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Integrated Network Pharmacology and Molecular Docking to Explore the Mechanisms of Ningshen Wendan Decoction in the Treatment of Schizophrenia

ABSTRACT

Objective: Schizophrenia (SCZ) is a prevalent chronic mental disorder characterized by a high recurrence rate and significant disability. Currently, no satisfactory pharmacological treatments have been identified. Although Ningshen Wendan decoction (NSWDD) has shown promising results in improving cognitive function in patients with schizophrenia, its underlying mechanism of action remains unclear.

Methods: This study systematically investigated the mechanisms of NSWDD in SCZ treatment using network pharmacology and molecular docking approaches.

Results: Analysis of the interaction genes revealed 307 common targets of NSWDD and SCZ. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses indicated the involvement of multiple signaling pathways including interleukin 17 signaling pathway, multiple virus infections, Advanced glycosylation end products (AGEs) - receptor of AGEs (AGEs-RAGE) signaling pathway, tumor necrosis factor signaling pathway, and Hypoxia-inducible factor-1 (HIF-1) signaling pathway as key pathways influenced by NSWDD in treating SCZ. These pathways are associated with various biological processes such as transcriptional regulation, apoptosis regulation, gene expression regulation, and external stimulus-response. Molecular docking simulations indicated favorable binding interactions between components of NSWDD and target proteins via intermolecular forces.

Conclusion: The study provided initial insights into the internal molecular mechanisms underlying the beneficial effect of NSWDD on SCZ through multi-target modulation across multiple pathways.

Keywords: Mechanism, molecular docking, network pharmacology, Ningshen Wendan decoction, schizophrenia

Introduction

Schizophrenia (SCZ) is a severe psychiatric disorder that affects approximately 1% of the global population.[1] This condition imposes a significant burden on individuals afflicted by it, their families, and society as a whole.[1,2] Schizophrenia is characterized by chronic and debilitating symptoms including hallucinations, delusions, disorganized thinking, and other negative symptoms.[3] The pathophysiology of SCZ involves multiple neurotransmitter systems, inflammatory processes, and oxidative stress.[4,5] Although conventional antipsychotic medications target specific neurotransmitter receptors, their therapeutic effects are limited and often accompanied by adverse side effects. Therefore, there is an urgent need for alternative treatments that have improved efficacy and tolerability. The primary approach to clinical management involves the administration of antipsychotic drugs. Risperidone is one antipsychotic drug used in clinical practice for SCZ treatment; but it shows limited efficacy in enhancing patient prognosis and also produces substantial drug-related side effects.[6] Consequently, it is imperative to explore effective therapeutic alternatives for SCZ and elucidate the underlying mechanisms of drug action.

Chunhua Qi[1]
Yanhua Yu[1]
Haibing Lv[2]
Xiaojie Ju[1]
Xiaocui Ji[1]
Pengfei Li[3]
Kuanjun He[1]

[1]School of Medical Technology, Baicheng Medical College, Baicheng, China
[2]College of Life Sciences and food Engineering, Inner Mongolia Minzu University, Tongliao, China
[3]Affiliated Hospital of Inner Mongolia Minzu University, Tongliao, China

Corresponding author:
Kuanjun He
✉ hekuanjun666@126.com

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The treatment of SCZ can be enhanced by specific compounds from Chinese Traditional Medicine (TCM), which contribute to liver function and release the mood.[7] The clinical efficacy of TCM in treating SCZ not only improves patient compliance but also mitigates the side effects and adverse reactions associated with contemporary Western anti-SCZ drugs. Additionally, TCM can be customized for different disease conditions, making it a promising therapeutic approach for SCZ and other challenging mental disorders. As a result, researchers have shown significant interest in this field.[8,9] Chinese Traditional Medicine is a valuable treasure of Chinese civilization; it contains certain TCM formulas that have been used for over 2000 years in the treatment of diseases resembling SCZ.[10]

Ningshen Wendan decoction (NSWDD) comes from the "Qianjin Yaofang," a collection of herbal recipes written by Sun Simiao (~ 581-682 C.E.), a doctor in the Tang Dynasty. Ningshen Wendan decoction is mainly composed of Buddha's hand, gardenia, coptis, calamus, tuckahoe, licorice, bamboo ru, orange peel, fructus aurantii, ginger, jujube, sour jujube kernel, and pinellia. Ningshen Wendan decoction is a well-established Chinese herbal formulation used for the treatment of psychotic symptoms; it is known for its safety, accessibility, and affordability.[11] The evidence suggests that NSWDD may exhibit positive short-term overall antipsychotic effects. Additionally, when used in combination with antipsychotics, NSWDD demonstrates a beneficial impact on both overall and mental status while minimizing adverse reactions.[12] Ningshen Wendan decoction has a rich history of utilization in the treatment of SCZ. A comprehensive analysis was conducted, consisting of 13 randomized controlled trials involving 1174 patients, to assess the advantages and disadvantages of Wendan decoction (WDD) for treating SCZ.[13] The findings indicated that WWD exhibited potential efficacy in ameliorating symptoms in individuals with SCZ.[13] Further analysis revealed that the therapeutic efficacy of NSWDD for treating SCZ was associated with decreased plasma γ-aminobutyric acid levels along with increased glutamate content.[14] The meta-analysis demonstrated that WDD treated patients showed significant improvement in short-term global state compared to those treated with placebo or no treatment, but did not show a significant difference from patients treated with antipsychotic drugs.[12] Furthermore, WDD was found to be associated with fewer extrapyramidal side effects than were other treatment options.[12] The rat model of insomnia was used to assess the therapeutic mechanisms of WDD; the data showed that WDD treatment potentially modulates negative emotions induced by sleep deprivation through the regulation of orexin-A and leptin expression in the brain.[15] Although NSWDD treatment has shown favorable antipsychotic effects in TCM practice, the specific mechanisms remain unclear. Therefore, it is crucial to elucidate the pharmacological components and mechanisms underlying the antipsychotic effects of NSWDD for SCZ prevention and treatment.

MAIN POINTS

- *The study successfully identified 307 key core targets and 199 effective ingredients of Ningshen Wendan decoction (NSWDD) for treating schizophrenia (SCZ).*
- *Protein–protein interaction, Gene Ontology, and Kyoto Encyclopedia of Genes and Genomes enrichment analyses elucidated the potential mechanisms and pathways involved.*
- *Molecular docking analysis to assess the binding activity between target proteins and compounds.*
- *We provide scientific evidence supporting the clinical application of NSWDD in treating SCZ.*
- *Of these, AKT1, ACTB, and ALB emerged as potential biomarkers and therapeutic targets for SCZ.*

Methods

The present study used network pharmacology and molecular docking methods to determine the principal bioactive compounds, potential targets, and signaling pathways associated with the therapeutic effects of NSWDD in SCZ. The flow chart illustrating this study is presented in Figure 1.

Screening of Ningshen Wendan Decoction-Related Disease Targets

Searches were conducted in the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, https://old.tcmsp-e.com/tcmsp.php), Symmap v.2 database (http://www.symmap.org/), and the Herbal Ingredients Targets Database (HERB, http://herb.ac.cn/), using the keywords "buddha's hand," "gardenia," "coptis," "calamus," "tuckahoe," "licorice," "bamboo ru," "orange peel," "fructus aurantii," "ginger," "jujube," "sour jujube kernel," and "pinellia" to identify active ingredients and target information of NSWDD. The screening criteria encompassed a minimum oral bioavailability threshold of 30% and drug-likeness exceeding 0.18, aiming to identify potential targets for the NSWDD among active ingredients.

Gene Screening of Schizophrenia-Related Targets

The targets related to SCZ were screened in disease databases Online Mendelian Inheritance in Man (OMIM) (https://www.omim.org), Comparative Toxicogenomics Database (CTD) (https://ctdbase.org), and GeneCards (https://www.genecards.org/).

Venn Diagram and Protein–Protein Interaction Network Construction

The Venn diagram was generated using Venny (http://www.liuxiaoyuyuan.cn) to visually represent the overlapping targets of NSWDD and SCZ. Subsequently, a protein–protein interaction (PPI) network was constructed by importing these targets into the STRING database (https://cn.string-db.org/). This network was then imported into Cytoscape_v3.9.1 for further analysis, using the Centiscape 2.2 plug-in to identify a core PPI network. Additionally, networks were established to explore compound–drug–active ingredient–target interactions and pathway–active ingredient–target interactions.

Gene Ontology and Kyoto Encyclopedia of Genes and Genomes Enrichment Analysis

By using the David database (https://david.ncifcrf.gov/), we performed Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses on the overlapping targets of NSWDD and SCZ, thereby elucidating potential biological processes (BP) and pathways associated with their involvement.

Molecular Docking

To validate the findings of network pharmacology, we used molecular docking methods to evaluate the selected active drugs

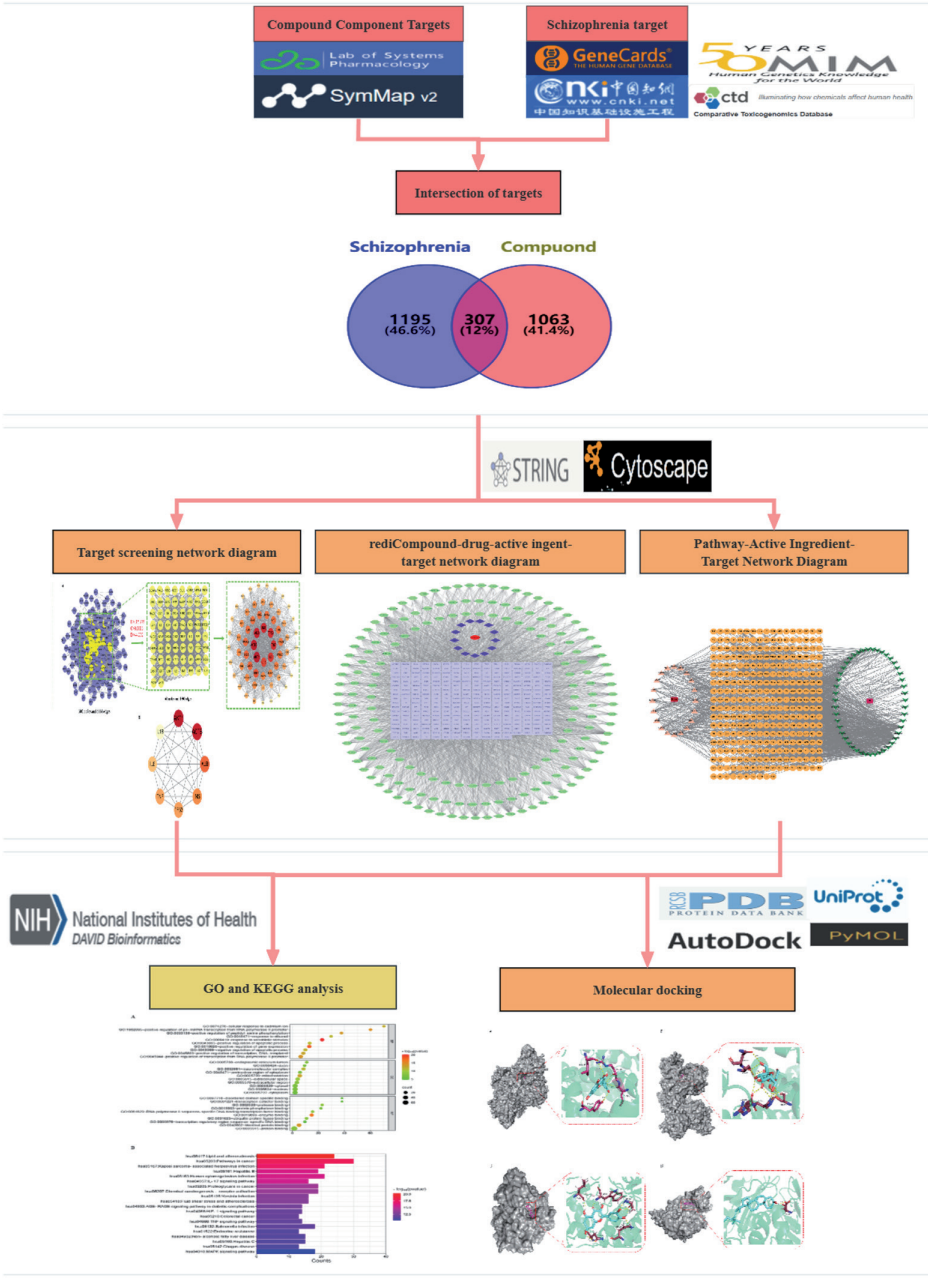

Figure 1. Workflow of the network pharmacological investigation strategy of Ningshen Wendan decoction in the treatment of schizophrenia. Four parts include database preparation, network construction, Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway analysis, and molecular docking verification.

and targets. The chemical structures of the main active components of NSWDD were retrieved from TCMSP and Symmap v.2 databases, whereas the 3D structures of core target proteins were obtained from RCSB PDB (https://www.rcsb.org) and UniProt (https://www.uniprot.org). Compound–target interactions and their binding patterns were visualized using PyMOL 2.3.2 and AutoDockTools 1.5.7.

Statistical Analysis

Statistical analysis methods that were used are included in each section of Methods. $P < .05$ was considered statistically significant in the study.

Results

Active Compounds and Potential Targets of Ningshen Wendan Decoction

The study identified 199 active ingredients in NSWDD. By searching the TCMSP and Symmap v.2 databases, a list of target proteins associated with these active ingredients was obtained, and duplicates were removed, resulting in 1370 unique targets.

The selection of SCZ treatment targets was performed using the diseases databases OMIM, CTD, and GeneCards. The filter conditions were as follows: for GeneCards, a relevance score > inference: 479; for

CTD, an inference score > 20. After summarization and deweighting, a total of 1502 SCZ-related targets remained.

Venn Diagram and Protein–Protein Interaction Network Construction

A total of 307 intersection targets between NSWDD and SCZ were identified (refer to Supplementary Figure 1). To investigate the mechanism underlying the treatment of SCZ by NSWDD, we utilized these 307 targets to construct a PPI network through integration with the STRING database. This resulting network consisted of 301 nodes and 6666 edges. Subsequently, we imported this network into Cytoscape_v.3.9.1 and used Centiscape 2.2 plugin for topology analysis, specifically focusing on metrics such as Betweenness (>315.28), Closeness (>0.002), and Degree (>44.29) in order to identify a core PPI network. As a result, we obtained a screened network comprising 66 nodes and 1500 edges, where each node's size corresponds to its target degree (Figure 2A). Through comprehensive network analysis, we identified 8 hub genes based on their degree centrality (Table 1 and Figure 2B). Furthermore, we constructed a compound–drug–active ingredient–target network (Figure 3) along with a pathway–active ingredient–target diagram (Supplementary Figure 2).

Gene Ontology and Kyoto Encyclopedia of Genes and Genomes Enrichment Analysis

The 307 intersection targets of NSWDD and SCZ were subjected to GO and KEGG enrichment analysis using the DAVID database, followed by visualization of the results. The GO enrichment analysis yielded a total of 698 items, including 544 in BP, 89 in molecular functions (MF), and 65 in cellular components (CC). The top 10 enriched BP, MF, and CC items were selected. In terms of BP, the target proteins primarily participated in apoptosis, cellular oxidative stress, and inflammatory response. The MF target proteins were mainly involved in receptor–ligand binding activity, protein ubiquitination, transcription factor binding, cytokine activity, etc. As for CC, the target proteins were categorized into plasma membrane, cell surface structures, among others such as endoplasmic reticulum tube structures. A total of 184 KEGG enrichment pathways were identified with the top 20 pathways screened based on KEGG analysis at a significance level of 0.05. The related enrichment results from GO (top 10) and KEGG (top 20) are visualized in Figure 4. These included interleukin 17 (IL-17) signaling pathway, multiple viral infections, AGE-RAGE signaling pathway, tumor necrosis factor (TNF) signaling pathway, and HIF-1 signaling pathway. The IL-17 signaling pathway of NSWDD for SCZ can be seen in Figure 5.

Molecular Docking

Based on the degree of common targets in the PPI network and KEGG results, we identified key targets associated with SCZ, namely, AKT1, ACTB, ALB, INS, and TP53. Subsequently, for molecular docking analysis, we selected 4 compounds from the Chinese herbal compound target network analysis based on their highest moderate value. The detailed information regarding the docking targets and compounds can be found in Table 2.

The results of molecular docking can be visualized in Figure 6. The calculated binding free energy ranged from 0.55 to −10.41 kcal/mol,

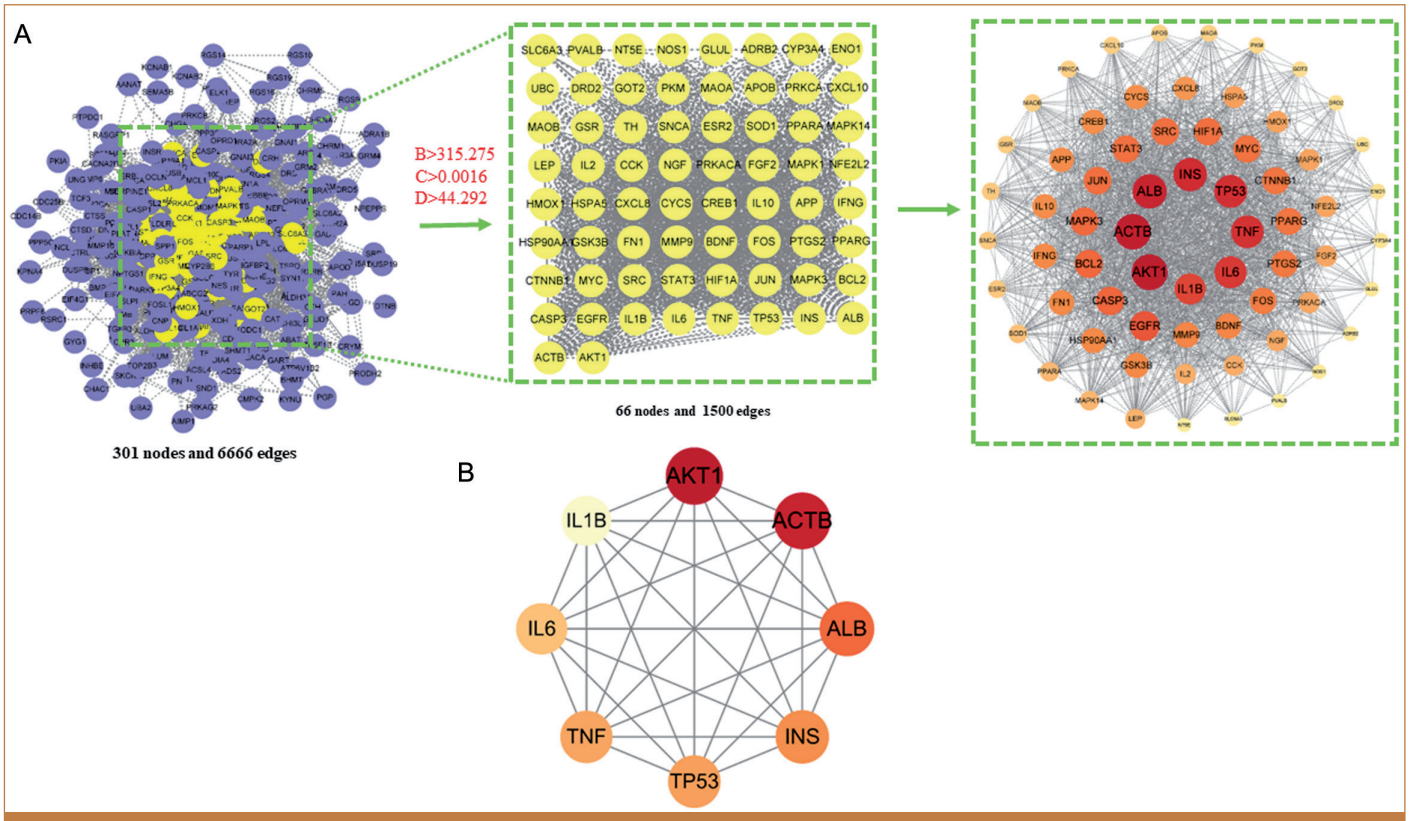

Figure 2. Identification of candidate targets via protein–protein interaction analysis. (A) The Centiscape 2.2 plug-in was utilized for the target screening process diagram (B: betweenness; C: closeness; D: degree); (B) Hub genes were selected based on their degree, with the node color transitioning from light yellow to red as the corresponding degree gradually increases.

Table 1. The First 8 Genes Were Identified as Hub Genes Based on Their Degree Centrality

Gene ID	Betweenness unDir	Closeness unDir	Degree unDir
AKT1	3564.48	0.002	177
ACTB	3031.34	0.002	175
ALB	2609.79	0.002	167
INS	2280.59	0.002	162
TP53	2905.45	0.002	159
TNF	1861.67	0.002	158
IL6	1399.91	0.002	154
IL1B	1206.58	0.002	148

indicating stable binding interactions. The visualization indicated a binding free energy of −8.28 kcal/mol between ALB and Quercetin, with the prediction of hydrogen bonding occurring between protein residues LEU-115 (3.5A), ARG-186 (3.2A), LEU-185 (3.0A), and TYR-138 (2.9A). These hydrogen bonds facilitate the formation of stable complexes between hydrophobic small molecules and the active cavity of the target protein. Additionally, ALB exhibits a binding free energy of -6.746 kcal/mol towards sucrose, with predicted hydrogen bond formations involving ASN-109, ASP-108, ARG-145 (3.0Å), HIS 146 (2.9Å), and SER-193 residues in the target protein's interaction interface region. The calculated binding affinity between AKT1 and quercetin was determined to be −5.77 kcal/mol, suggesting a strong interaction between them based on their energetic stability analysis results obtained through molecular docking simulations conducted above-mentioned study. Those findings indicated that quercetin forms hydrogen bonds with key residues LEU-78, TRP-80, GLN203, Lys268, and ASN53 within its target protein's active site region.

Discussion

Nowadays, there has been a gradual increase in the prevalence of mental disorders, resulting in significant economic and societal burdens.[16] Schizophrenia, a complex psychiatric disorder affecting millions worldwide, is characterized by an 83% disability rate and a lifetime suicide risk of 5%-10% among patients, predominantly occurring during adolescence or early adulthood.[17] The pathogenesis of SCZ involves the intricate interplay between multiple genes and signaling pathways, forming a complex network of interactions.[18] TCM, as a valuable and specialized treasure of Chinese civilization, has been utilized for centuries in the treatment of mental illnesses, including SCZ.[10] The advantages of TCM lie in its ability to target multiple pathways, its formulation with various components, and its utilization of a multimodal approach. Due to the clinical efficacy demonstrated by TCM in treating SCZ, it not only enhances patient compliance but also mitigates the side effects and adverse reactions associated with contemporary Western medicine.[19,20] Moreover, TCM can be customized according to different disease conditions, making

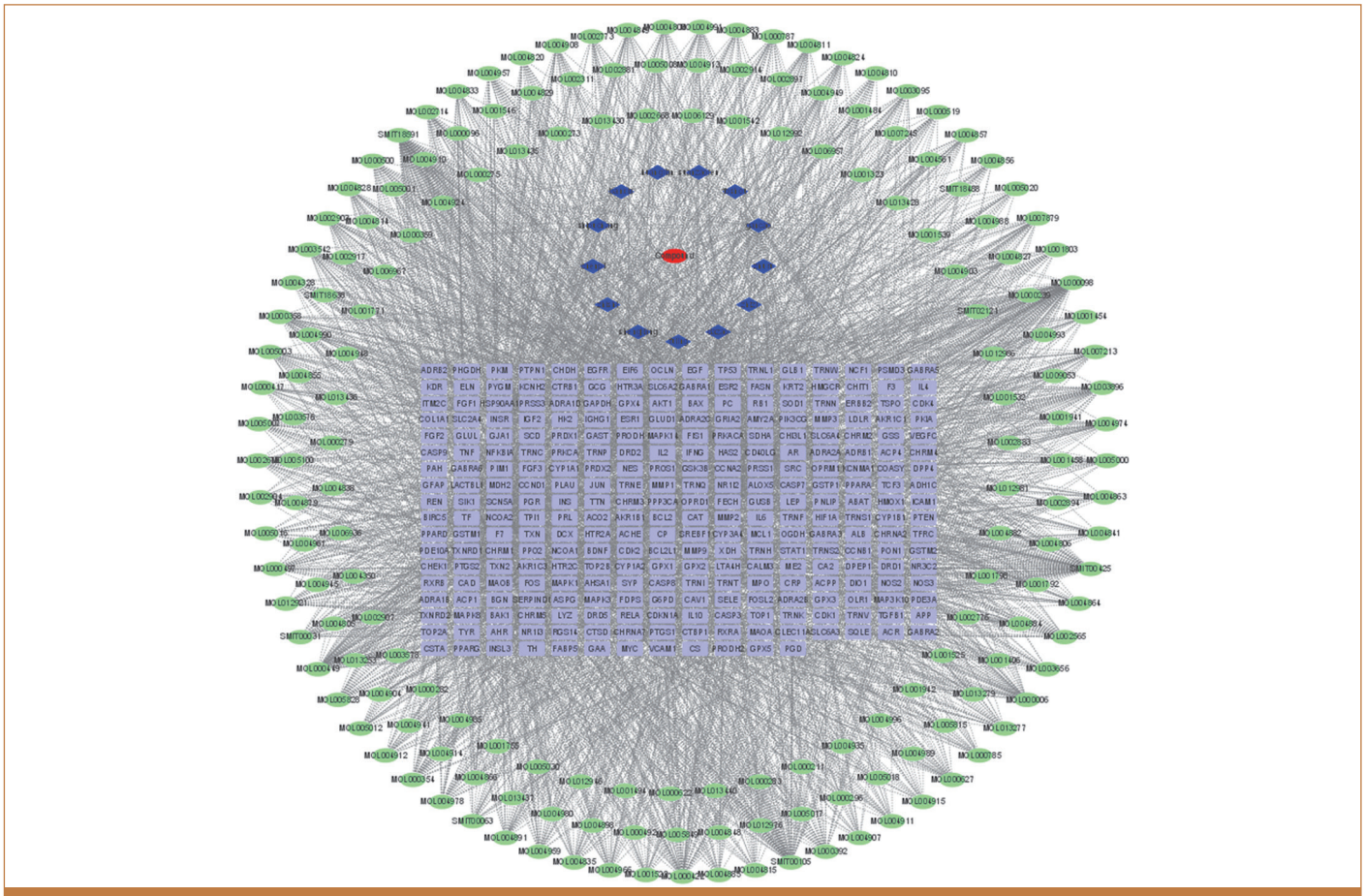

Figure 3. Compound–drug–active ingredient–target network diagram. The red ellipse symbolizes Ningshen Wendan decoction; the blue diamond represents the drug; green ovals depict active ingredients; the light blue square signifies the target.

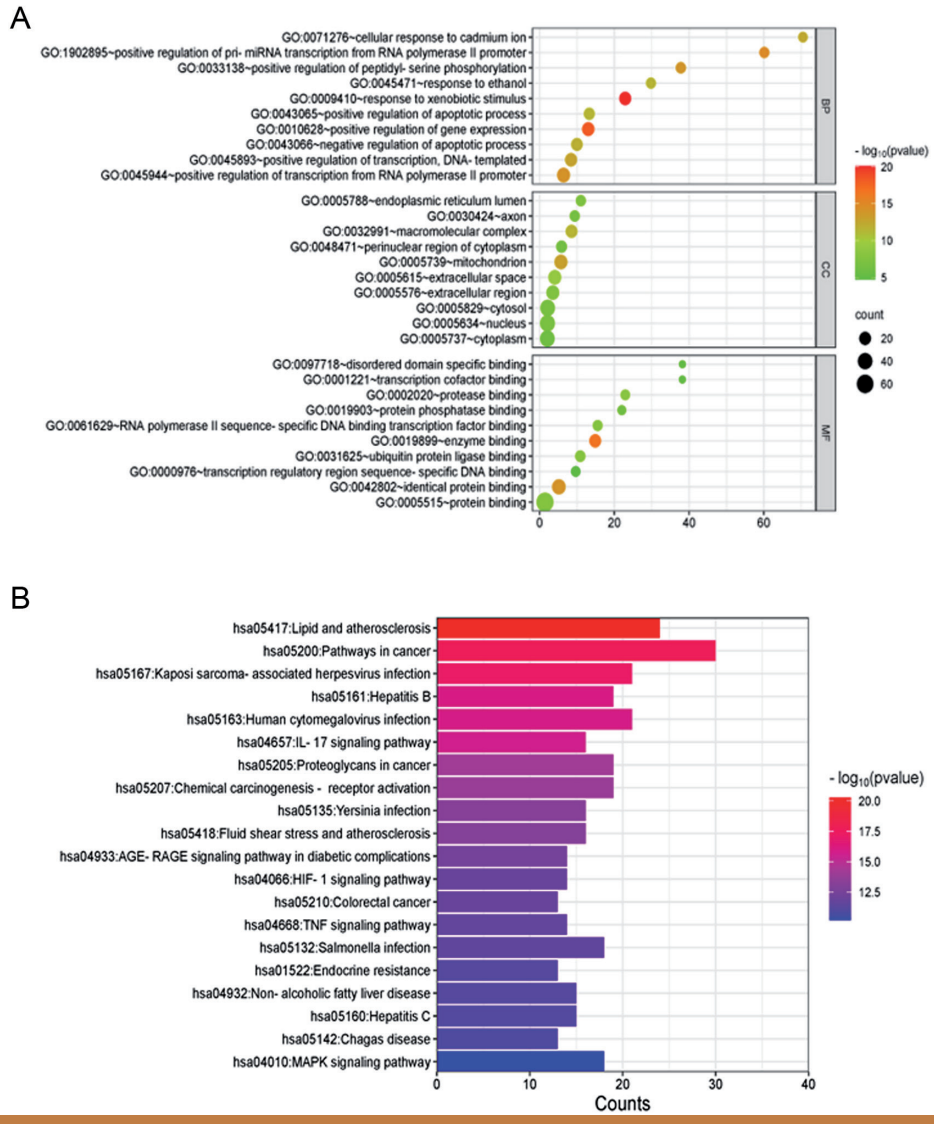

Figure 4. Results of Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis. (A) GO enrichment analysis: The bubble map illustrates the enriched biological processes, cellular components, and molecular functions of the top 10 results. (B) KEGG enrichment analysis: histogram displays the most significant 20 pathways identified through KEGG enrichment.

it a promising therapeutic approach for SCZ and other challenging mental disorders.

The concept of network pharmacology was initially proposed in 2007 by Andrew L. Hopkins, a pharmacologist at the University of Dundee, UK.[21] Chinese Traditional Medicine network pharmacology not only predicts the target characteristics and pharmacological actions of herbal compounds but also elucidates the combination rules and network regulatory effects of herbal formulas, offering novel research avenues for comprehending the therapeutic basis, mechanism, and effectiveness issues associated with TCM. The holistic approach and individualized diagnosis and treatment based on syndrome differentiation that characterize TCM align well with the holistic and systemic nature of network pharmacology. This presents a pioneering research direction for unraveling the foundation and mechanism underlying TCM pharmacodynamics as well as its effectiveness.[22,23] Network pharmacology is an emerging discipline that integrates bioinformatics, network analysis, and systems biology, in order to investigate the intricate interactions between multiple drug targets and diseases. The pathogenesis of SCZ involves the interplay and reciprocal influence of numerous genes and signaling pathways. By employing data mining techniques to explore the formulation principles of TCM in treating SCZ, network pharmacology will provide a theoretical foundation for drug therapy and novel drug discovery. The present study used an integrative approach, combining bioinformatics, network pharmacology, and molecular docking techniques to investigate the underlying mechanisms by which NSWDD works in the treatment of SCZ. Through comprehensive bioinformatics and network pharmacology analyses, we successfully identified key core targets and effective ingredients of NSWDD for treating SCZ. Additionally, PPI, GO, and KEGG enrichment analyses were conducted to elucidate the potential mechanisms and pathways involved. Furthermore, by employing molecular docking analysis to assess the binding activity between target proteins and

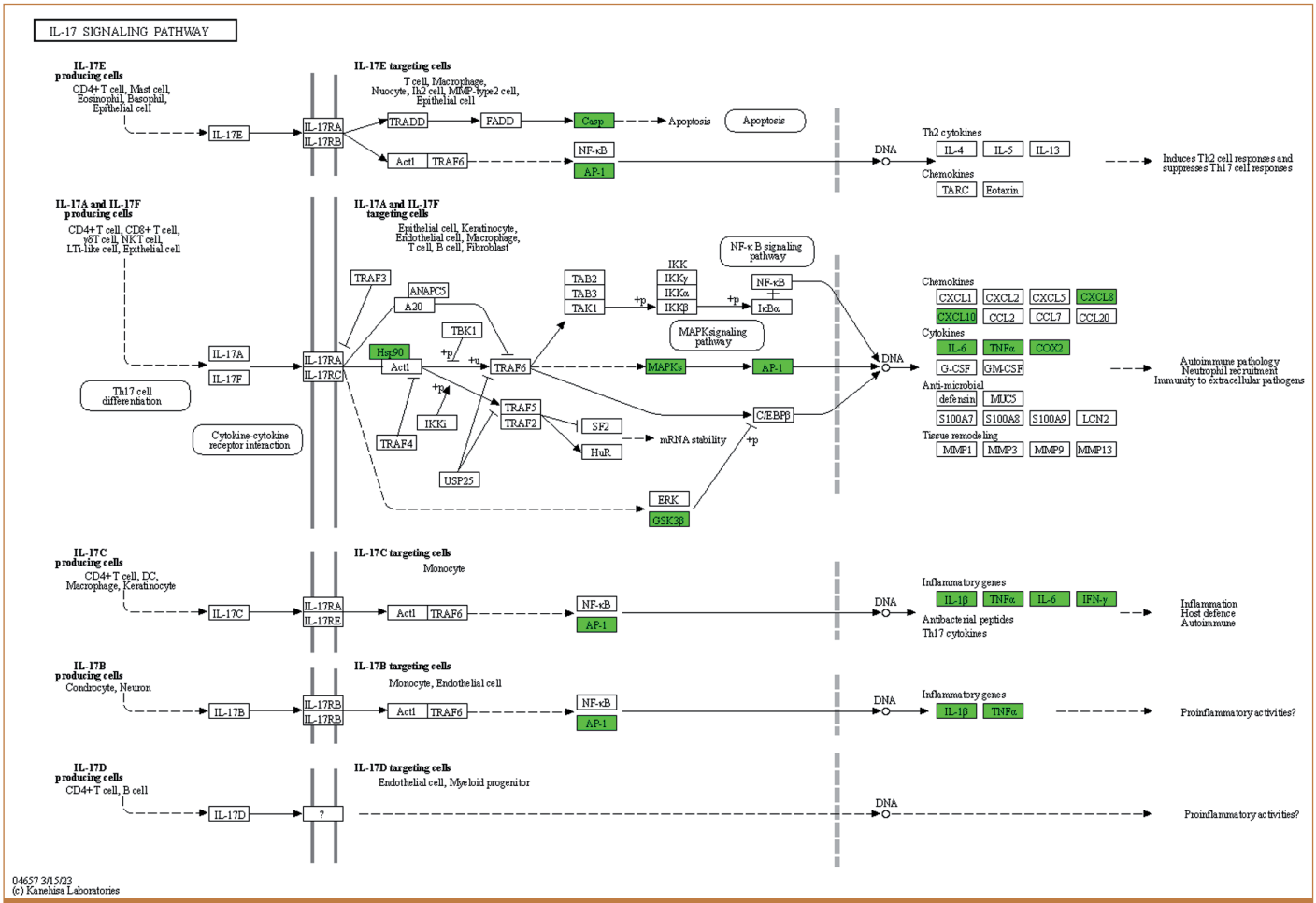

Figure 5. The interleukin 17 signaling pathway of Ningshen Wendan decoction (NSWDD) for schizophrenia (SCZ). The green targets in the figure represent the therapeutic targets of NSWDD for SCZ.

compounds, we provide scientific evidence supporting the clinical application of NSWDD in treating SCZ.

In the present study, a total of 307 common targets of NSWDD and SCZ were identified. Among them, AKT1, ACTB, and ALB emerged as potential biomarkers and therapeutic targets for SCZ. Moreover, our investigation revealed 199 active components in NSWDD with 307 potential targets for treating SCZ. The network pharmacology analysis indicated that NSWDD potentially targets several key pathways and BP implicated in SCZ, including IL-17 signaling pathway, multiple virus infection pathway, AGE-RAGE signaling pathway, TNF signaling pathway, and HIF-1 signaling pathway. The IL-17 signaling pathway is a crucial component of the immune response, primarily involved in inflammation and host defense against pathogens.[24] The IL-17 signaling pathway has emerged as a potential link to the pathogenesis of SCZ.[25,26] Research studies have demonstrated that immune system dysregulation may contribute to the development and progression of SCZ.[26,27] In recent years, accumulating evidence suggests that abnormalities in IL-17 signaling may contribute to neuroinflammation and neuronal dysfunction observed in SCZ.[28,29] Animal models have provided evidence that elevated levels of IL-17 can induce behavioral changes resembling symptoms seen in patients with SCZ.[30] Furthermore, genetic studies have identified variations within genes related to the IL-17 signaling pathway associated with an increased risk for developing SCZ.[31] These findings suggest a possible genetic susceptibility underlying the relationship between dysregulation of IL-17 and disease onset. Multiple virus infection pathways have been identified in association with SCZ.[32,33] Studies have demonstrated that diverse viruses can potentially contribute to the onset or progression of SCZ through distinct mechanisms.[33] For instance, specific viruses may directly invade brain cells and disrupt their normal functioning, leading to neuroinflammation and neuronal damage.[34] Other viruses may indirectly impact the brain by modulating immune responses or triggering autoimmune reactions targeting neural tissues.[34] Tumor necrosis factor signaling pathway plays a pivotal role in the regulation of inflammation and immune responses within the body, encompassing the activation of diverse proteins and molecules that ultimately culminate in the production and release of pro-inflammatory cytokines, such as TNF-alpha.[35] These cytokines have been implicated in various neurological disorders, including SCZ.[36] Research has demonstrated that dysregulation or abnormalities within the TNF signaling pathway may contribute to the development or progression of SCZ.[37] Moreover, compelling evidence suggests that specific genetic variations occurring within genes involved in the TNF signaling pathway may augment susceptibility to developing SCZ.[38] These pathways are associated with various crucial BP, such as transcriptional regulation, apoptosis, regulation of gene expression, and regulation of external stimulus

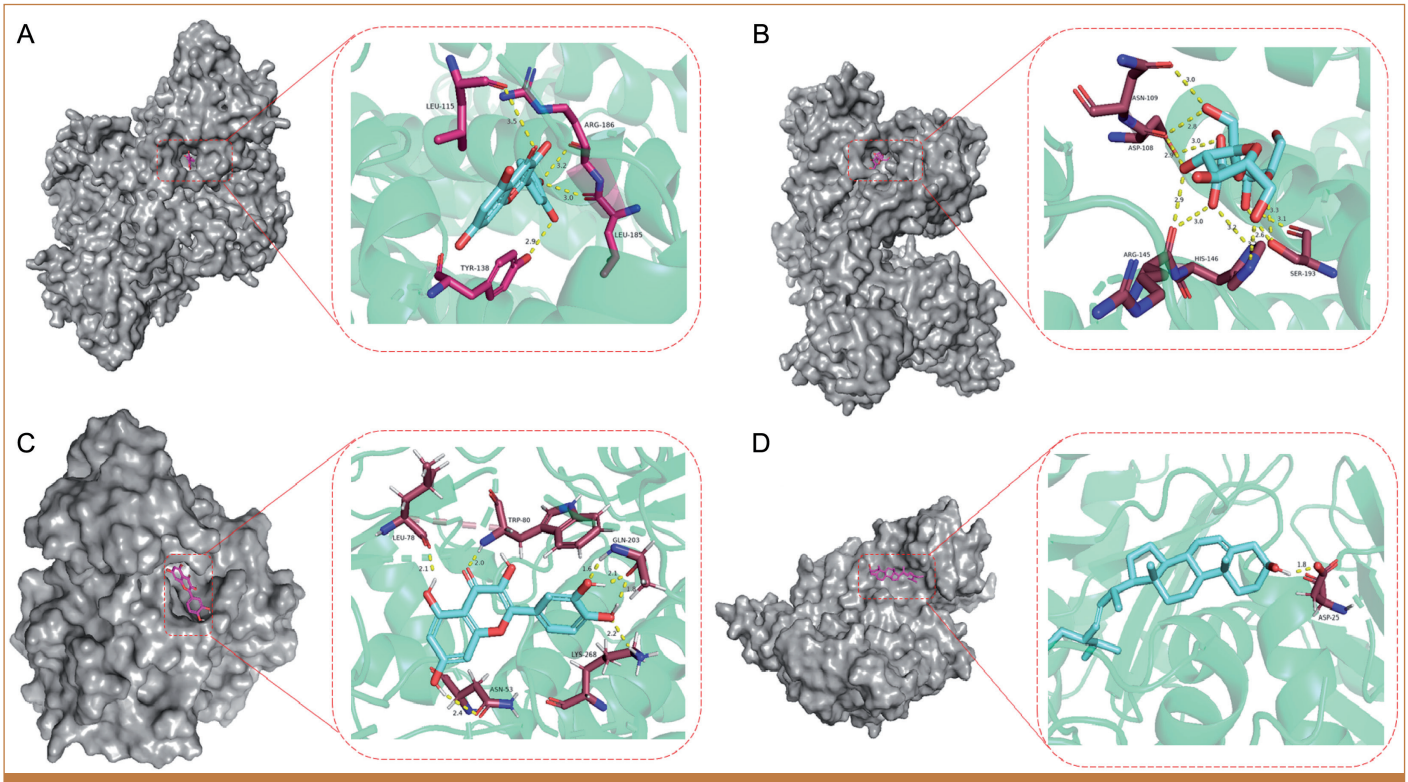

Figure 6. The results of molecular docking analysis between the active constituents of Ningshen Wendan decoction and the predicted target protein. (A) ALB (1AO6) and quercetin, (B) ALB (1AO6) and sucrose, (C) AKT1 (4EJN) and quercetin, and (D) ACTB (1YAG) and stigmasterol.

response. Furthermore, molecular docking simulations indicated favorable binding interactions between NSWDD components and target proteins via intermolecular forces.

In recent years, the integration of network pharmacology techniques with TCM diagnosis and treatment models has significantly accelerated the development of TCM. However, there are certain aspects missing in the computational methods for network pharmacology analysis, including error propagation and the risk of false positives. Additionally, although network pharmacology techniques provide qualitative predictions for drug components and targets, clear verification through animal experiments or even clinical trials is still necessary to confirm their pharmacological effects.

The present study offers insights into the potential mechanisms underlying the therapeutic effects of NSWDD in SCZ treatment. Our findings indicate that NSWDD exerts a multifaceted pharmacological role in SCZ, encompassing modulation of apoptosis, regulation of gene expression, response to external stimuli, and engagement with multiple signaling pathways. The results of our study suggest that NSWDD achieves its therapeutic effects in SCZ through diverse mechanisms.

Table 2. The Targets and Compounds Utilized for Docking Analysis

Targets	PDB ID	Compounds Mol ID	PubChem ID	Compounds Name
AKT1	4EJN	MOL000098	5280343	Quercetin
ACTB	1YAG	MOL000449	5280794	Stigmasterol
ALB	1AO6	MOL000842	5988	Sucrose
INS	6S34	MOL001456	311	Citric Acid
TP53	1TUP			

Availability of Data and Materials: *Requests to access the original data should be made directly to the corresponding author.*

Ethics Committee Approval: *Not applicable.*

Informed Consent: *Not applicable.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept – K.H.; Design – K.H.; Supervision – K.H., Y.Y.; Data Collection and/or Processing – C.Q., Y.Y., H.L., X.J.; Analysis and/or Interpretation – H.L., X.J., X.J., P.L.; Literature Review – X.J.; Writing – C.Q., H.L., K.H.; Critical Review – Y.Y., X.J., X.J., P.L., K.H.*

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Declaration of Interests: *The authors have no conflicts of interest to declare.*

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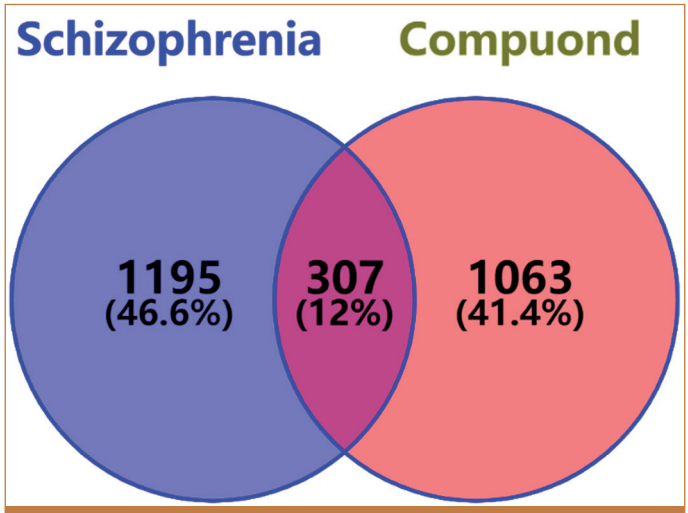
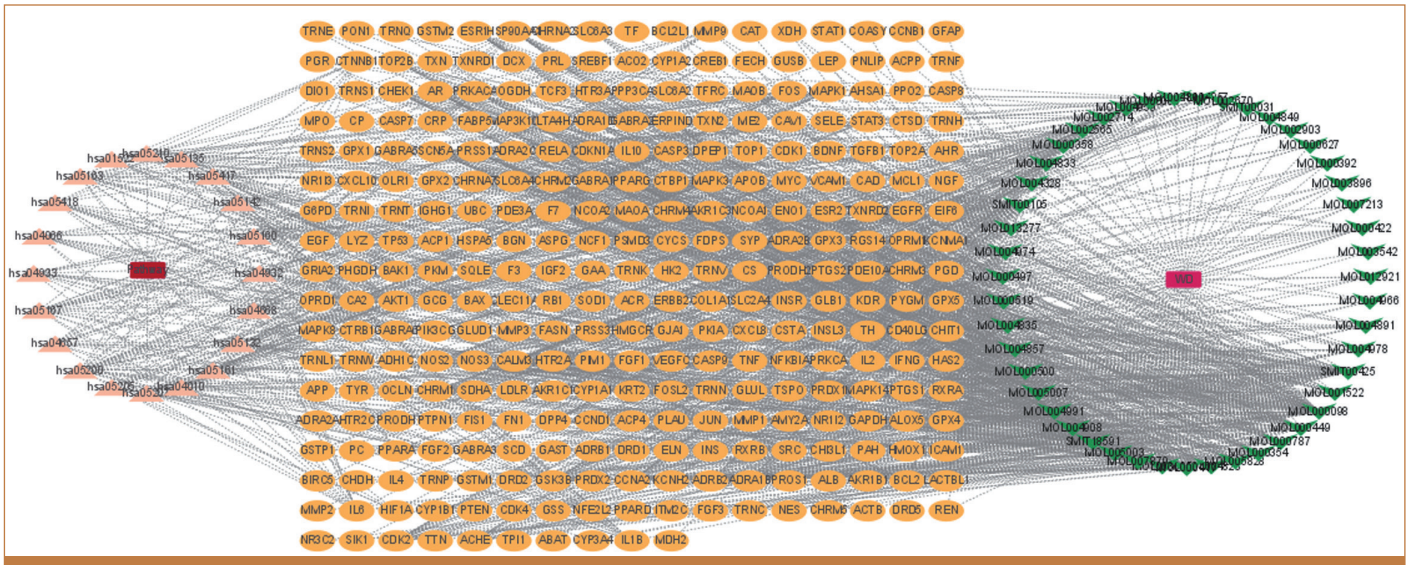
References

1. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia-an overview. *JAMA Psychiatry*. 2020;77(2):201-210. [CrossRef]
2. Tan G, Wang L, Liu Y, Zhang H, Feng W, Liu Z. The alterations of circular RNA expression in plasma exosomes from patients with schizophrenia. *J Cell Physiol*. 2021;236(1):458-467. [CrossRef]
3. Kahn RS, Sommer IE, Murray RM, et al. Schizophrenia. *Nat Rev Dis Primers*. 2015;1:15067. [CrossRef]

4. Matosin N, Nithianantharajah J, Dean B, Deng C. [editorial]. Mapping the pathophysiology of schizophrenia: interactions between multiple cellular pathways. *Front Cell Neurosci*. 2023;17:1232677. [CrossRef]
5. Murray AJ, Rogers JC, Katshu M, Liddle PF, Upthegrove R. Oxidative stress and the pathophysiology and symptom profile of schizophrenia spectrum disorders. *Front Psychiatry*. 2021;12:703452. [CrossRef]
6. Jafari S, Fernandez-Enright F, Huang XF. Structural contributions of antipsychotic drugs to their therapeutic profiles and metabolic side effects. *J Neurochem*. 2012;120(3):371-384. [CrossRef]
7. Rathbone J, Zhang L, Zhang M, et al. Chinese herbal medicine for schizophrenia: cochrane systematic review of randomised trials. *Br J Psychiatry*. 2007;190:379-384. [CrossRef]
8. Tatsumi L, Suzuki T, Yamada K, Mimura M, Uchida H. Kampo, A Japanese traditional medicinal system for psychiatric conditions: a narrative review. *Pharmacopsychiatry*. 2019;52(6):251-260. [CrossRef]
9. Shi XJ, Fan FC, Liu H, et al. Traditional Chinese medicine decoction combined with antipsychotic for chronic schizophrenia treatment: a systematic review and meta-analysis. *Front Pharmacol*. 2020;11:616088. [CrossRef]
10. Zhu M. *The Medical Classic of the Yellow Emperor*. Beijing: Foreign Languages Press; 2001
11. Deng H, Xu J. Wendan decoction for schizophrenia. *Schizophr Bull*. 2016;42(6):1320-1321. [CrossRef]
12. Deng H, Xu J. Wendan decoction (traditional Chinese medicine) for schizophrenia. *Cochrane Database Syst Rev*. 2017;6(6):CD012217. [CrossRef]
13. Che YW, Yao KY, Xi YP, et al. Wendan decoction (温胆汤) for treatment of schizophrenia: a systematic review of randomized controlled trials. *Chin J Integr Med*. 2016;22(4):302-310. [CrossRef]
14. Jiang X, Zhan J, He G, Yan W, Fu K. Therapeutic effect of ningshen wendan decoction on schizophrenia patients with predominantly negative symptoms and its influence on GABA and glu contents in plasma. *Chin Arch Trad Chin Med*. 2019;37(10):2500-2503.
15. Wu F, Song Y, Li F, et al. Wen-dan decoction improves negative emotions in sleep-deprived rats by regulating orexin-a and leptin expression. *Evid Based Complement Alternat Med*. 2014;2014:872547. [CrossRef]
16. Winkler P, Formanek T, Mlada K, et al. Increase in prevalence of current mental disorders in the context of COVID-19: analysis of repeated nationwide cross-sectional surveys. *Epidemiol Psychiatr Sci*. 2020;29:e173. [CrossRef]
17. Solmi M, Seitidis G, Mavridis D, et al. Incidence, prevalence, and global burden of schizophrenia - data, with critical appraisal, from the Global Burden of Disease (GBD) 2019. *Mol Psychiatry*. 2023;28(12):5319-5327. [CrossRef]
18. Kendler KS. Eugen Bleuler's views on the genetics of schizophrenia in 1917. *Schizophr Bull*. 2020;46(4):758-764. [CrossRef]
19. Deng H, Adams CE. Traditional Chinese medicine for schizophrenia: a survey of randomized trials. *Asia Pac Psychiatry*. 2017;9(1). [CrossRef]
20. Mikell CB, Sinha S, Sheth SA. Neurosurgery for schizophrenia: an update on pathophysiology and a novel therapeutic target. *J Neurosurg*. 2016;124(4):917-928. [CrossRef]
21. Hopkins AL. Network pharmacology. *Nat Biotechnol*. 2007;25(10):1110-1111. [CrossRef]
22. Cao H, Li S, Xie R, et al. Exploring the mechanism of Dangguiliuhuang decoction against hepatic fibrosis by network pharmacology and experimental validation. *Front Pharmacol*. 2018;9:187. [CrossRef]
23. Chang HL, Chang YM, Lai SC, et al. Naringenin inhibits migration of lung cancer cells via the inhibition of matrix metalloproteinases-2 and -9. *Exp Ther Med*. 2017;13(2):739-744. [CrossRef]
24. Iwakura Y, Ishigame H, Saijo S, Nakae S. Functional specialization of interleukin-17 family members. *Immunity*. 2011;34(2):149-162. [CrossRef]
25. Chenniappan R, Nandeesha H, Kattimani S, Nanjaiah ND. Interleukin-17 and interleukin-10 association with disease progression in schizophrenia. *Ann Neurosci*. 2020;27(1):24-28. [CrossRef]
26. Momtazmanesh S, Zare-Shahabadi A, Rezaei N. Cytokine alterations in schizophrenia: an updated review. *Front Psychiatry*. 2019;10:892. [CrossRef]
27. Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. *Lancet Psychiatry*. 2015;2(3):258-270. [CrossRef]
28. Lu Y, Zhang P, Xu F, Zheng Y, Zhao H. Advances in the study of IL-17 in neurological diseases and mental disorders. *Front Neurol*. 2023;14:1284304. [CrossRef]
29. Chen J, Liu X, Zhong Y. Interleukin-17A: the key cytokine in neurodegenerative diseases. *Front Aging Neurosci*. 2020;12:566922. [CrossRef]
30. McCutcheon RA, Keefe RSE, McGuire PK. Cognitive impairment in schizophrenia: aetiology, pathophysiology, and treatment. *Mol Psychiatry*. 2023;28(5):1902-1918. [CrossRef]
31. Ma C, Gu C, Huo Y, Li X, Luo XJ. The integrated landscape of causal genes and pathways in schizophrenia. *Transl Psychiatry*. 2018;8(1):67. [CrossRef]
32. Kotsiri I, Resta P, Spyrantis A, et al. Viral infections and schizophrenia: a comprehensive review. *Viruses*. 2023;15(6):1345. [CrossRef]
33. Kneeland RE, Fatemi SH. Viral infection, inflammation and schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;42:35-48. [CrossRef]
34. Koyuncu OO, Hogue IB, Enquist LW. Virus infections in the nervous system. *Cell Host Microbe*. 2013;13(4):379-393. [CrossRef]
35. Brenner D, Blaser H, Mak TW. Regulation of tumour necrosis factor signalling: live or let die. *Nat Rev Immunol*. 2015;15(6):362-374. [CrossRef]
36. Na KS, Jung HY, Kim YK. The role of pro-inflammatory cytokines in the neuroinflammation and neurogenesis of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;48:277-286. [CrossRef]
37. Hoseth EZ, Ueland T, Dieset I, et al. A study of TNF pathway activation in schizophrenia and bipolar disorder in plasma and brain tissue. *Schizophr Bull*. 2017;43(4):881-890. [CrossRef]
38. Ibrahim RR, Amer RA, Abozeid AA, Elsharaby RM, Shafik NM. Micro RNA 146a gene variant / TNF-α / IL-6 / IL-1 β; A cross-link axis inbetween oxidative stress, endothelial dysfunction and neuro-inflammation in acute ischemic stroke and chronic schizophrenic patients. *Arch Biochem Biophys*. 2020;679:108193. [CrossRef]



Supplementary Figure 1. The intersection targets between Ningshen Wendan decoction (NSWDD) and Schizophrenia (SCZ).



Supplementary Figure 2. The diagram of pathway-active ingredient-target.