactions, gene expression profiles, or metabolite changes. It has been frequently adopted for screening effective TCM components and the possible associations with disease

targets. For instance, in a study concerning AD, high-throughput technology was used to analyze different TCM compounds, and finally, multiple effective components with therapeutic effects were identified [36]. Molecular docking can simulate the drug molecule-target protein binding patterns, and predict the corresponding interactions. It contributes to validating binding sites and action mechanisms of TCM components with corresponding targets. For example, in a study regarding PD, molecular docking was used to discover the effective binding of ligustrazine to proteins associated with PI3K-Akt pathway, demonstrating the neuroprotection[37]. Systems biology integrates multi-level biological data (including proteins, genes, and metabolites) to illustrate interactions inside the complicated biological networks. In network pharmacology, it is applied to analyze the multi-dimensional mechanisms of TCM formulations. The combined application of these techniques can help researchers uncover the multi-target mechanisms of TCM formulations in treating complex diseases, transforming complex network interactions into visualized networks, and facitating the modernization of TCM and the development of precision medicine.

Steps in Network Pharmacology Research and Construction of Biological Networks

The typical steps in network pharmacology research are as follows. At first, bioactive components are screened from TCM. Second, the potential targets of these components are identified using relevant databases. Third, a "drug–component–target–disease" network model is constructed based on these targets and components, and network analysis is performed to identify key regulatory nodes[38]. Finally, these results should be validated by conducting biological experiments, aiming to ensure the reliability of the research. The construction and analysis of the network model are central to the research process, as they can reveal the complex mechanisms of TCM formulations and provide theoretical support for new drug development. Figure 2 shows the flowchart of network pharmacology analysis.

Applications of Network Pharmacology

Through systematic analysis using network pharmacology, researchers can predict new indications for TCM beyond its therapeutic effects. This process depends on the constructed biological networks. Relevant signaling pathways and targets can be identified. For instance, by examining the associations of TCM effective components with disease pathways, the possible therapeutic efficacy of TCM can be predicted under the novel pathology condition, which provides important support for new indication discovery[39]. Researchers can explore the multi-target effects of TCM formulations, screen for quality markers of TCM, further elucidate the mechanisms of TCM components, assess the safety of TCM, and explore the synergistic effects between TCM and modern drugs. These research directions can comprehensively enhance the scientific foundation and clinical application value of TCM, thereby promoting the modernization of TCM.

Finally, these results need to be validated through biological experiments to ensure the reliability of the study. Experimental validation is an indispensable part of network pharmacology research, as the results predicted by models are obtained solely through computational tools. Their accuracy and biological relevance need to be further confirmed. Common validation methods include cell experiments, animal studies, and molecular biology techniques. For example, in a study performed on the inhibitory potential of Lasunadya Ghrita (LG) extract against amyloid-beta (Aβ) aggregation in AD, the anti-AD potential of the water extract of Lasunadya Ghrita (LGWE) was explored. However, there existed insufficient logical connection between network pharmacology and experimental validation in the antioxidant mechanism. Although the study emphasized that LGWE's complex components may regulate antioxidant pathways (such as Nrf2, HO-1, SOD1) through multiple targets, it did not systematically employ network pharmacology tools to predict specific target genes and pathway associations, causing a lack of solid theoretical foundation. While the experiments demonstrated the phenomenon that LGWE inhibited Aβ-induced ROS generation, deeper verification on predicted targets, such as Nrf2 or mitochondrial

dysfunction, was not conducted, therefore leaving the mechanistic study at a superficial level. As a key tool for multi-target therapy, network pharmacology predictions require experimental validation to close the loop; otherwise, logical gaps may occur. The lack of network pharmacology integration and the limitations of experimental validation in this study weakened the comprehensive understanding of LGWE's antioxidant mechanisms. Moreover, research should integrate target prediction and validation tools, clarify the relationship between active components and antioxidant pathways, as well as supplement experiments related to antioxidant pathways to enhance the logical integrity and practical utility of the study.

Application of Network Pharmacology in Neurodegenerative Diseases

Application of TCM in AD

AD is a major neurodegenerative disorder affecting the elderly population globally, with the primary symptoms including memory loss, cognitive decline, and abnormal behavior. Approximately 50 million people globally suffer from dementia, and 60%–70% of them develop AD. The number is expected to reach 100 million by 2050[41]. With the acceleration of global aging, the incidence of AD exhibits a significantly increasing trend, making it urgent to develop new treatment methods[42]. The pathological mechanisms of AD are complex, and are suggested to involve β-amyloid (Aβ) aggregation, neuroinflammation, oxidative stress, and neuronal apoptosis[43]. Although acetylcholinesterase inhibitors and NMDA receptor antagonists are currently the main therapeutic agents for the treatment of AD, they only temporarily alleviate symptoms and are accompanied by side effects, without halting disease progression[44]. Therefore, it is urgently needed to develop multi-target treatments for AD. Recently, due to its multi-component and multi-target characteristics, TCM has attracted widespread attention in AD treatment. Through network pharmacology analysis, researchers predicted the potential active compounds and targets in the Hengqing II formula for treating AD, exerting the anti-inflammatory, antioxidant, and neuroprotective effects mainly by

regulating signaling pathways such as PI3K-Akt, NF-κB, and MAPK[45]. In another study, network pharmacology analysis was used to identify 30 candidate targets related to AD for the compound Paeoniflorin, which were enriched into the oxidative stress and inflammation pathways. Moreover, the key targets identified included Nrf2 (encoded by NFE2L2) and TLR4, which were closely associated with oxidative stress and neuroinflammation. *In vivo* experiments also confirmed the neuroprotective effects of Paeoniflorin on AD[46]. Network pharmacology analysis was conducted to identify 15 active compounds and 135 potential targets in the QZZD formulation (Qin-Zhi-Zhu-Dan). *In vitro* experiments demonstrated the impact of this formulation on alleviating neuroinflammation and slowing down neuronal death, exerting significant neuroprotective effects against AD[47]. Qiug et al. used network pharmacology and molecular docking techniques to explore the potential mechanisms of Acorus calamus in AD treatment, identifying four active components associated with multiple AD-related targets (e.g., AKT1 and MAPK14) that regulated the oxidative stress and anti-inflammatory pathways. Molecular docking further validated the binding abilities of these components to their targets, indicating the neuroprotective potential of Acorus calamus in AD[48]. Soleimani Zakeri et al. constructed protein-protein interaction networks to explore the gene complexes in AD and proposed drug repositioning candidates. Through bioinformatics analysis, they identified several key AD-related gene pathways and recommended two new potential treatments, namely, raloxifene and gentian violet[49]. These studies demonstrate the scientific significance of TCM in AD treatment, and the application of network pharmacology combined with *in vitro* experimental validation provides a better understanding of the multi-component, multi-target, and multi-pathway therapeutic properties of TCM. In addition, this offers a theoretical basis and support for future drug research and development for AD.

Application of TCM in PD

PD is a common neurodegenerative disease that primarily affects the elderly. Globally, the incidence of PD significantly increases with age, and it affects approximately 1% of people aged over 60 years and up to 3% of people over 80 years old[50]. With the global population aging, the incidence of PD is expected to rise further in the future[51]. The pathological mechanisms of PD are the progressive loss of dopaminergic neurons in the substantia nigra and the formation of Lewy bodies, which may be caused by abnormal aggregation of α-synuclein[52]. Mitochondrial dysfunction, oxidative stress, neuroinflammation, and immune responses are key factors for the pathogenesis of PD [53]. Existing treatments, including dopamine replacement therapy (like levodopa), dopamine receptor agonists, and MAO-B inhibitors, can temporarily relieve motor symptoms. However, as the disease progresses, the drug efficacy gradually decreases, and long-term use of these drugs may lead to side effects including motor complications[54]. Against this backdrop, developing the multi-target treatments that can delay neurodegeneration and protect dopaminergic neurons has become a research focus. Network pharmacology can provide vital support for the multi-target, multi-pathway TCM treatment for PD. For example, Liu et al. used network pharmacology to identify effective components and PD-related targets in Tianqi Pingchan Granules (TQF), discovering that these targets were mainly related to inflammatory responses through GO and KEGG pathway analyses. *In vivo* experiments showed that TPG could regulate gut microbiota, reduce peripheral inflammatory factors, inhibit microglial activation, alleviate neuroinflammation, and delay PD progression[55]. Wu et al. utilized transcriptome sequencing to identify DEGs between PD patients and healthy individuals. Combined with network pharmacology analysis, the authors determined the relationship between active compounds in Cordyceps sinensis capsules and PD targets, and constructed a "compound-disease-target" network. Quercetin and kaempferol, identified as the major anti-PD effective components, were found to exert anti-neuroinflammatory and neuroprotective effects by binding to key targets including matrix metalloproteinase-9 (MMP9)[56]. Another

study employed network pharmacology combined with molecular docking analysis to analyze 97 effective components of ginseng and 168 potential PD-related targets. Based on their experimental results, these targets were involved in regulating biological processes such as cellular metabolism and apoptosis, while further analysis indicated that the MAPK signaling pathway and AGE-RAGE signaling pathway might be associated with the treatment mechanisms for PD[57]. Wu et al., through network pharmacology, identified that the IL-17 signaling pathway and neuroactive ligand-receptor interaction were the key targets. *In vivo* experiments showed that DiHuangYin (DHY) reduced peripheral inflammation and central nervous system inflammation, thus protecting neurons[58]. Lin et al., by using network pharmacology and molecular docking techniques, revealed the main effective components of Liuwei Dihuang Wan, including quercetin, β-sitosterol, and kaempferol, which were closely related to multiple targets (such as AKT1, VEGFA, and IL6). Experimental studies indicated that Liuwei Dihuang Wan had potential neuroprotective effects against PD via the multi-target, multi-pathway mechanisms, particularly in regulating neuronal death, oxidative stress, and inflammatory responses[59]. The above results scientifically confirm the multi-target, multi-pathway mechanisms of TCM in PD treatment. Integrating network pharmacology and *in vitro* experiments can shed novel light on the complicated mechanisms and establish a solid basis for developing and applyingPD-related drugs.

Application of TCM in Huntington's Disease HD

HD refers to the uncommon inherited neurodegenerative disease, its global incidence is approximately 5–10/100,000 individuals, and it usually occurs in middle age[60]. HD shows the representative characteristics of involuntary movements, psychiatric symptoms and cognitive decline. The pathology includes mutant huntingtin protein aggregation, resulting in excessive neuronal apoptosis and serious central nervous system injury[61]. There are few treatments for HD, which mainly focus on managing its symptoms including applying antipsychotics in controlling psychiatric and motor symptoms. Nevertheless, these treatments

can not prevent disease progression and may lead to significant adverse reactions[62]. Therefore, developing treatments that can delay and reverse HD pathology is becoming the research focus. Network pharmacology offers a novel research direction to explore whether TCM can be applied to treat HD. Using the multi-target, multi-pathway methods can uncover the effects of TCM components on regulating inflammation and neuroprotection. HDNetDB database combines HD-related gene expression profiles and molecular interactions, contributing to exploring the complicated molecular mechanisms underlying HD and accelerating systematic study on HD[63]. For example, network pharmacology studies have illustrated interactions among several TCM effective components and HD-related biological targets, especially those related to apoptosis and neuroprotection pathways like PI3K/Akt, NF-κB and MAPK. Molecular docking and QSAR models can be used to predict the possible effects of TCM components on treating HD, aiming to provide a theoretical foundation for the multi-target application in the clinic [64]. Likewise, according to network pharmacology research, natural compounds can regulate critical targets of HD, particularly via the gene-protein interaction networks, which can investigate NF-κB and PI3K/Akt pathways within neuroinflammation. The above compounds are verified with neuroprotection through molecular dynamics simulations and *in vitro* experimental verification[65]. For instance, network pharmacology research suggests interactions of several TCM effective components with HD-related biological targets, especially by establishing the drug-target-disease networks, contributing to exploring the efficacy of TCM chemical components in treating diseases by modulating several pathways including MAPK and PI3K/Akt[66]. Therefore, integrating network pharmacology with *in vitro* experimental verification can validate the multi-component, multi-target TCM mechanisms in treating HD. The method provides a novel direction for analyzing the effect of TCM on treating HD and lays a solid foundation for drug development and clinical application [67].

Application of TCM in ALS

ALS represents the uncommon neurodegenerative disorder, whose incidence is around 1.9/100,000 individuals annually in the world. Patients usually die in 2–5 years after being diagnosed[68]. It is pathologically characterized by progressive motor neuronal degeneration and death, which causes muscle weakness and atrophy, finally leading to respiratory failure-related death [69]. ALS has a complicated etiology, which involves different pathological processes, like mitochondrial dysfunction, glutamate toxicity, neuroinflammation and oxidative stress[70]. At present, although there are few treatments available for ALS, and just two drugs are approved by the FDA (riluzole and edaravone) for delaying its progression, they can achieve limited therapeutic effects and are incapable of reversing neuronal injury[71]. Therefore, it is vital to search for multi-target treatments. Network pharmacology provides novel avenues for the application of TCM in treating ALS. For example, Li et al. employed network pharmacology for analyzing the multi-target, multi-pathway mechanisms of Bushen Jianpi(BSJP) formulation in mitigating ALS symptoms like muscle atrophy, hypoxia-related conditions and oxidative stress. As reported in a later randomized, double-blind, multicenter clinical study, BSJP significantly improved lung capacity and muscle strength among ALS cases, and delayed ALS progression with no significant adverse reactions. This formulation may bring benefits by modulating the level of vitamin D3 in serum and recovering renal and hepatic functions[72]. Lin et al. analyzed the multi-target mechanisms of effective components in BSJP using network pharmacology analysis. Their findings suggested that effective components like kaempferol and quercetin were vital for neuroprotection by modulating mitochondrial activity, anti-inflammatory response, and oxidative stress. Clinical studies indicated the therapeutic effect of this formulation on mitigating ALS symptoms, especially for alleviating neuronal injury and delaying ALS progression[73]. Through molecular docking and network pharmacology analyses, the

possible mechanisms by which nux vomica treated ALS were explored. The main components were examined and shown to mitigate oxidative stress and neuroinflammation in ALS through pathways including Ras, MAPK and PI3K-Akt. Moreover, *in vitro* experiments demonstrated that nux vomica components showed great affinity to key targets, demonstrating that nux vomica displayed neuroprotection in ALS and might be developed as the anti-ALS treatment[74]. Using molecular docking and network pharmacology analyses, Wu et al. revealed that the major components of the Rehmannia glutinosa, including glutathione and phytosterols, interacted with targets such as PTGS2, ESR1, and PPARG to regulate neuroprotection and oxidative stress pathways, especially via estrogen receptor pathway. This reduced glutamate toxicity and neuroinflammation, suggesting the potential of Rehmannia glutinosa in the treatment of ALS [75]. Network pharmacology and molecular docking techniques were used to explore the therapeutic potential of the TCM "Rehmannia glutinosa" in ALS. This study revealed its possible therapeutic mechanisms by analyzing the interactions of the effective components of Rehmannia glutinosa with different ALS-related targets and signaling pathways [76]. Noor et al. demonstrated that constructing the multi-level networks between drug components, targets, and diseases using network pharmacology helped reveal the multi-target properties of herbs. This multi-target, multi-pathway feature was especially vital for the treatment of multifactorial diseases such as ALS. The study also highlighted the immense potential of TCM and Ayurvedic herbs in treating complex diseases including ALS[77]. Another study introduced network pharmacology as a new "green" strategy, and demonstrated how predicting the behaviors of metabolites revealed the mechanisms of natural products as drug candidates. Through the combination of omics data, computational modeling, and chemical biology, this multidisciplinary approach contributed to elucidating the multi-target actions of drugs and guided drug discovery, especially in complex multi-component natural medicines, revealing their potential in ALS treatment[78]. Collectively, these studies demonstrate the significant multi-target, multi-pathway effects of TCM on

treating ALS. The application of network pharmacology combined with *in vitro* experiments can provide a scientific basis for fully uncovering the therapeutic mechanisms of TCM and open novel avenues for developing new drugs for ALS treatment.

Application of TCM in Multiple Sclerosis (MS)

MS is a chronic central nervous system disease, which primarily affects young adults, especially women. Approximately 2.5 million people worldwide suffer from MS. The disease is characterized by demyelination within the central nervous system, causing various neurological dysfunctions, including motor impairment, sensory abnormalities, and cognitive decline[79]. The pathogenesis of MS is complex, involving immune system abnormalities, neuroinflammation, and axonal damage[80]. Existing treatments for MS mainly depend on immunomodulatory drugs such as interferon-β and corticosteroids. While these drugs can delay disease recurrence, they cannot stop its progression, and long-term use may cause severe side effects[81]. Therefore, developing multi-target therapeutic strategies, particularly those based on natural compounds, has been a research focus. Noor et al. constructed a drug-target-disease network, finding that the key effective components of Yishen Daluo decoction included quercetin and kaempferol. Protein-protein interaction network analysis revealed that IL-6 and AKT1 were the key targets. *In vitro* experiments suggested that Yishen Daluo decoction reduced LPS-induced inflammatory responses, revealing its potential therapeutic mechanisms in MS[82]. To sum up, integrating network pharmacology and *in vitro* experimental verification can efficiently discover TCM targets for MS treatment, and provide the targeted treatments. The integrated method illustrates the TCM mechanisms in MS treatment and establishes a solid foundation for individualized treatments and drug development. The network pharmacology of TCM in treating neurodegenerative diseases is presented in Table 2.

Limitations and Improvement Directions of Network Pharmacology

Although network pharmacology has shown significant potential in elucidating the complex mechanisms of TCM in treating neurodegenerative diseases, its development still faces the following challenges. Firstly, existing databases suffer from outdated information and limited coverage, making it difficult to comprehensively reflect the multidimensional characteristics of Chinese herbal medicine. Future research should concentrate on dynamically updating and expanding databases to incorporate omics data such as genomics, proteomics, and metabolomics, while also enhancing data standardization to guarantee the integrity and consistency of compound information.

Secondly, most network pharmacology models are static and fail to simulate the dynamic processes of drugs *in vivo*, particularly in multi-component TCM formulas where time-dependent effects and synergistic actions have not been fully explored. The introduction of dynamic pharmacokinetic models, time-series analysis, and multi-scale modeling will help to uncover the metabolic pathways and dynamic synergistic effects of TCM components *in vivo*, therefore providing more accurate theoretical support for multi-target therapies.

Moreover, the variability of TCM formulations, which results from differences in origin, processing methods, and storage conditions, can lead to discrepancies in model predictions. Standardized analysis using chemical fingerprinting and metabolomics techniques, integrating variability data, and establishing dynamic adjustment mechanisms in models can effectively improve the reliability and applicability of predictions.

Insufficient experimental validation is another limiting factor. The lack of experimental support for computational predictions may restrict their clinical translation value. Combining efficient experimental systems such as organoid models, microfluidic chips, as well as cell experiments and animal models, can provide multi-layered validation of network pharmacology predictions, providing strong support for practical applications.

Finally, personalized medicine is a vital direction for future development. Current models have not adequately considered the impact of individual genetic differences on

responses to TCM treatments. Future research should integrate genomics and epigenetics to build personalized models, enabling the development of precise treatment plans that enhance efficacy and minimize adverse reactions. By integrating multi-omics data, dynamic modeling, and efficient experimental validation, network pharmacology is poised to further advance the modernization of TCM and precision medicine, thus offering innovative solutions for neurodegenerative diseases.

Acknowledgments

The authors are thankful for the support provided by the Natural Science Foundation of Hubei Province (Grant Nos. 2023AFB677, 2024AFB578) and the Intramural Research Program of Liyuan Hospital, Tongji Medical College, Huazhong University of Science and Technology (Grant Nos. 2023LYYYGZRP0003, 2023LYYYSZRP0001). We confirm that the funding sources had no role in the study design, data collection, analysis, interpretation, or manuscript preparation.

Conflict of Interest Statement

The authors declare that they have no commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

Q.C: Writing–review and editing, Supervision, Project administration, Funding acquisition, Conceptualization.G.H.C:Visualization, Software, Methodology, Writing–original draft, Investigation.Q.Y.W: Writing–originaldraft, Data curation. Investigation, Funding acquisition .

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Legends for Figures

Fig.1. Relationship between digestive diseases and network pharmacology.

Fig.2. Flowchart of network pharmacology analysis.

TABLE1. Public databases related to TCM network pharmacology.

Type	Name	Description	Website of database or tool
TCM related database	TCMSP	A database that can retrieve and screen for the key TCM compounds and target information.	http://tcmspw.com/tcmsp.php
Drug related database	KEGG	A database for understanding the high-level functions and utilities of biological systems, such as cells and organisms.	https://www.genome.jp/kegg/
Drug related database	STITCH	A database containing the known and predicted chemical compounds and protein interactions.	http://stitch.embl.de/
Target related database	STRING	A database of known or predicted interactions between proteins.	https://string-db.org/
Drug related database	PubChem	A free chemistry database maintained by the National Center for Biotechnology Information (NCBI), which provides information on chemical molecules and their activities in biological assays.	https:// pubchem.ncbi.nlm.nih.gov/
Drug related database	ChEMBL	A database integrating bioactive substances that possess drug-like characteristics.	https://www.ebi.ac.uk/chembl

TABLE2. Network pharmacology of TCM in treating neurodegenerative diseases.

Reference	Disease	Formulas and Herbs	Subjects	Main Compounds	Main Target	Main Signaling Pathway	Outcome
[46]	AD	***Paeoniflorin***	*In vivo* experiment	Paeoniflorin	Multiple targets	PI3K-AKT	Demonstrates neuroprotective effects
[47]	AD	Qinqi Zhudan Formula	Network pharmacology analysis	Multiple effective components	Multiple targets	PI3K-AKT	Enhances neuroprotective effect of the formulation
[48]	AD	***Arisaema Rhizome***	Molecular docking in network pharmacology	Active compounds of Arisaema Rhizome	Multiple targets	Multiple pathways	Reveals the potential therapeutic effects of Arisaema Rhizome
[49]	AD	Drug repurposing strategy	Protein-protein interaction networks	Multiple drugs	Multiple protein networks	Protein interaction pathways	Identifies the potential therapeutic drugs for AD
[55]	PD	Tianma Pingchan Granules	Rat model	Multiple effective components	Neural junction-related pathways	PI3K-AKT	Alleviates symptoms related to PD

[56]	PD	Jichuan Decoction	Transcriptome analysis	Multiple effective components	Key genes	Critical signaling pathways	Reduces inflammation and neurodegenerative factors

TABLE2. (Continued) Network pharmacology of TCM in treating neurodegenerative diseases.

Reference	Disease	Formulas and Herbs	Subjects	Main Compounds	Main Target	Main Signaling Pathway	Outcome
[57]	PD	Ginseng	Neuron cell model	Ginseng extracts	Multiple targets	PI3K-AKT	Inhibits apoptosis and protects neurons
[58]	PD	*Dihuang Decoction*	Animal model	Multiple active ingredients	Neuroprotective targets	NF-κB	Shows significant neuroprotective effects
[59]	PD	*Liuwei Dihuang Pills*	Neuron cell model	Components of Liuwei Dihuang Pills	Multiple targets	Inflammation pathway	Reduces inflammation and inhibits apoptosis
[63]	HD	TCM Compound Formula	Network pharmacology analysis	Multiple compounds	Multiple targets	Inflammation pathways	Reduces inflammation and improves symptoms

[64]	HD	Novel TCM formula	Molecular docking and *in vitro* experiments	Multiple compounds	Multiple targets	Inflammation and neuroprotection pathways	Demonstrates significant neuroprotective effects
[65]	HD	Natural compounds from Dictyostelium discoideum	Neuronal cell model	Multiple compounds	Multiple targets	Apoptosis and inflammation pathways	Demonstrates significant cell-protective effects

Reference	Disease	Formulas and Herbs	Subjects	Main Compounds	Main Target	Main Signaling Pathway	Outcome
[66]	HD	Active components of TCM	Network pharmacology analysis	Multiple TCM components	Multiple targets	Neuroprotection and apoptosis pathways	Shows strong neuroprotective effects
[72]	ALS	Bu-Shen-Jian-Pi Decoction	Neuron and muscle cell models	Multiple effective components	Multiple targets	Oxidative stress and inflammation pathways	Relieves hypoxia and muscle atrophy, improves motor function
[73]	ALS	Bu-Shen-Jian-Pi Decoction	ALS rat model	Multiple components	Multiple targets	Neuroinflammation and oxidative stress pathways	Delays disease progression and improves motor function

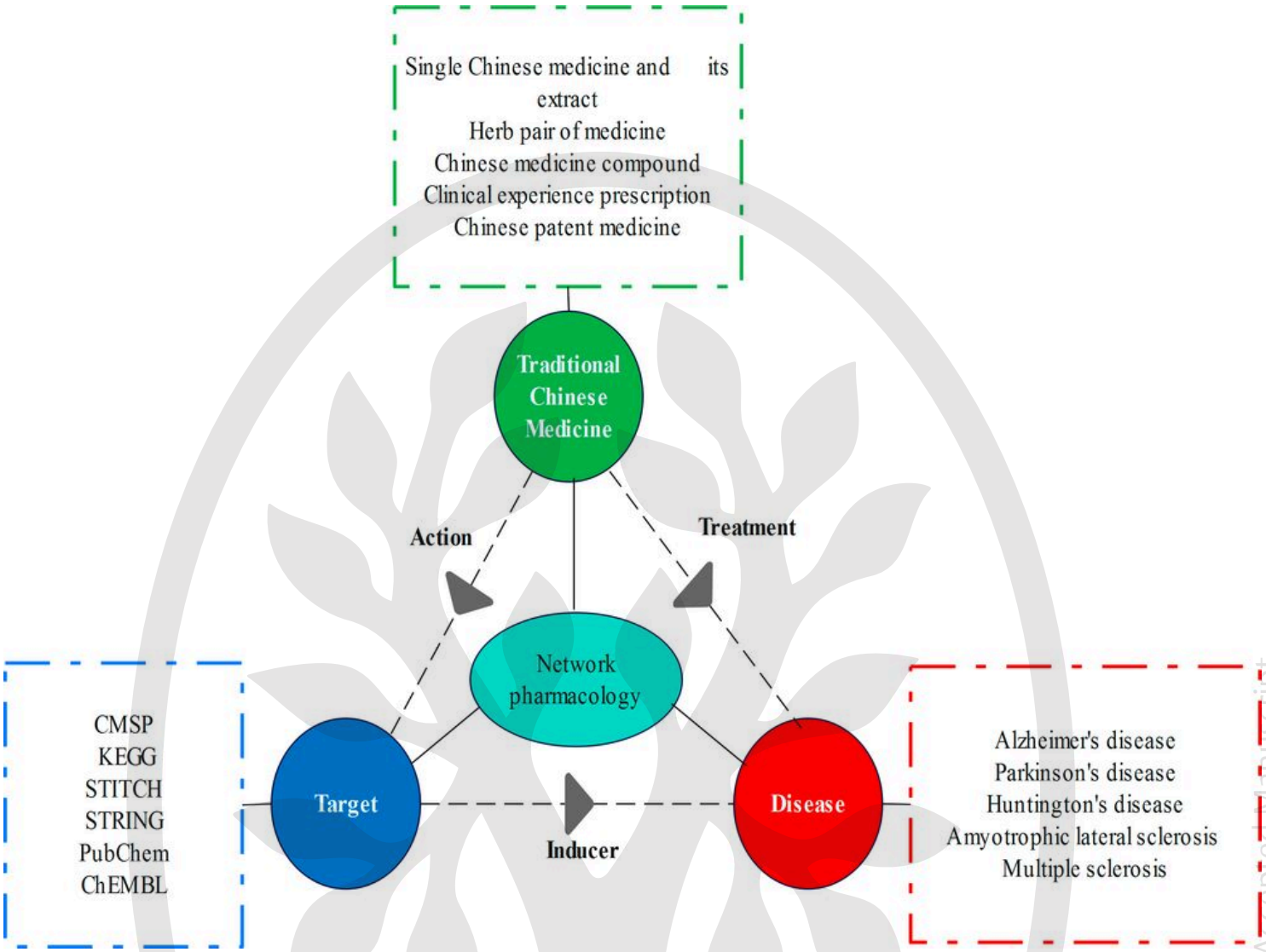
[74]	ALS	*Strychnos Nux-vomica*	Neuron cell model	Extract of Strychnos Nux-vomica	Multiple targets	Neuroinflammation pathways	Demonstrates significant neuroprotective effects
[75]	ALS	*Prepared Rehmannia*	Cell model	Extracts of Prepared Rehmannia	Multiple targets	Inflammation and apoptosis pathways	Inhibits apoptosis and inflammation significantly

TABLE2. (Continued) Network pharmacology of TCM in treating neurodegenerative diseases.

[81]	MS	Yishen Daluo Decoction	Immune cell model and animal experiments	Multiple components	Multiple targets	PI3K-AKT	Reduces inflammation and protects neurons

TABLE2. (Continued) Network pharmacology of TCM in treating neurodegenerative diseases.

Reference	Disease	Formulas and Herbs	Subjects	Main Compounds	Main Target	Main Signaling Pathway	Outcome
[82]	MS	*Nigella sativa*	Neuroinflammation model	Extract of Nigella sativa	Multiple targets	Immune pathways	Demonstrates strong anti-inflammatory effects, and reduces inflammatory cytokines



Flowchart of network pharmacology