Original Article

The mechanism of Taohong Siwu decoction in treating chemotherapy-induced peripheral neuropathy: a network pharmacology and molecular docking study

Meiyu Zhou, Li Liu, Yonghong Tan, Rui Huang, Zailiang Yang

Division of Hematology, The Comprehensive Cancer Center, Chongqing University Fuling Hospital, Chongqing, China

Contributions: (I) Conception and design: Z Yang; (II) Administrative support: M Zhou; (III) Provision of study materials or patients: L Liu; (IV) Collection and assembly of data: Y Tan; (V) Data analysis and interpretation: R Huang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Zailiang Yang, MD. Division of Hematology, The Comprehensive Cancer Center, Chongqing University Fuling Hospital, No. 2 Gaosuntang Road, Fuling District, Chongqing 408000, China. Email: yangzailiang408000@cqu.edu.cn.

Background: Taohong Siwu decoction (THSWD) is a classic traditional Chinese medicine (TCM) formula known for its effects in promoting blood circulation, removing blood stasis, and rejuvenating energy. There have been clinical reports of THSWD treating chemotherapy-induced peripheral neuropathy (CIPN) caused by paclitaxel. We conducted a network pharmacology and molecular docking analysis to further clarify the molecular mechanisms by which THSWD exerts its protective effects against CIPN.

Methods: Chemical components of THSWD and their corresponding targets were obtained through the traditional Chinese medicine systems pharmacology database and analysis platform (TCMSP), and related targets of CIPN were searched in disease databases including Online Mendelian Inheritance in Man (OMIM), Therapeutic Target Database (TTD), GeneCards, and DrugBank. Common targets between THSWD and CIPN were identified using Venn diagrams. A protein-protein interaction (PPI) network was constructed using Search Tool for the Retrieval of Interacting Genes/Proteins (STRING), which was followed by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. AutoDock and PyMOL were used for the molecular docking validation of the key components of THSWD with core targets.

Results: At total of 69 chemical components of THSWD were identified, corresponding to 856 targets; 2,297 targets were associated with CIPN, with an intersection of 105 common targets. PPI analysis identified eight core targets: *MYC*, *TNF*, *MAPK14*, *AKT1*, *ESR1*, *RELA*, *TP53*, and *HSP90AA1*; KEGG enrichment analysis implicated signaling pathways such as PI3K-Akt, NF-κB, and HIF-1, etc. Molecular docking results indicated that the selected active components and their corresponding target proteins have good binding activity.

Conclusions: Through network pharmacology, this study found that THSWD has significant advantages in treating CIPN. By analyzing potential core targets, biological functions, and involved signaling pathways, we clarified the potential molecular biological mechanisms involved in THSWD's treatment effect. This study provides a theoretical basis for the clinical application of THSWD in treating CIPN.

Keywords: Network pharmacology; molecular docking; Taohong Siwu decoction (THSWD); chemotherapy-induced peripheral neuropathy (CIPN)

Submitted Jun 21, 2024. Accepted for publication Jul 19, 2024. Published online Jul 26, 2024.
doi: 10.21037/tcr-24-1019
View this article at: https://dx.doi.org/10.21037/tcr-24-1019

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting neurotoxic toxicity observed in clinical settings (1) that is characterized by its progressive, persistent, and irreversible nature. The severity of CIPN is associated with the cumulative dose of chemotherapy drugs, duration of treatment, history of neuropathy, and the combined effects of treatment and genetic polymorphisms (2). Moderate-to-severe CIPN may require dose reduction, prolongation of chemotherapy, or even cessation of treatment, thereby reducing the effectiveness of chemotherapy and shortening patient survival time while also potentially damaging patients' quality of life (3). Various antitumor drugs can cause CIPN. It is reported that the incidence rates of CIPN are approximately 72.3% for oxaliplatin, about 70.8% for paclitaxel, and 40–60% for bortezomib. Approximately 68% of patients develop CIPN symptoms one month after chemotherapy, and after more than 6 months after chemotherapy, 30% of patients still experience CIPN, with the incidence rate showing an increasing trend annually (4). CIPN mainly manifests as chronic, distal, or symmetrical sensory abnormalities; abnormal pain; hyperalgesia; and limb lesions that are symmetrically distributed, often in a "stocking-glove" pattern (5). The exact mechanisms underlying the similar neuropathies caused by different chemotherapy drugs remain unclear. The etiology of CIPN is complex, involving factors related to neuropathic pain such as mitochondrial dysfunction, oxidative stress response, glial cell activation, and ion channel alterations, all of which can lead to the development of CIPN (6).

Currently, the benefit of medical treatment for is CIPN unsatisfactory. Physical medicine is used for its ameliorative treatment with patients' self-exercise (electrotherapy, balneology, thermotherapy, mechanotherapy), but many of them is only experienced-based medicine approach that lack strong scientific evidence (7,8). There are three main categories of drugs for CIPN which are neurotrophic drugs (amifostine, cobalamin, vitamin E), analgesics (tramadol, lidocaine, capsaicin patches, strong opioids such as morphine and oxycodone) and antidepressants (amitriptyline, duloxetine, gabapentin, pregabalin). Neurotrophic drugs are slower and less effective. Analgesics will be addictive and inconvenient to use. Antidepressants can cause serious complications (9,10). Traditional Chinese medicine (TCM) categorizes CIPN under the diseases of "bi syndrome", "blood bi", and "numbness", treating it with methods that warm the meridians to dispel cold, activate blood circulation to dissipate blood stasis, and supplement qi to nourish the blood, achieving certain clinical effects (11-13). The Taohong Siwu decoction (THSWD), composed of peach kernel, safflower, prepared rehmannia root, angelica, white peony, and Szechuan lovage root, has been clinically applied in the treatment of paclitaxel-induced CIPN. There have been clinical studies reported that THSWD can be safely used in malignant tumors and other diseases (14-17). A preclinical study has found that THSWD exerts a neuroprotective effect against paclitaxel-induced CIPN in rats by exerting antioxidative and anti-inflammatory activity and by enhancing the expression of autophagy proteins to clear myelin debris (18). However, the molecular mechanisms underlying THSWD's antioxidative and anti-inflammatory actions and activation of autophagy are not fully understood.

With glowing data involved in the research of TCM network pharmacology, artificial intelligence has shown a strong advantage in data processing, and the combination of artificial intelligence algorithm and network pharmacology has become the development trend of TCM network pharmacology. The techniques of single-cell transcriptomics, spatial transcriptomics, quasi-time series analysis and subcellular cluster analysis are on the rise, which would provide the convenient research methods (19-21). Thus, to clarify the mechanism by which THSWD ameliorates CIPN, we employed network pharmacology and molecular

Highlight box

Key findings

- This study elucidates the molecular mechanisms by which Taohong Siwu decoction (THSWD) exerts its therapeutic effects on chemotherapy-induced peripheral neuropathy (CIPN).
- THSWD shows significant advantages in treating CIPN.

What is known and what is new?

- It is known that THSWD has been reported clinically to have protective effects against paclitaxel-induced peripheral neuropathy.
- This manuscript adds new insights into the molecular mechanisms of THSWD in treating CIPN, demonstrating that it activates the MAPK/NF-κB signaling pathway through core targets such as *MYC* and *MAPK14*, thereby preventing and repairing neuronal cell damage.

What is the implication, and what should change now?

- The findings of this study suggest that further validation through animal models is necessary to substantiate the theoretical mechanisms identified.

docking, starting with the screening of THSWD's chemical components and corresponding targets, selecting CIPN-related targets through multiple databases, and analyzing the mechanism of action of THSWD in treating CIPN through Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses. Finally, by molecular docking, the study validated the selected key active components and targets, comprehensively exploring the complex network of THSWD treatment for CIPN and provide evidence-based results for finding precise therapeutic targets in the next researches. We present this article in accordance with the STREGA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1019/rc).

Methods

Study design

We used network pharmacology and molecular docking to clarify the mechanisms underlying THSWD's therapeutic effect against CIPN. First, the active components of THSWD and their targets were identified via the traditional Chinese medicine systems pharmacology database and analysis platform (TCMSP), while CIPN-related targets were gathered from databases including Online Mendelian Inheritance in Man (OMIM) and GeneCards. These data informed the construction of a protein-protein interaction (PPI) network via the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database, which was used to identify key targets for subsequent molecular docking analyses with AutoDock Tools-1.5.7 and PyMOL 2.6.0 software.

Active ingredients and candidate target screening

The primary active components and their action targets in THSWD were screened through the TCMSP database (https://tcmsp-e.com/) for the six Chinese herbs: peach kernel, safflower, prepared rehmannia root, angelica, white peony, and Szechuan lovage root. The active pharmaceutical ingredients were selected based on oral bioavailability (OB) ≥30% and drug likeness (DL) ≥0.18 criteria (22). Subsequently, the effective component action targets were screened and standardized within the UniProt protein database (https://www.uniprot.org).

Identification of CIPN-related targets

Disease target genes related to the keywords "chemotherapy-induced peripheral neuropathy" were searched for on five databases: GeneCards (https://www.genecards.org/), OMIM (https://omim.org/), DrugBank (https://go.drugbank.com/), Pharmacogenomics Knowledgebase (PharmGKB) (https://www.pharmgkb.org/), and Therapeutic Target Database (TTD) (http://db.idrblab.net/ttd/). The criteria for selecting CIPN-related disease target genes were $P<0.05$ and an absolute log fold change (FC) value >1. Duplicate genes were merged to finalize the CIPN target genes. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

PPI network construction

The intersection of the THSWD target gene set and CIPN-related target genes was used to identify the potential targets for the THSWD treatment of CIPN. Candidate targets obtained via Venn diagram were introduced into the STRING database (https://string-db.org/) to construct the PPI network (22). We selected multiple proteins with parameters set to high confidence (0.900), limiting the biological species to "humans" and retaining the "string_interactions.tsv" file.

Construction of a compound-target network and critical subnetwork

A compound-target network was established to clarify the relationship between active compounds and potential targets. "string_interactions.tsv" was imported into Cytoscape 3.8.0 software for visual analysis. The network analyzer feature in Cytoscape 3.8.0 was used to analyze topological parameters (23), with core targets being collected based on degree values (24). Nodes in the network represented drug chemical components or targets, with edges indicating their relationships. Topologically significant genes were first identified by calculating the degree centrality (DC), closeness centrality (CC), betweenness centrality (BC), eigenvector centrality (EC), local average connectivity-based centrality (LAC), and network centrality (NC). Nodes exceeding twice the median degree value formed a significant intersecting PPI network. Furthermore, nodes exceeding the median values of the aforementioned five topological parameters constituted

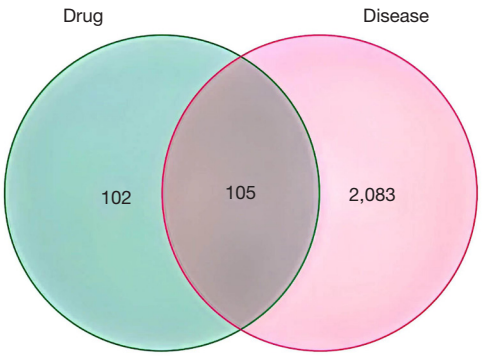

Figure 1 Venn diagram of active THSWD components and CIPN targets. THSWD, Taohong Siwu decoction; CIPN, chemotherapy-induced peripheral neuropathy.

the core PPI network.

GO and KEGG enrichment analysis

GO and KEGG enrichment analyses were conducted to explore the potential functions of candidate targets. GO enrichment analysis covered biological processes (BPs), cellular components (CCs), and molecular functions (MFs), while KEGG enrichment analysis focused on potential biological pathways and functions related to the targets. With $P<0.01$, the main BPs and metabolic pathways were analyzed and enriched, with the results being visualized in bubble charts.

Molecular docking technology

Key subnetwork intersections were selected as core genes to select receptor proteins. Core receptor proteins' structures were downloaded from the Protein Data Bank (PDB) database (http://www.rcsb.org/pdb/home/home.do), PyMOL software was used to simulate the dehydration separation of ligands and receptor proteins, and AutoDockTools was used for hydrogenation. Based on the degree values in the compound-target network, top active components were employed as molecular ligands. Molecular ligands' 2D structures, downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), were converted to 3D structures using Chem3D software, which also calculated and exported 3D structures by minimizing the energy related to molecular structures. Original PDB file formats were converted to PDBQT file formats recognized by the AutoDock Vina program. Key proteins in the subnetwork with higher significance and corresponding molecular ligands with higher values in the compound-target network were selected. AutoDock Vina was then used to calculate docking scores, which indicated binding affinity. Lower docking scores suggested more stable binding between the ligand and protein.

Results

Screening of active THSWD components and drug-related targets

Chemical components of the six herbs in THSWD were collected from the TCMP database, which included 23 components for peach kernel, 22 for safflower, 2 for prepared rehmannia root, 13 for white peony, 2 for angelica, and 7 for Szechuan lovage root. A total of 856 target proteins corresponding to these active components were identified in the UniProt database. After removal of duplicates, 208 unique targets remained.

Screening of the potential targets related to the action of THSWD against CIPN

CIPN-related disease target gene information was screened through the GeneCards, OMIM, DrugBank, PharmGKB, and TTD databases, yielding 2,297 target genes for CIPN after the merger of duplicates. A Venn diagram was used to identify 105 common targets between THSWD active components and CIPN, as presented in *Figure 1*; the green represents the active drug component targets, the pink represents the CIPN targets, and the intersection represents the common targets.

Construction of the compound-target network

A diagram visualizing the drug-compound-target-disease network for THSWD was created using Cytoscape software and consisted of 41 active THSWD components on the outer circle and 105 CIPN targets on the inner circle (*Figure 2*). The active drug components with numerous connections included quercetin, kaempferol, β-carotene, stigmasterol, luteolin, baicalein, and myristicin.

PPI network construction and the critical subnetwork analysis of the core targets

The 105 common target genes were input into the

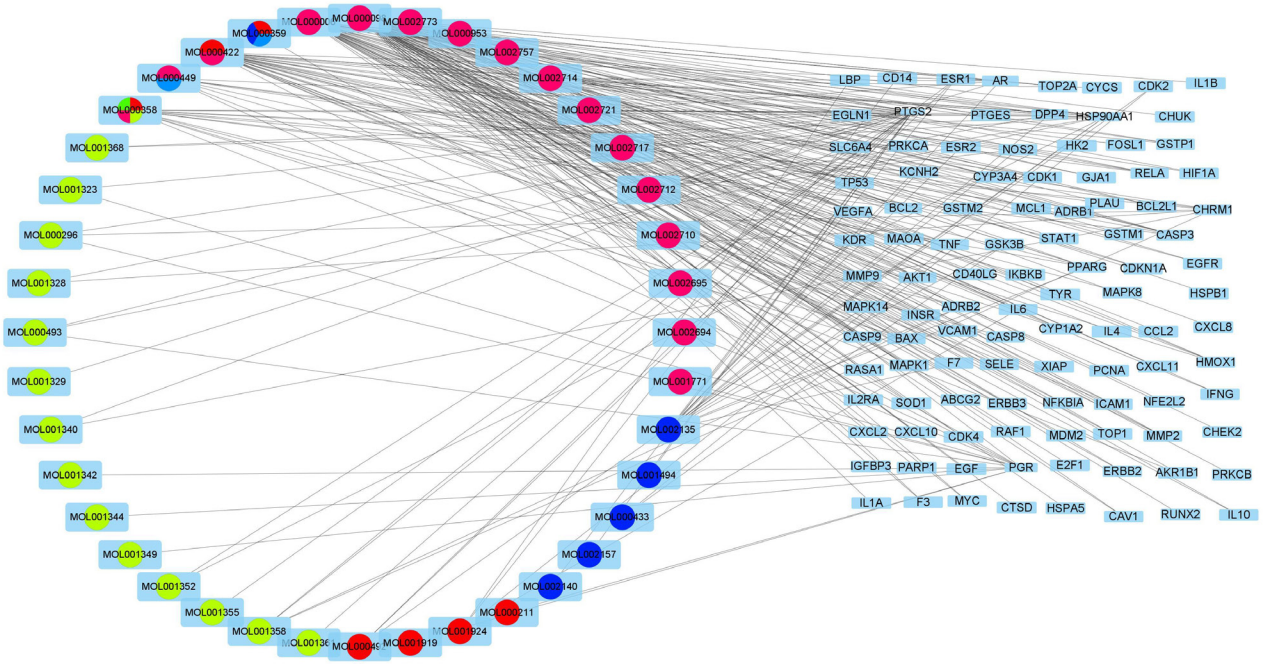

Figure 2 THSWD drug-compound-target-CIPN network diagram. The central blue rectangles represent target genes. The edges' different colors represent the compounds of various Chinese medicines: red for safflower, blue for Szechuan lovage root, yellow for white peony, and green for peach kernel. THSWD, Taohong Siwu decoction; CIPN, chemotherapy-induced peripheral neuropathy.

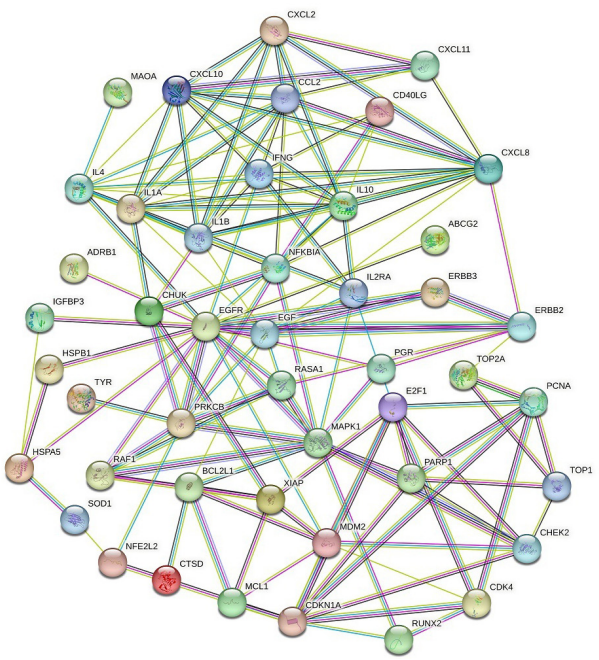

Figure 3 PPI network diagram of the common targets of THSWD and CIPN. PPI, protein-protein interaction; THSWD, Taohong Siwu decoction; CIPN, chemotherapy-induced peripheral neuropathy.

STRING database for PPI network analysis and included 93 nodes and 594 edges (*Figure 3*). Using the CytoNCA plugin, median values for BC, CC, DC, EC, LAC, and NC were calculated. Further target candidate screening identified eight core genes with significant values. The final core PPI network of THSWD targets consisted of *MYC*, *TNF*, *MAPK14*, *AKT1*, *ESR1*, *RELA*, *TP53*, and *HSP90AA1* (*Figure 4*).

GO and KEGG enrichment analysis

The Bioconductor package in R software was used to conduct GO enrichment analysis on 105 common target genes, resulting in 2,999 identified GO terms. These included 2,190 BP terms, 58 CC terms, and 151 MF terms. The GO terms were ranked according to their P value, and the top ten were visualized in a bubble chart (*Figure 5A*). The horizontal axis of the chart represents the number of gene enrichments, while the vertical axis represents functional enrichment. The results indicated that THSWD mainly acts on membrane rafts, extracellular organelle membranes, and outer mitochondrial membranes. It exerts its effects through processes such as DNA-binding transcription

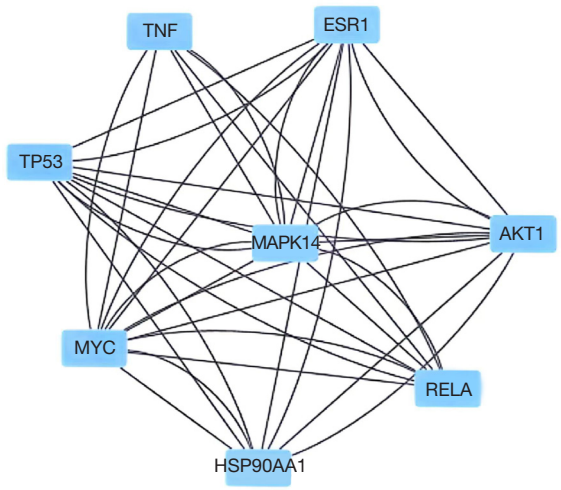

Figure 4 PPI network diagram of the core targets. PPI, protein-protein interaction.

factor binding, cytokine receptor binding, ubiquitin-like protein ligase binding, protein serine/threonine kinase activity, and receptor ligand activity. These target genes play a crucial role in responses to chemical stress, oxidative stress, antibiotics, and lipopolysaccharides.

KEGG enrichment analysis was also performed on the 105 common target genes via the Bioconductor package in R software, with 168 pathways being identified. The pathways were ranked according to their P value, and the top 30 are visualized in *Figure 5B*. In this figure, the horizontal axis represents the number of enriched genes in the pathway, while the vertical axis represents pathway enrichment. THSWD may exert its therapeutic effects on CIPN by regulating signaling pathways such as the PI3K-Akt signaling pathway, MAPK signaling pathway, TNF signaling pathway, IL-17 signaling pathway, and NF-κB signaling pathway.

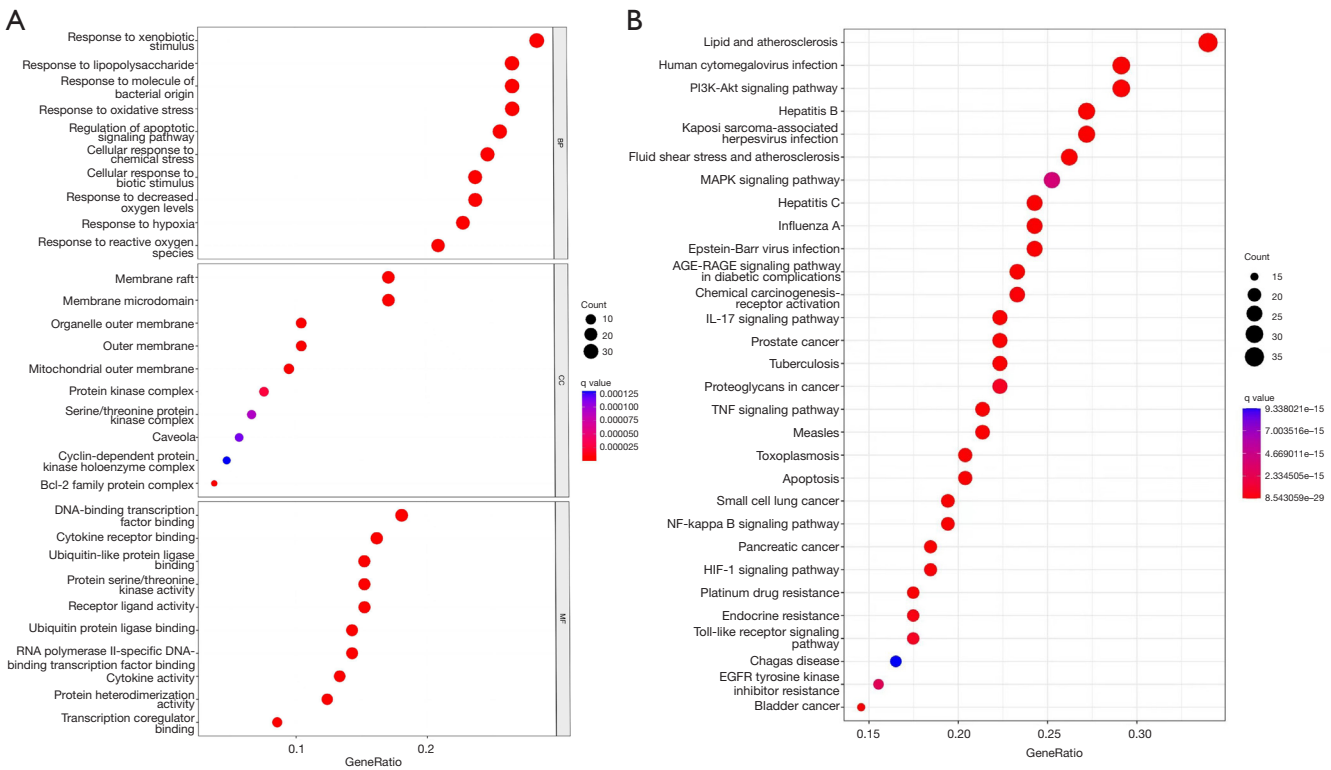

Figure 5 GO and KEGG enrichment analysis of THSWD and CIPN. (A) GO enrichment analysis bubble chart of the top 10 terms. (B) KEGG pathway enrichment analysis of the top 30 terms. BP, biological process; CC, cellular component; MF, molecular function; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; THSWD, Taohong Siwu decoction; CIPN, chemotherapy-induced peripheral neuropathy; MAPK, mitogen-activated protein kinase; AGE, advanced glycation end products; RAGE, receptor for advanced glycation end products; TNF, tumor necrosis factor; HIF-1, hypoxia inducible factor-1; EGFR, epidermal growth factor receptor.

Molecular docking technology

The eight core genes (*MYC*, *TNF*, *MAPK14*, *AKT1*, *ESR1*, *RELA*, *TP53*, and *HSP90AA1*) were chosen for molecular docking analysis. From the compound-target interaction network, we identified homologous active compounds targeting receptor proteins. These compounds included quercetin, luteolin, kaempferol, baicalein, catechin, and beta-carotene. Molecular docking analysis was performed to validate the interactions between these molecular ligands and receptor proteins. Docking scores lower than −5.0 kcal/mol indicated good binding interactions, while scores lower than −7.0 kcal/mol indicated strong binding interactions (25). Typically, the lower the binding energy between the ligand and the receptor, the more stable the conformation. Key targets with high degree values in the active component-target-pathway network, including *MAPK14* (8.768) and *MYC* (8.006), were selected. The docking scores were −7.5 and −6.2 kJ/mol, respectively. The core components of *MAPK14* (myristicin) (*Figure 6*) and the core component of *MYC* (quercetin) (*Figure 7*) were subjected to molecular docking validation using AutoDock.

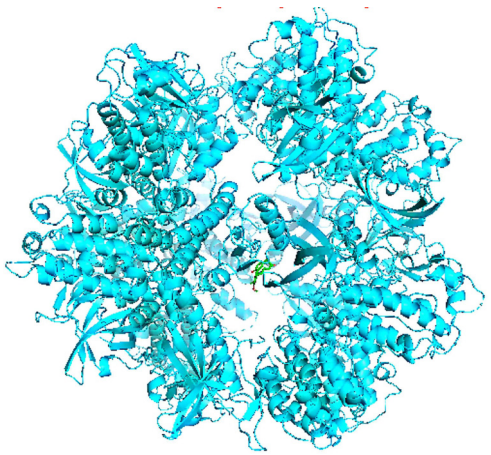

Figure 6 Molecular docking of *MAPK14* with myristicin.

Discussion

Peripheral neuropathy refers to nerve damage caused by any form of injury, inflammation, or degeneration in the peripheral nervous system. CIPN is a common complication during cancer treatment and is often classified as dose-limiting toxicity. Symptoms of CIPN can progressively worsen with the continuous accumulation of chemotherapy drug doses, potentially leading to permanent nerve damage. CIPN can persist or even worsen after chemotherapy is stopped, significantly affecting the patient's quality of life. Therefore, early prevention, timely detection and assessment, and effective treatment are crucial for managing CIPN. Currently, as no preventative measures for CIPN are recommended in guidelines, clinicians often manage it by reducing the dose or stopping chemotherapy, and safe and effective prevention and treatment methods are still lacking. The integration of TCM and Western medicine is a unique treatment model in China. TCM categorizes CIPN under conditions such as "bi syndrome", which is characterized by blockage and lack of flow due to external pathogenic factors such as wind, cold, damp, and heat invading the body, obstructing the meridians, and hindering the circulation of qi and blood. This results in clinical manifestations such as muscle soreness, numbness, heaviness, difficulty in stretching and flexing, or even joint swelling and heat. The primary pathogenesis of CIPN

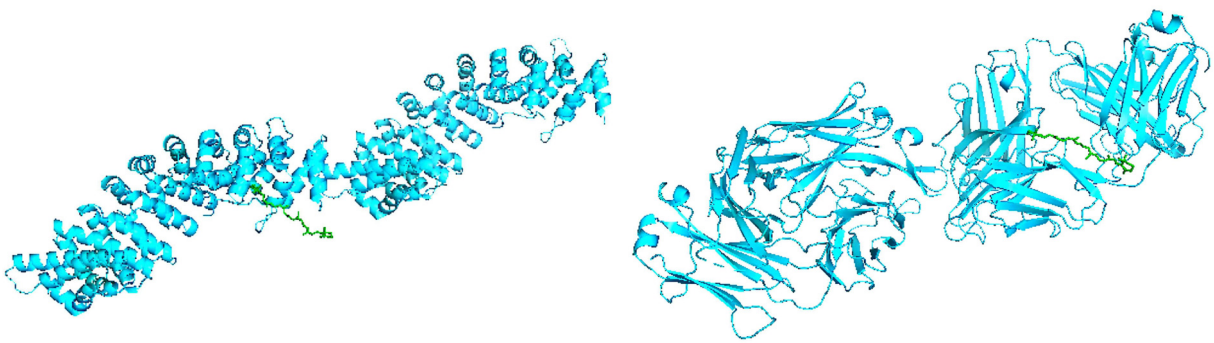

Figure 7 Molecular socking of *MYC* with quercetin.

can be attributed to the severe injury of qi and blood by chemotherapy drugs, blockage of meridians by pathogens, and numbness due to blood not nourishing the tendons or numbness exacerbated by wind-cold due to deficiency in the meridians and inadequate defensive qi reaching the extremities (26). For CIPN treatment, the prevention stage focuses on invigorating qi and promoting blood circulation, while the treatment stage emphasizes warming the meridians and promoting circulation (27). THSWD has the effects of promoting circulation, removing blood stasis, invigorating qi, nourishing blood, dispelling stasis, and relieving pain (28), which align with the numbness and pain symptoms of CIPN. There have been clinical reports of using THSWD to treat CIPN, but studies on its mechanism of action are limited. The high content of active components in TCM formulas, combined with variables such as binding sites and involvement in signaling cascades, hinders their clinical application and promotion. Therefore, constructing a multi-compound, multi-target, and multi-pathway regulatory network based on systematic and standardized bioinformatics methods for screening and analyzing data on active components and core targets is gradually becoming a new method for researching the molecular mechanisms of TCM formulas. With the proposal of network pharmacology technology, the research idea of single target and single component has begun to change to the overall exploration and systematic regulation (19). It can be used to predict and identify the target of TCM decoction action and the active ingredient group, clarify the mechanism of action, and systematically reveal the core molecular target and pharmacodynamic biological network of TCM decoction. Finally, omics techniques [proteomics (20), metabolomics, gene chip (21)] were used to obtain bioeffect spectra of experimental animals before and after modeling and drug intervention, from which key targets and pathways were screened, and cross-referenced with the network model. This study employed network pharmacology and molecular docking techniques to explore the potential mechanisms of action for THSWD in the treatment of CIPN, with the aim of providing new avenues for CIPN treatment.

Risk factors for CIPN include diabetes, a history of chronic heavy alcohol use, thyroid dysfunction, and HIV infection (29). The mechanisms underlying CIPN are not yet fully understood and may vary depending on the chemotherapeutic agents used. Potential mechanisms involve the disruption of microtubule architecture, mitochondrial oxidative stress, abnormalities in autophagy, alterations in the activity of Na^+ channels, demyelination, damage to normal cellular DNA, and processes involving immune activation and inflammation, including activation of monocyte/macrophage-associated receptors (30). This study analyzed the components of THSWD using network pharmacology, identifying the top seven chemical components to be quercetin, β-carotene, myristicin, stigmasterol, luteolin, baicalein, and kaempferol. These compounds are primarily found in safflower and Szechuan lovage root, two herbs known for their efficacy in promoting qi (energy flow), activating blood circulation, and unblocking channels. Quercetin, kaempferol, luteolin, and baicalein are significant members of the flavonoid family, known for their anti-inflammatory, antioxidative, immune-modulatory, and neuroprotective effects. Research has shown that quercetin mitigates the oxidative stress, autophagy, and apoptosis induced by cisplatin, significantly improving cisplatin-induced neurotoxicity (31). Kaempferol was reported to alleviate neuropathic pain in a rat model of neuropathy by modulating the TLR4/MyD88/NF-κB signaling pathway, aligning with the symptomatic treatment of CIPN (32). Luteolin offers neuroprotection by enhancing nerve conduction velocity and inhibiting the growth of nerve fibers; clinically, it can regulate immune responses to inhibit the growth of tumor cells, thereby ameliorating symptoms of CIPN (33). Baicalein has been found to reduce reactive oxygen species and mitochondrial superoxide levels induced by oxaliplatin, thus decreasing the incidence of neuritis and significantly preventing oxaliplatin-induced sensory nerve conduction deficits (34). Myristicin exerts warming, qi-moving, anti-inflammatory, and analgesic effects and can improve the numbness and pain symptoms associated with CIPN (35). β-carotene reduces the production of pro-inflammatory cytokines and inhibits the activation of spinal cord astrocytes, significantly suppressing NF-κB pathway activation, thereby offering protection against oxidative stress and neuroinflammation (36). Stigmasterol modulates microglial M1/M2 polarization through the TLR4/NF-κB pathway, alleviating neuropathic pain (37). Hence, the primary chemical components of THSWD can be characterize by their reduction of neuropathic damage and alleviation of pain in the treatment of CIPN.

This study identified 105 common target proteins between drugs and diseases, which primarily act on the cell membrane and are involved in oxidative stress, inflammatory responses, and cell apoptosis through signaling pathways such as PI3K-Akt, MAPK, TNF, IL-17, and NF-κB. Previous research has found that TNFα, IL-1β,

and IL-6 play roles in neuropathic pain, reducing neuronal excitability via the MAPK/p38 pathway and thus alleviating mechanical allodynia in rats (38). It has been reported that MAPK and NF-κB are key signaling pathways in regulating inflammation-related neuropathogenic mechanisms (39). The increase in levels of inflammatory cytokines such as tumor necrosis factor α, IL-1β, and IL-17 promotes the occurrence of CIPN (40). The activation of MAPK/NF-κB promotes the production of TNFα, IL-1β, and IL-6 (41); these findings indicate that TNFα, IL-1β, IL-6, MAPK, and NF-κB play a crucial role in the onset and maintenance of neuropathic pain. Molecular docking of the main active components with key targets in the active component-target-pathway network, such as *MAPK14* and *MYC*, showed docking scores of –7.5 and –6.2 kJ/mol, respectively. Docking scores lower than –5.0 kcal/mol indicated that the conformations had good binding interactions (25), confirming the high binding activity between the molecules and targets. *MAPK14*, a principal member of the MAPK family, leads to the phosphorylation of *p38MAPK* mediated by the activation of microglial pathways, resulting in the release of inflammatory factors and the occurrence and development of CIPN (42). *HSP90AA1*, an important member of the heat shock protein family and a critical molecular chaperone between cells, is involved in cellular survival, signal transcription, transcription regulation, and inflammatory responses (43), and plays a significant role in the occurrence and development of CIPN. Therefore, THSWD may alleviate CIPN-induced neuronal cell damage and reduce pain sensitization by activating the MAPK/NF-κB signaling pathway and by preventing and repairing neuronal cell damage.

Although this study provides insights into the mechanistic pathways of THSWD in the treatment of CIPN through network pharmacology and molecular docking, it has certain limitations that should be addressed. Most notably, the reliance on database-derived targets and components may not fully capture the complexity of *in vivo* interactions, and pharmacokinetics and dynamic molecular responses might have been overlooked. Furthermore, the molecular docking approach, despite offering valuable predictions on binding affinities, cannot serve as a substitute for empirical validation in biological systems. The absence of experimental validation of the identified pathways and targets within clinical or physiological contexts marks a significant caveat, necessitating subsequent *in vitro* and *in vivo* studies to confirm the theoretical predictions and to evaluate the clinical applicability of THSWD in managing CIPN.

In this study, network pharmacology and molecular docking methods were employed to identify core genes, which included *MYC*, *TNF*, *MAPK14*, *AKT1*, *ESR1*, *RELA*, *TP53*, and *HSP90AA1*. Subsequent enrichment analysis identified related pathways, and the molecular docking of key compounds with core targets was compared to simulate the *in vivo* binding process. A literature review revealed that these genes and pathways are primarily involved in oxidative stress, inflammatory responses, and apoptosis, processes which are also associated with the pathogenesis of CIPN and the pharmacological actions of THSWD. Therefore, our findings suggest that the mechanism by which THSWD ameliorates CIPN could be realized by directly and indirectly controlling the aforementioned major targets and related pathways, represent a new avenue for future experimental research. Due to the limitations of network pharmacology, we need check the above results (eight core targets that identified by PPI analysis in this study: *MYC*, *TNF*, *MAPK14*, *AKT1*, *ESR1*, *RELA*, *TP53*, and *HSP90AA1*) in a suitable model to obtained correlation data.

Conclusions

This study aimed to investigate the mechanisms of THSWD in the treatment of CIPN using a network pharmacology approach. We performed compound and target predictions, followed by network analysis. Through network pharmacology, we analyzed the composition and targets of THSWD, screened 69 compounds and 856 genes, and ultimately identified 105 genes related to CIPN. THSWD primarily treats CIPN through six key compounds, including kaempferol, quercetin, luteolin, myricanone, beta-sitosterol, and baicalein, and eight key target genes (*MYC*, *TNF*, *MAPK14*, *AKT1*, *ESR1*, *RELA*, *TP53*, and *HSP90AA1*). These genes are implicated in five main signaling pathways: PI3K-Akt signaling pathway, MAPK signaling pathway, TNF signaling pathway, IL-17 signaling pathway, and NF-κB signaling pathway. This network pharmacology study reveals the potential multi-target and multi-component mechanisms of THSWD in treating CIPN and provides a scientific basis for further research into its therapeutic mechanisms.

Acknowledgments

Funding: This work was supported by Health and Wellness Development Promotion Project-Supporting Public

Benefit Project for Enhancing the Scientific Research Capability of National Public Hospitals (No. KM-ZLGJ-048), the Natural Science Foundation of Chongqing (No. CSTB2022NSCQ-MSX1362), and the Chongqing Fuling District Medical Science Research Project (No. 2023KWLH013).

Footnote

Reporting Checklist: The authors have completed the STREGA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1019/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1019/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1019/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Burgess J, Ferdousi M, Gosal D, et al. Chemotherapy-Induced Peripheral Neuropathy: Epidemiology, Pathomechanisms and Treatment. Oncol Ther 2021;9:385-450.
2. Greenwald MK, Ruterbusch JJ, Beebe-Dimmer JL, et al. Risk of incident claims for chemotherapy-induced peripheral neuropathy among women with breast cancer in a Medicare population. Cancer 2019;125:269-77.
3. Sreeram K, Seaton R, Greenwald MK, et al. Chemotherapy-induced peripheral neuropathy in the detroit research on cancer survivors (ROCS) cohort. Cancer Causes Control 2023;34:459-68.
4. Arkema EV, Cozier YC. Sarcoidosis epidemiology: recent estimates of incidence, prevalence and risk factors. Curr Opin Pulm Med 2020;26:527-34.
5. Zhou L, Yang H, Wang J, et al. The Therapeutic Potential of Antioxidants in Chemotherapy-Induced Peripheral Neuropathy: Evidence from Preclinical and Clinical Studies. Neurotherapeutics 2023;20:339-58.
6. Bae EH, Greenwald MK, Schwartz AG. Chemotherapy-Induced Peripheral Neuropathy: Mechanisms and Therapeutic Avenues. Neurotherapeutics 2021;18:2384-96.
7. van der Leeden M, Huijsmans RJ, Geleijn E, et al. Tailoring exercise interventions to comorbidities and treatment-induced adverse effects in patients with early stage breast cancer undergoing chemotherapy: a framework to support clinical decisions. Disabil Rehabil 2018;40:486-96.
8. Crevenna R, Ashbury FD. Physical interventions for patients suffering from chemotherapy-induced polyneuropathy. Support Care Cancer 2018;26:1017-8.
9. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. J Clin Oncol 2020;38:3325-48.
10. Licht T, Keilani M, Crevenna R. Chemotherapy-induced peripheral neuropathy (CIPN). memo - Magazine of European Medical Oncology 2021;14:34-8.
11. Finnerup NB, Kuner R, Jensen TS. Neuropathic Pain: From Mechanisms to Treatment. Physiol Rev 2021;101:259-301.
12. Velasco R, Alberti P, Bruna J, et al. Bortezomib and other proteosome inhibitors-induced peripheral neurotoxicity: From pathogenesis to treatment. J Peripher Nerv Syst 2019;24 Suppl 2:S52-62.
13. Luo BY, Zhou HS, Xiao QX, et al. An exploratory study on the mechanism of Huangqi Guizhi Wuwu Decoction in the treatment of neuropathic pain. Ibrain 2022;8:127-40.
14. Jiang H, Li M, Du K, et al. Traditional Chinese Medicine for adjuvant treatment of breast cancer: Taohong Siwu Decoction. Chin Med 2021;16:129.
15. Zhao C, Chen J, Yu B, et al. Effect of modified taohongsiwu decoction on patients with chemotherapy-induced hand-foot syndrome. J Tradit Chin Med 2014;34:10-4.

16. Hui YY, Bai YY, Gao GY, et al. The famous Chinese medicine doctor Xue Jing-Dong Taohong Siwu Decoction cured 1 case of primary liver cancer stage IIIa. TMR Cancer 2021;4:19.
17. Wang G, Wang G, Zhao K, et al. Modulation of T Cell Differentiation in Mice with COPD Combined with Lung Cancer Through Key Targets of PD-1 by Tao Hong Si Wu Tang. Appl Biochem Biotechnol 2024. [Epub ahead of print]. doi: 10.1007/s12010-024-04904-8.
18. Han B, Hao CW, Dong M, et al. Protective effect and potential mechanism of Taohong Siwu decoction on peripheral nerve injury of paclitaxel. Medical Journal of Chinese People's Liberation Army 2023;48:570-6.
19. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. Nat Chem Biol 2008;4:682-90.
20. Sun H, Zhang A, Yan G, et al. Proteomics study on the hepatoprotective effects of traditional Chinese medicine formulae Yin-Chen-Hao-Tang by a combination of two-dimensional polyacrylamide gel electrophoresis and matrix-assisted laser desorption/ionization-time of flight mass spectrometry. J Pharm Biomed Anal 2013;75:173-9.
21. Xiang Z, Sun H, Cai X, et al. The study on the material basis and the mechanism for anti-renal interstitial fibrosis efficacy of rhubarb through integration of metabonomics and network pharmacology. Mol Biosyst 2015;11:1067-78.
22. Szklarczyk D, Gable AL, Lyon D, et al. STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Res 2019;47:D607-13.
23. Li R, Li Y, Liang X, et al. Network Pharmacology and bioinformatics analyses identify intersection genes of niacin and COVID-19 as potential therapeutic targets. Brief Bioinform 2021;22:1279-90.
24. Xiao H, Qin X, Wan J, et al. Pharmacological Targets and the Biological Mechanisms of Formononetin for Alzheimer's Disease: A Network Analysis. Med Sci Monit 2019;25:4273-7.
25. Chen R, Song C, Qiu J, et al. Exploring the potential mechanism of Taohong Siwu decoction in the treatment of avascular necrosis of the femoral head based on network pharmacology and molecular docking. Medicine (Baltimore) 2023;102:e35312.
26. Li QY, Cai FH, Lu Y, et al. External Treatment With Chinese Herbal Medicine for Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review and Meta-Analysis. Front Pharmacol 2022;13:764473.
27. Liu YW, Chen YJ, Chen YH, et al. Therapeutic Efficacy of Traditional Chinese Medicine Syndrome-Based Formulae to Neuropathic Pain Caused by Chemotherapy. Integr Cancer Ther 2022;21:15347354221121095.
28. Chen G, Xie Y, Liu Y, et al. Taohong Siwu decoction for femoral head necrosis: A protocol for systematic review. Medicine (Baltimore) 2020;99:e19368.
29. Timmins HC, Mizrahi D, Li T, et al. Metabolic and lifestyle risk factors for chemotherapy-induced peripheral neuropathy in taxane and platinum-treated patients: a systematic review. J Cancer Surviv 2023;17:222-36.
30. Kacem H, Cimini A, d'Angelo M, et al. Molecular and Cellular Involvement in CIPN. Biomedicines 2024;12:751.
31. Mahmoud HA, Horany HEE, Aboalsoud M, et al. Targeting Oxidative Stress, Autophagy, and Apoptosis by Quercetin to Ameliorate Cisplatin-induced Peripheral Neuropathy in Rats. J Microsc Ultrastruct 2023;11:107-14.
32. Zhao B, Zhang Q, Liang X, et al. Quercetin reduces inflammation in a rat model of diabetic peripheral neuropathy by regulating the TLR4/MyD88/NF-κB signalling pathway. Eur J Pharmacol 2021;912:174607.
33. Rakoczy K, Kaczor J, Sołtyk A, et al. Application of Luteolin in Neoplasms and Nonneoplastic Diseases. Int J Mol Sci 2023;24:15995.
34. Ji Y, Han J, Lee N, et al. Neuroprotective Effects of Baicalein, Wogonin, and Oroxylin A on Amyloid Beta-Induced Toxicity via NF-κB/MAPK Pathway Modulation. Molecules 2020;25:5087.
35. Ebrahimi F, Farzaei MH, Bahramsoltani R, et al. Plant-derived medicines for neuropathies: a comprehensive review of clinical evidence. Rev Neurosci 2019;30:671-84.
36. Zhou L, Ouyang L, Lin S, et al. Protective role of β-carotene against oxidative stress and neuroinflammation in a rat model of spinal cord injury. Int Immunopharmacol 2018;61:92-9.
37. Si W, Li X, Jing B, et al. Stigmasterol regulates microglial M1/M2 polarization via the TLR4/NF-κB pathway to alleviate neuropathic pain. Phytother Res 2024;38:265-79.
38. Liang F, Liu M, Fu X, et al. Dexmedetomidine attenuates neuropathic pain in chronic constriction injury by suppressing NR2B, NF-κB, and iNOS activation. Saudi Pharm J 2017;25:649-54.
39. Chen X, Wu S, Chen C, et al. Omega-3 polyunsaturated fatty acid supplementation attenuates microglial-induced inflammation by inhibiting the HMGB1/TLR4/NF-κB pathway following experimental traumatic brain injury. J Neuroinflammation 2017;14:143.
40. Kim Y, Jung YH, Park SB, et al. TMI-1, TNF-α-Converting Enzyme Inhibitor, Protects Against Paclitaxel-

Induced Neurotoxicity in the DRG Neuronal Cells In Vitro. Front Pharmacol 2022;13:842779.
41. Chen X, Chen C, Fan S, et al. Omega-3 polyunsaturated fatty acid attenuates the inflammatory response by modulating microglia polarization through SIRT1-mediated deacetylation of the HMGB1/NF-κB pathway following experimental traumatic brain injury. J Neuroinflammation 2018;15:116.
42. Qin B, Li Y, Liu X, et al. Notch activation enhances microglial CX3CR1/P38 MAPK pathway in rats model of vincristine-induced peripheral neuropathy. Neurosci Lett 2020;715:134624.
43. Liu C, Zhao W, Su J, et al. HSP90AA1 interacts with CSFV NS5A protein and regulates CSFV replication via the JAK/STAT and NF-κB signaling pathway. Front Immunol 2022;13:1031868.

(English Language Editor: J. Gray)

Cite this article as: Zhou M, Liu L, Tan Y, Huang R, Yang Z. The mechanism of Taohong Siwu decoction in treating chemotherapy-induced peripheral neuropathy: a network pharmacology and molecular docking study. Transl Cancer Res 2024;13(7):3842-3853. doi: 10.21037/tcr-24-1019

