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Exploring the mechanism of Shenqi Longmu Mixture in the treatment of chronic kidney disease based on network pharmacology and molecular docking

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Abstract. Objective: To analyze the mechanism of Shenqi Longmu Mixture in treating the progression of Chronic Kidney Disease (CKD) by network pharmacology. Methods: The active ingredients of Shenqi Longmu Mixture with potential pharmacological effects were screened using the TCMSP and HERB databases. Target prediction and analysis were performed using the PubChem database and Swiss Target Prediction platform to identify the potential targets of the prescription. Cytoscape software was employed to construct a multi-level "drug-active ingredient-target" network, and core chemical components were determined according to degree values. CKD disease targets were obtained from the OMIM and GeneCard databases, and the common targets of the drug and disease were identified. Core targets were acquired by constructing a Protein-Protein Interaction (PPI) network, followed by Gene Ontology (GO) functional enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses of the intersecting targets. Molecular docking was carried out with MOE software, and visualization analysis was implemented using PyMol software. Results: A total of 90 active ingredients were screened, among which quercetin, kaempferol, β-sitosterol, luteolin, taxifolin, and naringenin were the core components. There were 95 intersecting targets with CKD. GO enrichment analysis identified 2,206 biological processes, 126 cellular components, and 156 molecular functions. KEGG enrichment analysis yielded 160 signaling pathways. Conclusion: Shenqi Longmu Mixture may exert therapeutic effects on CKD through a multi-component, multi-target, and multi-pathway mode, providing a new theoretical basis for subsequent research.

Keywords: Shenqi Longmu Mixture, chronic kidney disease, network pharmacology, molecular docking

1. Introduction

Chronic Kidney Disease (CKD) is defined as abnormal renal structure or function lasting for more than 3 months. Its core clinical manifestations include progressive decline in renal function, accumulation of metabolic wastes in the body, and imbalance of the body's internal environmental homeostasis [1]. The global prevalence of CKD is 11%–13%, and the prevalence among Chinese adults is 13.1% [2]. This disease imposes

a heavy economic burden on individuals, families, and society as a whole, and has become an increasingly severe global public health problem. However, due to the severe shortage of kidney donors, most patients can only rely on blood purification to sustain life, and the high treatment cost places a heavy burden on the socio-economic and public health systems. At present, Western medicine treatments are mainly symptomatic, and renal replacement therapy is performed only after patients enter the uremic stage. In contrast, Traditional Chinese Medicine (TCM) has shown positive effects in delaying renal function decline and postponing dialysis, thereby helping to reduce the overall medical burden. The "chronic kidney disease-colonic axis" theory describes the bidirectional interaction between the kidney and the intestine. This theory holds that decreased renal function leads to intestinal microecological dysregulation and impaired barrier function; on the other hand, intestinal flora enter the blood circulation through the damaged intestinal mucosa, activate the immune system (such as the mononuclear phagocyte system), promote the release of various inflammatory factors, oxygen free radicals and other toxic substances, induce a chronic inflammatory state, and further aggravate the progression of kidney disease [3]. The gut-kidney axis unifies the kidney and intestine, providing theoretical support for the TCM external therapy of retention enema and a new method for the treatment of CKD.

As a specific application of TCM "purgation therapy", enema therapy originates from the principles of "opening the sweat pores, purifying the fu organs, and eliminating stagnant turbid substances" proposed in *Huangdi Neijing (The Yellow Emperor's Internal Classic)*. Based on syndrome differentiation and treatment, it promotes the excretion of accumulated metabolic wastes and toxins from the intestine by purging fu-organs to eliminate turbidity and guiding the pathogenic factors out according to the situation. Shenqi Longmu Mixture, composed of Astragali Radix, Codonopsis Radix, Cinnamomi Ramulus, Os Draconis Preparata, Concha Ostreae Preparata, Carthami Flos, and Rhei Radix et Rhizoma, has been clinically used in Yunnan Provincial Hospital of Traditional Chinese Medicine for many years, with the effects of tonifying the spleen and kidney, and detoxifying and purging turbidity. The specific action pathways and targets of this prescription in regulating the molecular mechanism of CKD pathological progression remain unclear. In this study, network pharmacology was used to screen the potential pharmacological active ingredients, as well as the action targets and signaling pathways for CKD, and a pharmacological network was established to further reveal its molecular mechanism, providing a theoretical basis for the subsequent clinical application research of this prescription.

2. Materials and methods

2.1. Screening of active ingredients and related targets in Shenqi Longmu Mixture

The main active ingredients of the seven Chinese herbs (Astragali Radix, Codonopsis Radix, Cinnamomi Ramulus, Os Draconis Preparata, Concha Ostreae Preparata, Carthami Flos, Rhei Radix et Rhizoma) in this prescription were obtained from the TCMSP database (https://old.tcmsp-e.com/tcmsp.php). Thresholds were set for screening: oral bioavailability (OB $\geq$ 30%), drug-likeness (DL $\geq$ 0.18), and intestinal epithelial permeability (Caco-2 ≥ -0.4 nm/s), and finally the active ingredients and target gene information of Shenqi Longmu Mixture were obtained. For Concha Ostreae and Os Draconis, which were not included in the TCMSP database, their chemical components were retrieved from the HERB database. The Smiles numbers were searched using the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), and then imported into the Swiss Target Prediction database (http://www.swisstargetprediction.ch/) to predict the related targets, with the species set to Homo sapiens. The merged targets were deduplicated to determine the final action targets of Shenqi Longmu Mixture.

2.2. Screening of CKD-related targets

In this study, "Chronic Kidney Disease" was set as the keyword, and the GeneCards (https://www.genecards.org/) and OMIM databases (https://omim.org/) were used for retrieval. After merging and removing duplicates, the related targets of CKD were obtained.

2.3. Screening of common targets between CKD and Shenqi Longmu Mixture

The Venn diagram was drawn with the help of the Bioinformatics website (https://www.bioinformatics.com.cn). The disease and drug targets were imported into this website to obtain the intersection and generate the Venn diagram.

2.4. Construction of the "drug-active ingredient-target" network

To study the core components of Shenqi Longmu Mixture acting on CKD, the screened active ingredients and intersecting targets of Shenqi Longmu Mixture were imported into Cytoscape 3.9.1 software. A "drug-ingredient-target" network was constructed, combined with topological analysis using the CytoNCA plugin, and the core components of Shenqi Longmu Mixture for the treatment of CKD were screened according to node degree values.

2.5. Construction of PPI network

The intersecting genes were imported into the STRING database, the species was limited to *Homo sapiens*, and the minimum interaction confidence was set to ≥ 0.7 to obtain the PPI network. Then the key targets were screened according to node values, and the core protein-protein interaction network was drawn with Cytoscape 3.9.1.

2.6. GO functional and KEGG pathway enrichment analysis

The intersecting targets of the drug and disease were imported into the DAVID database (http://david.ncifcrf.gov). GO functional and KEGG pathway enrichment analyses were performed on the potential targets of Shenqi Longmu Mixture in the treatment of CKD, and then the GO bar chart and KEGG bubble chart were drawn with the help of the Bioinformatics platform.

2.7. Molecular docking

The top 6 active ingredients by node value in the "drug-ingredient-target-disease" network and the top 6 proteins by node value in the PPI network were selected for molecular docking. The protein structures were obtained from the PDB database, and water molecules and ligands in the structures were removed using PyMol. The three-dimensional structures of the active ingredients were obtained from the PubChem database and converted to PDB format using Open Babel. AutoDock-Tools 1.5.6 software was used to add hydrogen atoms to the receptor proteins and ligands, which were saved in PDBQT format, and the relevant active pocket parameters were recorded. Finally, molecular docking was completed using AutoDock Vina software, and visualization analysis was performed with PyMol.

3. Results

3.1. Screening of active ingredients and targets of the drug

Based on TCMSP and HERB, the active ingredients and action targets of Astragali Radix, Codonopsis Radix, Cinnamomi Ramulus, Os Draconis Preparata, Concha Ostreae Preparata, Carthami Flos, and Rhei Radix et Rhizoma were obtained, with a total of 90 active ingredients and 3,429 action targets. Among them, Astragali Radix had 20 active ingredients and 1,229 action targets, Codonopsis Radix had 21 active ingredients and 747 action targets, Cinnamomi Ramulus had 7 active ingredients and 113 action targets, Carthami Flos had 22 active ingredients and 1,048 action targets, Rhei Radix et Rhizoma had 16 active ingredients and 292 action targets, and Os Draconis and Concha Ostreae each had 2 active ingredients. After integrating all targets and removing duplicates, 662 targets were obtained.

3.2. Acquisition of CKD targets and construction of venn diagram

After integration and deduplication, 1,034 disease targets were screened from the OMIM and GeneCards databases. The intersection of these disease targets and drug targets was obtained through the Bioinformatics Venn diagram platform, and finally 95 common action targets were obtained, as shown in Figure 1.

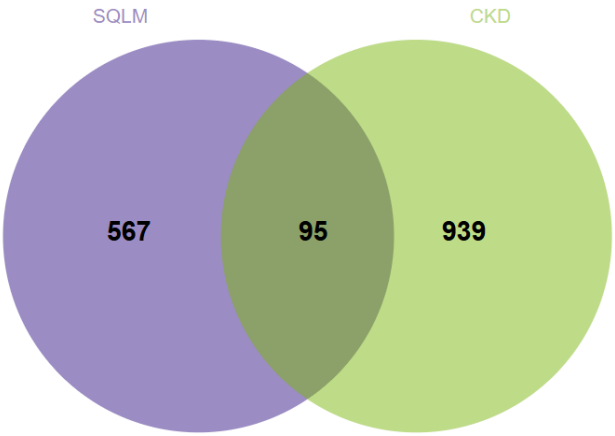

Figure 1. Venn diagram of drug and disease targets of Shenqi Longmu Mixture in the treatment of chronic kidney disease

3.3. Construction of the "drug-active ingredient-target" network

The active ingredients and intersecting targets of Shenqi Longmu Mixture were imported into Cytoscape 3.9.1 to obtain the "drug-active ingredient-target" network, as shown in Figure 2. The network contained 186 nodes and 1,011 edges. The top 6 components sorted by degree value from high to low were quercetin, kaempferol, β-sitosterol, luteolin, taxifolin, and naringenin.

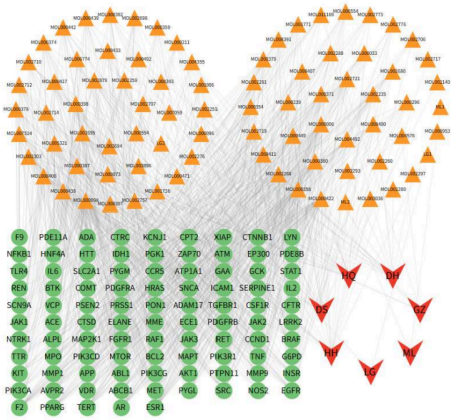

Figure 2. "Drug-active ingredient-target" network of Shenqi Longmu Mixture in the treatment of chronic kidney disease (Note: Yellow triangles represent drug active ingredients, red triangles represent drugs, and circles represent intersecting targets)

3.4. Construction of PPI network

The 95 intersecting targets of Shenqi Longmu Mixture and chronic kidney disease were imported into the STRING database to generate a PPI network, as shown in Figure 3. After processing with Cytoscape 3.9.1 and removing isolated nodes, the network contained 85 nodes and 524 edges, as shown in Figure 4. The top 6 targets by degree value were Epidermal Growth Factor Receptor (EGFR), tyrosine protein kinase Src (Src), Serine/Threonine Protein Kinase 1 (AKT1), Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (PIK3CA), Interleukin-6 (IL-6), and Phosphoinositide-3-Kinase Regulatory Subunit 1 (PIK3R1).

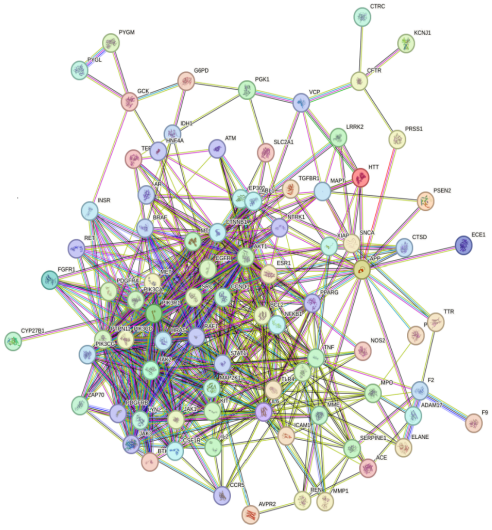

Figure 3. PPI network diagram of drug-disease intersecting targets of Shenqi Longmu Mixture in the treatment of chronic kidney disease

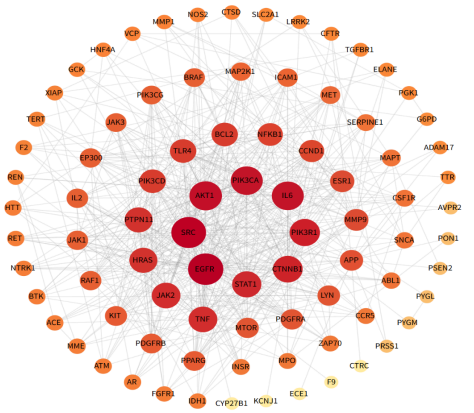

Figure 4. PPI visualization analysis diagram of drug-disease intersecting targets of Shenqi Longmu Mixture in the treatment of chronic kidney disease

3.5. GO functional and KEGG pathway enrichment analysis

A total of 2,491 statistically significant items were obtained by GO enrichment analysis (screening condition: $p < 0.05$), covering 2,209 biological processes, 126 cellular components, and 156 molecular functions. Biological processes were mainly related to the regulation of kinase activity, peptidyl-tyrosine phosphorylation and modification, MAPK cascade, cellular response to chemical/oxidative stress, and protein autophosphorylation. Cellular components were significantly enriched in membrane rafts, membrane microdomains, vesicle lumen, plasma membrane rafts, caveolae, cytoplasmic vesicle lumen, intercellular junctions, external side of plasma membrane, secretory granule lumen, and leading edge of cells. Molecular functions mainly included transmembrane receptor protein tyrosine kinase activity, protein tyrosine kinase activity/non-transmembrane protein tyrosine kinase activity, protein phosphatase binding, insulin receptor substrate binding, phosphoprotein binding, endopeptidase activity, and growth factor receptor binding, as shown in Figure 5. KEGG enrichment analysis identified 160 metabolic pathways, including PI3K-Akt, JAK-STAT and other signaling pathways, which are crucial for the occurrence and development of chronic kidney disease, as shown in Figure 6.

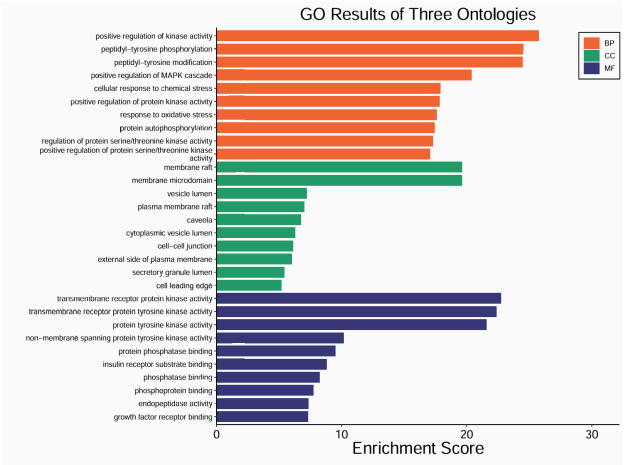

Figure 5. GO functional enrichment analysis

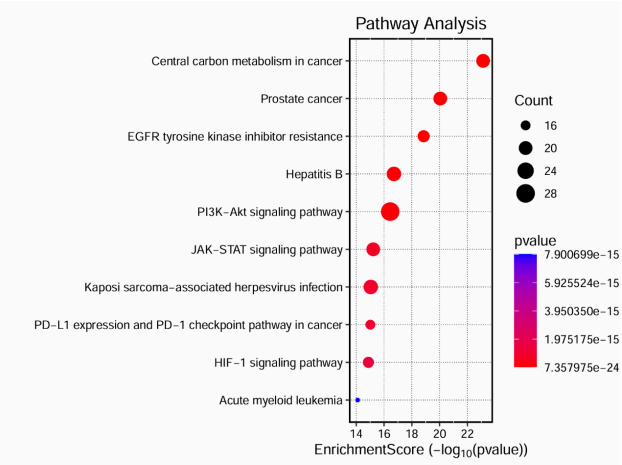

Figure 6. KEGG enrichment analysis

3.6. Molecular docking results

Molecular docking verification was performed on the core components (quercetin, kaempferol, β-sitosterol) and key targets (EGFR, Src, AKT1). The binding energies of all docking combinations ranged from -4.7451 to -6.6646 kcal/mol. According to the evaluation criteria of binding energy (binding energy < -4.25 kcal/mol indicates certain activity, < -5.0 kcal/mol indicates good binding state, and < -7.0 kcal/mol indicates strong binding), the experimental results showed that 7 docking combinations had good binding states, and the other 2 docking combinations had certain binding activity. Among them, Quercetin-EGFR (-5.4496 kcal/mol), beta-sitosterol–EGFR (-6.6646 kcal/mol), and Kaempferol–Src (-5.7363 kcal/mol) showed low binding energies in their respective compounds, and were visualized using PyMol software, as shown in Figure 7.

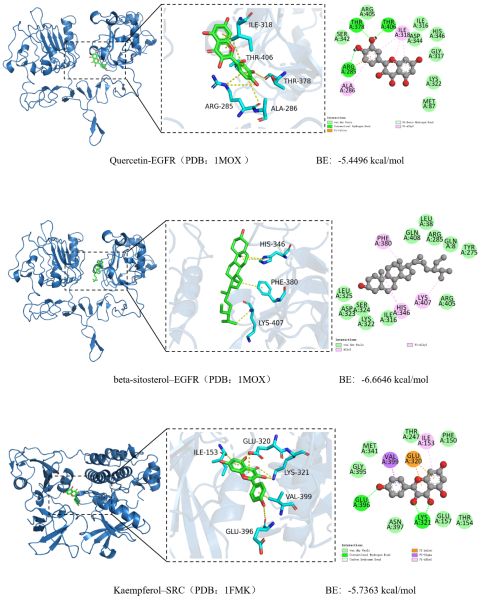

Figure 7. Molecular docking site diagram of ligands and receptors of Shenqi Longmu Mixture in the treatment of CKD

4. Discussion

Shenqi Longmu Mixture is a commonly used prescription in the Nephrology Department of Yunnan Provincial Hospital of Traditional Chinese Medicine with remarkable clinical efficacy. In this prescription, Astragali Radix strongly invigorates qi of the spleen and kidney and consolidates qi to astringe, while Rhei Radix et Rhizoma purges turbid toxins and removes blood stasis to unblock the fu organs, both serving as the monarch drugs. Codonopsis Radix, Os Draconis Preparata, and Concha Ostreae Preparata are the ministerial drugs: Codonopsis Radix combined with Astragali Radix enhances the effect of tonifying the middle-jiao and invigorating qi, which is the fundamental treatment for CKD due to its prolonged course; Os Draconis Preparata combined with Concha Ostreae Preparata exerts the effect of "softening and resolving hard masses", dissolving the internal stagnated pathogenic factors; meanwhile, they play the role of "astringing and consolidating", which can not only adsorb intestinal turbid toxins but also consolidate healthy qi. Cinnamomi Ramulus (warming yang and activating qi) and Carthami Flos (promoting blood circulation and removing blood stasis) serve as adjuvant drugs. The combination of all drugs not only invigorates qi and consolidates the kidney but also promotes blood circulation to remove blood stasis and purge fu-organs to eliminate turbidity. Studies have confirmed that emodin in Rhei Radix et Rhizoma inhibits the TLR4/MyD88/NF-κB signaling pathway, alleviating inflammatory response, renal tissue cell apoptosis, and renal tissue injury [4]; astragaloside IV in Astragali Radix alleviates renal fibrosis by inhibiting the calcineurin/NFAT pathway [5]. Codonopsis Radix can improve renal fibrosis and correct anemia in patients with chronic renal failure [6]. Trace metal elements in Os Draconis regulate immune function and accelerate the repair of damaged tissues [7]. Concha Ostreae Preparata regulates calcium and phosphorus metabolism disorders; calcium carbonate in Concha Ostreae is not easily absorbed by the intestine, and combines with increased phosphate radicals in the intestine to form calcium phosphate and excrete it [8]. Cinnamomi Ramulus extract downregulates the levels of multiple inflammatory factors in the body and exerts a significant anti-inflammatory effect [9]. Hydroxysafflor yellow A, the water-soluble monomer of Carthami Flos, significantly inhibits the release of inflammatory factors by regulating the AMPK/NF-κB/NLRP3 signaling pathway [10].

In this study, network pharmacology was used to analyze the active ingredients and mechanism of Shenqi Longmu Mixture, and quercetin, kaempferol, β-sitosterol, luteolin, taxifolin, and naringenin were screened as the core components for the treatment of CKD. Studies have shown that quercetin is involved in the regulation of multiple key signaling pathways such as Nrf2/HO-1, TGF-β1, and NF-κB, and exerts therapeutic effects by inhibiting oxidative stress, inflammatory response, apoptosis, and fibrosis, with a clear renal protective effect on CKD [11]. Relevant studies by Wang Chao et al. [12] confirmed that kaempferol can effectively regulate oxidative stress in renal tubular epithelial cells, synergistically inhibit p38 phosphorylation and the expression of its downstream inflammatory factors, thereby achieving renal protection. Sharmila et al. [13] found that β-sitosterol activates the NRF-2 signaling pathway in a chemically induced nephrotoxicity mouse model, improving the body's antioxidant defense level. This mechanism not only effectively removes excessive peroxides and toxins but also significantly reduces abnormally elevated serum creatinine, urea, and uric acid. Relevant studies have confirmed that luteolin intervention in rats with chronic renal failure can significantly reduce the activity of the TLR4/NF-κB signaling pathway, thereby alleviating the body's inflammatory response and improving renal injury [14]. Alanezi et al. [15] found that taxifolin alleviates renal tissue injury and significantly reduces blood urea nitrogen and serum creatinine levels by activating the Nrf2/HO-1 signaling pathway in a cisplatin-induced nephrotoxicity mouse model, thus protecting the kidneys. Zhu et al. [16] confirmed that naringenin can downregulate key factors such as TNF-α, IL-1β, and 5-HT by regulating intestinal flora in constipated mice, improve intestinal peristalsis, accelerate the transport of intestinal contents, and maintain the mucus barrier function.

The PPI network diagram shows that the core target proteins of Shenqi Longmu Mixture are EGFR, Src, AKT1, PIK3CA, IL-6, and PIK3R1. Excessive upregulation of EGFR caused by persistent inflammation, oxidative stress and other injuries can lead to the release of pro-fibrotic factors, further aggravating renal fibrosis [17]. Studies have shown that the Src-mediated PI3K-Akt signaling pathway can promote serine phosphorylation of endothelial nitric oxide synthase [18]. This process exerts endothelial-dependent vasodilation, thereby reducing peripheral resistance or inhibiting tubular-glomerular feedback, and ultimately increasing the glomerular filtration rate [19]. Studies have shown that inhibition of mitochondrial AKT1 activity leads to two key pathological changes in renal tubular cells: mitochondrial respiratory uncoupling and significantly increased oxidative stress; enhanced oxidative stress is the core factor causing renal cell damage [20]. Gain-of-function mutation of PIK3CA causes excessive activation of the PI3K/AKT pathway in podocytes, the key glomerular cells, leading to abnormal proliferation and dedifferentiation of podocytes; such podocyte dysfunction further damages the glomerular filtration barrier [21]. As a key factor mediating inflammatory response, IL-6 can induce a micro-inflammatory state in the body, which has been confirmed as an important risk factor for increased all-cause mortality in CKD patients [22]. PIK3R1 plays a key regulatory role in the PI3K/Akt signaling pathway. Enhanced PIK3R1 signaling causes renal tubular epithelial cells to release a large number of inflammatory mediators, which induce immune cell accumulation in renal tissue, forming an amplification effect of local inflammation, further damaging the structural integrity and normal physiological function of renal tubules [23].

The results of KEGG enrichment analysis indicate that JAK-STAT and PI3K-Akt are the main regulatory pathways of Shenqi Longmu Mixture. Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathway is involved in cell proliferation, differentiation, and apoptosis, as well as immune function regulation and inflammatory response. After establishing a rat model of renal ischemia-reperfusion injury, researchers detected that the phosphorylation levels of JAK2, STAT1, and STAT3 proteins in renal tissue of model rats were significantly increased. To clarify the function of JAK2 in this injury process, researchers conducted an intervention experiment using the JAK2 selective inhibitor AG490: when AG490 was administered immediately before and after renal ischemia-reperfusion, the expression of phosphorylated JAK2, STAT1, and STAT3 in the kidney was significantly inhibited; on this basis, the renal function of rats was significantly improved, the apoptosis and necrosis of renal tubular epithelial cells were greatly reduced, and the infiltration of macrophages in renal interstitial tissue was effectively alleviated [24]. Studies by Dube et al. [25] confirmed that STAT3 plays an important role in renal injury, mainly in two aspects: first, by regulating oxidative stress, STAT3 can significantly reduce the oxidative damage of proximal renal tubules, thus protecting the normal physiological function of this region; second, STAT3 can significantly inhibit the abnormal adhesion between leukocytes and vascular endothelial cells, reduce the migration and infiltration of inflammatory cells into renal tissue, thereby alleviating secondary renal injury caused by inflammatory response and delaying the progression of renal injury. The mTOR pathway, a key energy sensor in the kidney, plays a core role in cell metabolism and function regulation [26]. Studies have confirmed that inhibiting the mTOR signaling pathway through intervention can effectively alleviate the pathological process of renal interstitial fibrosis, thereby improving renal function [27]. Activated by phosphorylation, Akt directly acts on mTOR as an important upstream factor regulating mTOR activity. Meanwhile, Akt is also a key downstream molecule of the PI3K signaling pathway; as the core mediator of signal transduction in this pathway, its activation promotes subsequent signal transmission by phosphorylating a variety of downstream substrate molecules. Maintaining appropriate activity levels of PI3K and Akt is crucial for normal growth, development, function maintenance, and cell survival of organisms [28]. Studies by Liu et al. [29] showed that inhibiting the PI3K/AKT pathway can reverse lipid metabolism disorders such as glycerophospholipids and sphingolipids in

the kidneys of CKD rats, reduce lipid toxicity-mediated renal tubular injury, and further delay the progression of kidney disease.

5. Conclusion

In summary, based on network pharmacology and molecular docking technology, this study systematically analyzed the overall action mode and molecular mechanism of Shenqi Longmu Mixture in the treatment of chronic kidney disease. A total of 90 active ingredients and 95 common disease targets of the prescription were screened, and quercetin, kaempferol, β-sitosterol, luteolin, taxifolin, and naringenin were identified as the core pharmacodynamic substances, with EGFR, Src, AKT1, PIK3CA, IL-6, and PIK3R1 as the key action targets. GO functional and KEGG pathway enrichment analyses showed that it exerts renal protective effects mainly by regulating biological processes such as kinase activity, oxidative stress, inflammatory response, apoptosis, and fibrosis, and targeting core signaling pathways such as PI3K-Akt and JAK-STAT. Molecular docking results confirmed that the core components bind stably to key targets with good activity, verifying the rationality of the compatibility at the molecular level.

Overall, Shenqi Longmu Mixture achieves the TCM efficacy of invigorating qi and consolidating the kidney, promoting blood circulation to remove blood stasis, and purging fu-organs to eliminate turbidity through a synergistic mode of multi-component, multi-target, and multi-pathway, corresponding to pharmacological effects such as anti-inflammation, anti-oxidation, anti-fibrosis, regulation of immune and calcium-phosphorus metabolism, and protection of renal tubules and glomerular filtration barrier, thereby delaying the progressive decline of renal function and blocking the progression of chronic kidney disease. This study provides scientific network pharmacology evidence for the clinical application of Shenqi Longmu Mixture, lays a theoretical foundation for the subsequent animal experiments, cell verification, and precise clinical research, and has important reference value for the mechanism exploration and new drug development of TCM in the prevention and treatment of chronic kidney disease.

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