The Study on the Action Mechanism of the Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) Couplet Herbs on Membranous Nephropathy Based on Network Pharmacology

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Abstract

Objective Our objective was to explore the action mechanism of the Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) couplet herbs in the treatment of membranous nephropathy (MN) based on network pharmacology.

Methods The active ingredients and targets of Jinyingzi (Rosae Laevigatae Fructus) and Qianshi (Euryales Semen) were screened by systematic pharmacology database and analysis platform. Online Human Mendelian Genetic database and GeneCards database were used to retrieve MN-related targets. The active ingredient-related targets and MN disease targets were introduced into Venny 2.1, and Wayne diagram was drawn. The intersection targets were the potential targets of the Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) couplet herbs in the treatment of MN. The protein interaction network of potential targets was constructed, and the core targets were screened with String platform. Metascape platform was used for functional enrichment analysis of gene ontology (GO) and pathway enrichment analysis of Kyoto Encyclopedia of Genes and Genomes (KEGG). The “herb-active ingredient-target-pathway” networks were drawn by using Cytoscape software, and the key components, targets, and signaling pathways were screened.

Results A total of 8 active ingredients and 193 related targets in Jinyingzi (Rosae Laevigatae Fructus) and Qianshi (Euryales Semen) were screened out; a total of 1,621 targets of MN disease and 105 potential targets for the treatment of MN were obtained in the treatment with Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) couplet herbs; 40 core targets were screened by protein–protein interaction network topology analysis; a total of 1,978 results were obtained by GO function enrichment analysis, and 206 signal pathways were obtained by KEGG pathway enrichment analysis and screening. The network topology analysis of “herb-active ingredient-target-pathway” showed that the key components included quercetin, kaempferol, β-sitosterol, etc.; the key targets included...
**Introduction**

Membranous nephropathy (MN) is a common glomerular disease in China, with a large number of clinical manifestations of proteinuria, hypoalbuminemia, edema, and hyperlipidemia. It is one of the most common pathological types of nephrotic syndrome, with uniform thickening of glomerular capillary matrix and diffuse deposition of subcutaneous immune complexes as its pathological characteristics. Studies have shown that the detection rate of MN in all renal biopsy samples is about 23.4%, which is the second most common glomerular disease after immunoglobulin A (IgA) nephropathy. It has been found that in idiopathic MN, about 30% of patients can completely spontaneously resolve, 30% would develop lifelong proteinuria while maintaining normal renal function, and the rest would progress to end-stage renal failure. At present, the Western medicine treatments for MN are mainly glucocorticoids combined with immunosuppressive agents. However, these treatments, with expensive treatment costs, often produce serious adverse reactions and their side effects can further aggravate the renal burden. For the limitations of Western medicine, more and more patients and clinicians choose to combine it with Chinese herbs for the treatment of MN.

There is no discussion on the name, etiology, pathogenesis and related treatment of MN in traditional Chinese medicine (TCM). According to the symptoms and signs, modern doctors classify MN into the categories of edema, low back pain, fatigue, kidney wind, etc., and summarize that the pathogenesis lies in deficient foundation with excess external manifestations, and the deficiency is mainly about the spleen and kidney, and the excess is mainly about wind pathogen and blood stasis. If spleen qi becomes deficient and fails to transport, transform and ascend the lucid, it will lead to disordered distribution of the body fluid which will accumulate locally or overflow to the skin and result in edema; failure of lucid qi to ascend and leakage of essence will bring about proteinuria. Deficient kidney qi, dysfunction of the bladder to transpire and fluid immersion in the skin will cause edema; insufficient kidney qi to consolidate and store essence may lead to proteinuria. When Chinese herbs are applied to treat MN, it is based on tonifying the spleen and kidney, supplemented by promoting diuresis and detumescence, and eliminating proteins. Protein belongs to the category of “essence” and “essential qi” in the theory of TCM. Therefore, the application of essence-consolidating and urine-astringing herbs in the treatment of MN has significant clinical efficacy in eliminating urinary protein. Professor Pingdong Zheng, in the treatment of proteinuria, advocated consolidating essence to achieve the purpose of “plugging the flow” while consolidating the foundation. He chose jinyingzi (Rosae Laevigatae Fructus), qiansi (Euryales Semen), fupenzi (Rubi Fructus), wuweizi (Schisandraceae Chinensis Fructus) to consolidate the kidney and astringe essence. In the treatment of MN, Professor Liqun Song applied the jinyingzi (Rosae Laevigatae Fructus)–qianshi (Euryales Semen) couplet herbs to achieve the efficacy of tonifying the kidney, strengthening the spleen, astringing, and consolidating the essence of the lower energizer. Professor Hongtao Yang often applied the method of tonifying the kidney and spleen with jinyingzi (Rosae Laevigatae Fructus) and qiansi (Euryales Semen) to consolidate the kidney and essence. It is obvious that when many doctors treat MN, they choose kidney-nourishing and essence-consolidating herbs represented by jinyingzi (Rosae Laevigatae Fructus) and qiansi (Euryales Semen). Jinyingzi (Rosae Laevigatae Fructus) is sour in taste and mild in nature and pertains to the lung, spleen, kidney, and bladder meridians. It has the effects of consolidating essence and astringing urine, checking mottluggage and leukorrhagia, astringing the large intestine, and relieving diarrhea. It is often used in clinical treatment of spermatorrhea, metrorrhagia, leukorrhagia, and diarrhea, etc. Modern pharmacological studies have confirmed that the chemical components contained in jinyingzi (Rosae Laevigatae Fructus) are phenolic acid, steroids, triterpenes, phenylpropanoids, etc., which have antioxidant, anti-inflammatory, and bacteriostatic effects and can improve renal function and immunity, reduce blood sugar and fight against tumor, etc. Qianshi (Euryales Semen) is sweet and astringent in taste, mild in nature, and pertains to the spleen and kidney meridians. It has the functions of invigorating the spleen and stopping diarrhea, tonifying the...
Materials and Methods

The Active Ingredients of the Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) Couplet Herbs and Screening of Their Related Action Targets

The chemical components were retrieved from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, http://tcmspw.com/tcmsp.php) with the keywords of Jinyingzi (Rosae Laevigatae Fructus) and Qianshi (Euryales Semen). The active ingredients of the above herbs were obtained according to the screening criteria of oral bioavailability ≥ 30% and herb-like properties (drug likeness) ≥ 0.18. Target proteins associated with the active ingredients were obtained on the TCMSP and the target protein names were standardized through the UniProt database (http://www.UniProt.org).

Acquisition of Targets for Membranous Nephropathy and Potential Targets for the Treatment of Membranous Nephropathy by Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) Couplet Herbs

With the keyword of “membranous nephropathy,” the Online Human Mendelian Inheritance in Man (OMIM, https://www.omim.org) and GeneCards database (https://www.genecards.org) were used to search the targets related to MN, integrate the collected disease targets, remove the duplicate values, and finally obtain MN disease targets. The selected herb active ingredient-related targets and MN disease targets were introduced into Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/), Wayne diagram was drawn, and the intersection targets of the Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) couplet herbs for active ingredient treatment of MN were obtained, which were the potential targets of these couplet herbs for the treatment of MN.

Establishment of Protein–Protein Interaction Network

The potential targets were input into the online String 11.5 database (https://string-db.org/), the specie was selected as “Homo sapiens”, the “highest configuration” was set to 0.9, the single node was deleted, the protein–protein interaction (PPI) network was drawn, and the results in TSV format were exported. The obtained data were input into Cytoscape 3.9.0, topology analysis was visualized and performed with a network analyzer, and the core targets were selected according to the network node degree value (degree).

Functional Enrichment Analysis of Gene Ontology and Pathway Enrichment Analysis of Kyoto Encyclopedia of Genes and Genes

The screened core targets were uploaded to the Metascape database (https://metascape.org/) for gene ontology (GO) function enrichment analysis and Kyoto Encyclopedia of Genes and Genes (KEGG) pathway enrichment analysis. p < 0.01 was set as the screening criteria, and the enrichment results were visualized through the bioinformatics cloud platform (http://www.bioinformations.com.cn/).

Construction of Herb-Active Ingredient-Target-Pathway Network

The active ingredients, core targets, and KEGG pathways of Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) were uploaded to Cytoscape 3.9.0 software to construct a “herb-active ingredient-target-pathway” visualization network. A network analyzer was used to analyze the topology of the network, and key components, key targets, and key pathways were screened according to the network node degree.

Results

Active Ingredients and Related Targets of Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) Couplet Herbs

Seven active ingredients of Jinyingzi (Rosae Laevigatae Fructus) and two active ingredients of Qianshi (Euryales Semen) were retrieved in TCMSP, and nine compounds in total. The active ingredients for which target information could not be obtained were eliminated, and eight active ingredients of Jinyingzi (Rosae Laevigatae Fructus) and Qianshi (Euryales Semen) were finally obtained. The relevant targets of active ingredients were obtained from the TCMSP database, and the targets were standardized using the UniProt database. One hundred and ninety-three targets were obtained after deduplication. See → Table 1.

Membranous Nephropathy-Related Targets and Potential Targets of Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) Couplet Herbs for the Treatment of Membranous Nephropathy

GeneCards database was used to retrieve the targets of MN, and the score was set to be greater than the average for screening, and 1,186 targets related to MN were obtained.
The OMIM database was used to retrieve 476 targets related to MN. The retrieved disease targets were combined, and the duplicate values were removed. Finally, 1,621 targets related to MN were obtained. The active-ingredient targets and the MN targets were passed through a Venny platform to draw a Wayne diagram, and the intersection targets were taken to obtain 105 potential targets for the treatment of MN by Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) couplet herbs. See Fig. 1.

Protein–Protein Interaction Network and Core Targets
The obtained intersection targets were uploaded to the String platform, the single node was deleted, the PPI network relationship of the intersection targets was obtained, and the TSV file was exported. The TSV file was imported into Cytoscape 3.9.0 for visualization, and the network consisted of 105 nodes and 378 edges. A total of 40 core targets were obtained, including AKT1, interleukin-2 (IL-2), tumor protein p53, caspase 3 (CASP3), caveolin-1, signal transducer and activator of transcription 1, androgen receptor, MYC, epidermal growth factor receptor, CASP8, mitogen-activated protein kinase 8 (MAPK8), MAPK1, tumor necrosis factor (TNF), IL-10 and IL-6, etc. See Fig. 2.

Gene Ontology Function Enrichment Analysis and Kyoto Encyclopedia of Genes and Genes Pathway Enrichment Analysis
Metascape Platform was used for GO function enrichment analysis and KEGG pathway enrichment analysis of the core targets for the treatment of MN with Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) couplet herbs, and the analysis results were visualized by using the Bioinformatics Cloud Platform, as shown in Fig. 3. A total of 1,978 results were obtained by GO function enrichment analysis (p < 0.01), in which the biological process involved response to an inorganic substance, regulation of cell motility, response to cytokine, response to bacterium, response to hormone, etc.; cell composition mainly included membrane raft, membrane microdomain, side of membrane, etc.; molecular function mainly involved cytokine receptor binding, receptor ligand activity, cytokine activity, DNA-transcription factor binding, etc. A total of 206 signaling pathways were obtained through KEG pathway enrichment analysis and screening (p < 0.01), mainly including HIF-1 signaling pathway, MAPK signaling pathway, PI3K/AKT signaling pathway, JAK kinase/STAT signaling pathway, advanced glycation end (AGE)/receptor of AGE (RAGE) signaling pathway, TNF signaling pathway, IL-17 signaling pathway, Toll-like receptor signaling pathway, p53 signaling pathway, NF-κB signaling pathway, VEGF signaling pathway, etc. The top 20 enrichment analysis items were selected to draw the bubble diagram. The results are shown in Figs. 3 to 6.

Herb-Active Ingredient-Target-Pathway Network
The herbs, active ingredients, core targets, and pathways were introduced into Cytoscape 3.9.0 software to construct the “herb-active ingredient-target-pathway” network diagram, as shown in Fig. 7. The analysis by network analyzer showed that quercetin was the main ingredient in the treatment of MN with Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) couplet herbs; the other ingredients, respectively, included kaempferol, β-sitosterol, 4’-methyl-N-Methyl chlorophyll and β-carotene, as shown in Table 2. The top key targets of connectivity, media and compactness in the network were AKT1, MAPK1, JUN, B-cell lymphoma-2 (BCL2), prostaglandin-endoperoxide synthase

### Table 1 Active ingredients of jinyingzi (Rosae Laevigatae Fructus)–qianshi (Euryales Semen) couplet herbs

| Chinese herbs                        | MOLID   | Marks | Active ingredients          | OB/% | DL |
|--------------------------------------|---------|-------|----------------------------|------|----|
| Jinyingzi (Rosae Laevigatae Fructus) | MOL001494 | JYZ1  | Mannitol                   | 42.00 | 0.19 |
|                                      | MOL000358 | JYZ2  | β-sitosterol               | 36.91 | 0.75 |
|                                      | MOL000422 | JYZ3  | Kaempferol                | 41.88 | 0.24 |
|                                      | MOL005030 | JYZ4  | Gondor acid               | 30.70 | 0.20 |
|                                      | MOL008628 | JYZ5  | 4’-Methyl-N-Methyl Chlorophyll | 53.43 | 0.26 |
| Qianshi (Euryales Semen)             | MOL002773 | QS    | β-carotene               | 37.18 | 0.58 |
|                                      | MOL007180 | QS1   | Vitamin E                 | 32.29 | 0.70 |

Abbreviation: OB, oral bioavailability.
2 (PTGS2), RELA, CASP3, TNF, protein kinase C alpha (PRKCA), VEGFA, MAPK8 and IL-6, as shown in ►Table 3. Key pathways mainly include AGE/RAGE signaling pathway, PI3K/AKT signaling pathway, MAPK signaling pathway, TNF signaling pathway, JAK/STAT signaling pathway, HIF-1 signaling pathway, IL-17 signaling pathway, Ras signaling pathway, NF-κB signaling pathway, Toll-like receptor signaling pathway, p53 signaling pathway, VEGF signaling pathway, and mTOR signaling pathway in diabetic complications, as shown in ►Table 4.

Discussion
In TCM, it believes that the basic therapeutic principle of MN is to tonify the kidney and consolidate essence, and the herbs represented by Jinyingzi (Rosae Laevigatae Fructus) and Qianshi (Euryales Semen) have been widely used in clinical practice and have achieved remarkable clinical efficacy. For example, Professor Chuanhui Ye’s self-formulated Ye’s Xiao-bai prescription was used to eliminate proteinuria with Jinyingzi (Rosae Laevigatae Fructus) and Qianshi (Euryales Semen) to tonify the kidney and consolidate essence. For example, Professor Yueyi Deng used Jinyingzi (Rosae Laevigatae Fructus) to nourish the kidney and fill the essence. Professor Daning Zhang also likes to use Jinyingzi (Rosae Laevigatae Fructus) to consolidate essence and astringe urine, Qianshi (Euryales Semen), and Shayuanzi (Astragali Complanati Semen) to tonify the kidney and consolidate essence in the treatment of MN. In the treatment of MN in the nonedema stage, Professor Qinguo Hong also chose the herbs Jinyingzi
(Rosae Laevigatae Fructus) and Qianshi (Euryales Semen) to strengthen the kidney and consolidate essence, which means that sufficient kidney qi ensures sealed and consolidated essence, and the essence will be controlled rather than being leaked out. 

Professor Shili Cao also treated MN by benefiting the kidney and consolidating essence with Jinyingzi (Rosae Laevigatae Fructus) and Qianshi (Euryales Semen). 

According to this study and related studies, the main active ingredient quercetin in Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) couplet herbs has anti-inflammatory, antioxidant, antidiabetic and immunity-regulating effects, and it has certain renal protection efficacy. Quercetin can effectively inhibit the expression of TNF, IL-1β, IL-17, IL-6, and also inhibit the phosphorylation of inflammatory signaling pathways such as NF-κB, TLR4, and STAT3, and reduce the expression of inflammatory factors and renal inflammatory response by inhibiting the activation of PI3K/AKT signaling pathway, thereby improving renal function. Kaempferol has antioxidation, anticancer, antiviral and immunity-regulating effects, and it has been proved by experiments that kaempferol can significantly reduce the expression of IL-6 and TNF-α inflammatory factors in kidney tissues and inhibit inflammatory response. β-sitosterol has antioxidant, anti-inflammatory, and antitumor effects and plays an important role in kidney diseases and immune diseases. β-carotene has antioxidation, inflammatory response-regulating effects, which can enhance body immunity and improve the anticancer effect. Experiments have proved that β-carotene could inhibit the expression of NF-κB and IL-6.

Through KEGG enrichment analysis, it was found that Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) couplet herbs involved multiple signaling pathways in the treatment of MN and was closely related to the main targets. It was found that PI3K/AKT, as an upstream signaling pathway, could regulate and control the downstream mTOR signaling pathway, and excessive activation of PI3K/AKT/mTOR pathway could accelerate the occurrence and development of renal fibrosis in rats with MN. Inhibition of PI3K/AKT/mTOR pathway can slow down podocyte injury in rats with MN, thus achieving the purpose of protecting renal function in rats with MN. MAPK-related signaling pathways have also been confirmed to be involved in the process of renal fibrosis, and c-Jun amino-terminal kinase is a key mediator. MAPK signaling pathways reduce the thickening of glomerular basement membrane by inhibiting the phosphorylation of c-Jun. Studies have shown that overexpression of IL-17 can be used as one of the indicators to determine the progression of renal fibrosis. IL-17 signaling pathway, as an inflammatory pathway, can promote the secretion of inflammatory factors such as IL-6, TNF-α, thus playing a proinflammatory role. Inhibiting this pathway...
**Fig. 4** CC Bubble diagram of GO function enrichment analysis. CC, cell composition; GO, gene ontology.

**Fig. 5** MF Bubble diagram for GO function enrichment analysis. MF, molecular function; GO, gene ontology.
Fig. 6  Bubble diagram of KEGG pathway enrichment analysis. KEGG, Kyoto Encyclopedia of Genes and Genomes.

Fig. 7  Herb-active ingredient-target-pathway network diagram. Notes: JYZ: jinyingzi (Rosae Laevigatae Fructus); QS: Qianshi (Euryales Semen); diamond: the target; round: the active ingredient; inverted triangle: the pathway; larger node area and darker color indicate that the node is more important.
can effectively reduce the production of inflammatory factors in patients with MN. HIF-1 signaling pathway is directly related to hypoxia in the body and can induce increased apoptosis of glomeruli and renal tubules through oxidative stress. However, there is an obvious oxidative stress response in rats with MN. Down-regulation of HIF-1 signaling pathway can antagonize oxidative stress response and achieve renal protection.  

Activation of NF-κB signaling pathway is critical in the occurrence and development of kidney disease. Studies have found that up-regulation of NF-κB expression in renal tissues of rats with MN can promote glomerular mesangial cell proliferation. Therefore, inhibiting the excessive activation of NF-κB signaling pathway, reducing the release of inflammatory factors, and reducing glomerular mesangial cell proliferation can delay the progression of MN.

Through analysis, it was found that the Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) couplet herbs
could act on key targets such as AKT1, MAPK1, JUN, CASP3, TNF, VEGFA, MAPK8, IL-6, so as to inhibit signaling pathways of PI3K/AKT, MAPK, TNF, HIF-1, IL-17, NF-κB, VEGF, mTOR, etc., which plays a role in down-regulating inflammatory response, reducing urinary protein excretion and edema, and thus achieving the purpose of treating MN. This study has preliminarily confirmed the multicomponent, multitarget, multipathway synergistic effect of Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) couplet herbs in the treatment of MN, which provides the theoretical evidence for the clinical application of this couplet herbs and provides directions and references for future experimental studies.

**Conclusion**

The Jinyingzi (Rosae Laevigatae Fructus)–Qianshi (Euryales Semen) couplet herbs can regulate PI3K/AKT, MAPK, NF-κB signaling pathways in MN by targeting proteins of AKT1, MAPK8, PTGS2 through key components of quercetin, β-sitosterol and kaempferol, so as to inhibit the overexpression of inflammatory factors in renal tissues, regulate inflammatory response, and improve renal function.

CRediT Authorship Contribution Statement

**Haoyi Tian:** Conceptualization, data curation, formal analysis, visualization, and writing – original draft. **Tian Yun:** Funding acquisition, supervision, writing – review & editing.

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Conflict of Interest

The authors declare no conflict of interest.

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