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Based on Network Pharmacology and Molecular Docking: Exploring the Mechanism of Salvia Miltiorrhiza - Tripterygium Wilfordii Combination Therapy for Diabetic Nephropathy

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Abstract: ***Objective:*** *To explore the mechanism of Salvia miltiorrhiza-Tripterygium wilfordii Hook. f. in the treatment of diabetic nephropathy based on network pharmacology and molecular docking.* ***Methods:*** *Effective components of the drug pair Salvia miltiorrhiza and Tripterygium wilfordii were screened from the TCMSP database. Relevant targets of the drug pair components were obtained from SwissTargetPrediction. Diabetic nephropathy (DN) targets were acquired through GeneCards, OMIM, and DisGeNET databases. The relevant targets of the drug pair components and the disease targets were uploaded to an online Venn diagram to obtain their intersection targets. The intersection targets were uploaded to the STRING database to construct a protein-protein interaction (PPI) network diagram. Cytoscape 3.9.1 software was used to filter core targets and construct a "drug pair-effective components-intersection targets" network diagram. GO and KEGG enrichment analysis were performed in the Metascape database, and the results were visualized using the online graphing website, "VennDiagram". The core targets predicted by network pharmacology and components were validated using molecular docking technology.* ***Results:*** *A total of 56 effective components of Salvia miltiorrhiza and 34 effective components of Tripterygium wilfordii were collected from the databases. There were 682 related targets for Salvia miltiorrhiza components and 654 for Tripterygium wilfordii components. A total of 1653 DN targets were obtained from the disease database. After the intersection of disease targets and drug pair component targets, 129 potential action targets were obtained. The key targets for the treatment of DN through PPI network were identified as TNF, AKT1, PPARG, and SRC, with key components such as luteolin and kaempferol. GO and KEGG enrichment analysis showed that the treatment of DN with Salvia miltiorrhiza-Tripterygium wilfordii mainly involves pathways related to cancer, lipid and atherosclerosis, IL-17 signaling pathway, and diabetic complications AGE/RAGE, among others. Molecular docking results showed that active components have good binding ability with core targets.* ***Conclusion:*** *Salvia miltiorrhiza-Tripterygium wilfordii mainly exerts its therapeutic effect on DN through active components such as luteolin and kaempferol, targeting related targets such as TNF, AKT1, PPARG, and SRC, and participating in multiple signaling pathways such as cancer-related pathways, lipid and atherosclerosis, IL-17 signaling pathway, and diabetic complication AGE/RAGE.*

Keywords: Salvia miltiorrhiza; Tripterygium wilfordii; Network pharmacology; Molecular docking; Diabetic nephropathy.

1. Introduction

Diabetic nephropathy (DN) is a common microvascular complication, occurring in approximately 40% of diabetic patients. It is a major cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD), and is also a leading cause of mortality and morbidity in diabetic patients [1]. The pathology of DN can involve the glomeruli, tubules, and interstitium of the kidney, with the main pathological mechanisms being tubular fibrosis, mesangial hypertrophy and expansion, inflammatory cell infiltration, accumulation of extracellular matrix, and podocyte autophagy [2]. Traditional Chinese Medicine (TCM) considers DN to be a manifestation of "thirst-thirst syndrome," falling within the categories of "turbid urine" and "edema," with the main pathophysiological mechanisms being qi deficiency, yin deficiency, and blood stasis. The deficiency of both qi and yin leads to blood stasis, which, when long-standing, deeply lurks in the renal network, forming minute accumulations, thereby leading to the occurrence of DN. Therefore, "qi and yin deficiency leading to blood stasis and accumulation obstructing the renal network" is the fundamental pathophysiology of this disease [3].

The current standard treatment for DN patients still focuses on controlling blood sugar and blood pressure to prevent the progression of DN and promote the resolution of proteinuria [4]. However, it cannot effectively halt the development of DN, and the incidence of severe adverse reactions during treatment is also continuously increasing. Therefore, finding a safe and effective treatment method has become a hot topic of current research. In recent years, the role of Traditional Chinese Medicine (TCM) therapy in regulating blood sugar and lipid metabolism, reducing kidney damage, delaying nephropathy, preventing glomerular sclerosis, and fibrosis has gradually been revealed. Chinese herbal medicine, with its multiple components, multiple targets, good efficacy, and minimal side effects, therefore, has a good protective effect on the kidneys of DN patients [5].

Salvia miltiorrhiza, derived from the dried roots and rhizomes of a plant in the Lamiaceae family, has a bitter taste and a slightly cold nature, and is associated with the heart, liver, and kidney meridians. It is revered as a sacred medicine for activating blood circulation and removing blood stasis. Over a hundred chemical constituents have been identified in Salvia miltiorrhiza, including tanshinones, salvianolic acids, volatile oils, polysaccharides, and nitrogen-containing compounds. Modern pharmacological research has found [6, 7] that Salvia miltiorrhiza and its related components possess strong anti-inflammatory, antioxidant, antihyperlipidemic, anticoagulant, antifibrotic properties, and can improve renal tissue ischemia-reperfusion and promote tissue repair. They protect renal cells and alleviate renal fibrosis through various pathways.

Tripterygium wilfordii, a root from a plant in the Celastraceae family, is documented in "Shennong's Herbal Classic" as having a pungent flavor and entering the liver and spleen meridians, and it is believed to unblock the twelve meridians. It is known for its effects in dispelling wind, dredging collaterals, and promoting blood circulation. More than 80 components have been isolated from Tripterygium wilfordii, mainly including diterpenoids, triterpenoids, alkaloids, and sugars. Modern studies have shown that Tripterygium wilfordii has anti-inflammatory, immunomodulatory, and antitumor effects [8]. Tripterygium wilfordii and its related preparations have protective effects on the kidneys, including reducing proteinuria, inhibiting renal fibrosis, and improving renal function, and are clinically used to treat diabetic nephropathy [9, 10].

However, the mechanisms by which Salvia miltiorrhiza and Tripterygium wilfordii, which contain multiple compounds and targets, exert their therapeutic effects on diabetic nephropathy (DN) are not well understood. This study predicts the mechanism of Salvia miltiorrhiza-Tripterygium wilfordii combination therapy for DN using network pharmacology and molecular docking. It analyzes and

screens effective components, active targets, and disease treatment targets and signaling pathways, providing a scientific basis for the experimental research and clinical application of the Salvia miltiorrhiza-Tripterygium wilfordii combination therapy for DN.

2. Materials and Methods

2.1 Potential Target Prediction of Salvia Miltiorrhiza and Tripterygium Wilfordii

Use the search term "danshen", "(" in TCMSP (Traditional Chinese Medicine Systems Pharmacology, https://tcmspw.com/tcmsp.php), The main bioactive components were selected according to the conditions of oral bioavailability (OB) ≥30% and drug likeness (DL) ≥0.18. To screen out the active ingredient in PubChem database (https://pubchem.ncbi.nlm.nih.gov) to get the molecular structure to "Canonical SMILES" format into the Swiss Target Prediction database (http://www. swisstargetprediction.ch), the query to predict the active ingredient targets, to predict the reliability of target screened, and remove duplicate targets, salvia miltiorrhiza respectively, tripterygium wilfordii potential targets.

2.2 DN Target Gene Prediction

In the Gene Cards database (https://www.genecards.org), DisGeNet database (http://www.disgenet. org/home/), OMIM database (http://www.omim.org) in search keywords "diabet ic kidney disease ", to obtain DN target protein genes. The targets obtained from the above databases were merged after removing duplicate values. The DN pathogenesis related targets and potential targets through Venny2.1 map Wayne (https://bioinfogp.cnb.csic.es/tools/venny/index.html), get the intersection targets.

2.3 Construction of Protein-protein Interaction (PPI) Network and Screening of Core Targets

The intersection targets were uploaded to the STRING12.0 database (https://string-db.org), the species was selected as "Homo sapiens", and the confidence of target association was set to 0.40. PPI analysis was performed on the intersection targets. The "tsv" file obtained through the STRING database was imported into Cytoscape 3.9.1 software, and three parameters were selected to evaluate the topological characteristics of nodes in the protein interaction network: Degree, Betweenness and Closeness were positively correlated with the importance of node network. According to these three parameters, the core targets of Salvia miltiorrhiz-Tripterygium willedii for DN were screened.

2.4 Screening of Key Components of Salvia Miltiorrhiza and Tripterygium Wilfordii in the Treatment of DN

Cytoscape 3.9.1 software was used to construct the drug-pair components-intersection target network, and the key components were screened according to the Degree value.

2.5 Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) Enrichment Analysis

Through the Metascape (http://metascape.org/) database, $P<0.01$ was used as the screening condition, and GO analysis and KEGG enrichment analysis of the core targets were performed. Through microscopic letter online platform (http://www.bioinformatics.com.cn/) drawn respectively GO analysis results triad bar graph and KEGG bubble chart analysis results.

2.6 Molecular Docking Verification

Molecular docking was performed between the screened core targets and the key components, and the "mol2" file of the screened key components was obtained from the TCMSP database. AutoDockTool 1.5.7 software was used to add polar hydrogen atoms to the ligand small molecules and save the corresponding PDBQT format. The 3D structure of the ligand protein was obtained by searching in the PDB database (https://www.rcsb.org/). The original PDB protein molecules were divided into protein and ligand, dewatering, hydrogenation and other operations by PyMOL, and saved in PDBQT format. Autodock Vina software was used to perform molecular docking of key components and core targets, and PyMOL was used to visualize the binding mode with the lowest energy.

3. Results

3.1 Collection of Active Ingredients and Targets for Drug Pairs

By searching the TCMSP database, with OB≥30% and DL≥0.18 as the screening conditions, the unmatched potential targets in the active ingredients were removed, and the repeated active ingredients were excluded, 56 active ingredients of salvia miltiorrhiza and 34 active ingredients of tripterygium wilfordii were obtained. Through the Swiss Target Prediction database, 682 targets related to the components of Salvia miltiorrhiza and 654 targets related to the components of tripterygium wilfordii were obtained.

3.2 PPI Network Analysis of Intersection Targets

Using "diabetic kidney disease" as the key word, we screened in GeneCards, OMIM and DisGeNET databases, and after removing duplicates, 1653 disease gene targets were obtained. Salvia miltiorrhiza and tripterygium wilfordii drug pairs were mapped to component-related targets and disease targets, and 129 intersection targets were obtained. The protein-protein interaction data were obtained from the STRING database, and the PPI network diagram of the core targets was established. See Figure 1 for details. The topology of Cytoscape3.9.1 was used to screen out the top 23 core targets from the common target sequence, and the PPI network diagram of the core targets was established. See Figure 2 for details.

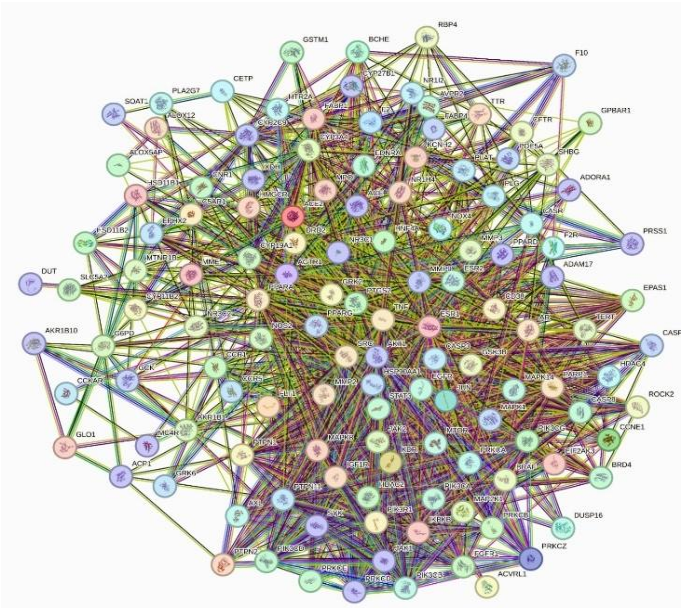

Figure 1: Intersection target protein network mapping

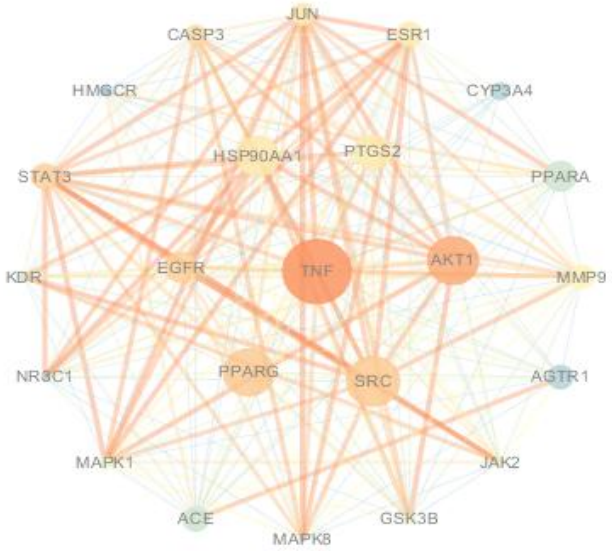

Figure 2: Key intersection target protein network mapping

3.3 Network Diagram Analysis of Drug Pair-effective Components-core Targets

The network graph included 2 drug nodes, 90 active component nodes (56 active component nodes of salvia miltiorrhiza and 34 active component nodes of tripterygium wilfordii) and 131 intersection target nodes, with a total of 221 nodes. See Figure 3 for details. According to the results of network diagram analysis, according to the Degree value, the effective components such as luteolin and kaempferol may be related to the treatment of diabetic nephropathy. TNF, AKT1, PPARG, SRC may play an important role. Among them, the active component luteolin and the core target TNF have more connecting edges, which play an important role.

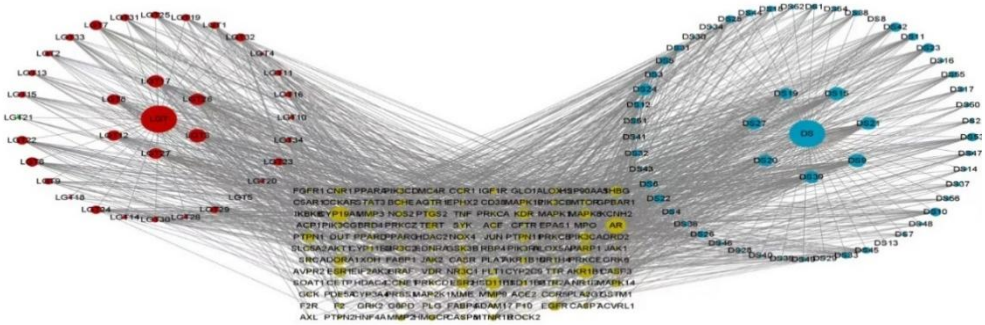

Figure 3: Drug pairs - Effective components - Intersection target network

Note: LGT: Tripterygium wilfordii; DS: miltiorrhiza; The red nodes represent the effective components of Tripterygium wilfordii, the blue nodes represent the effective components of Salvia miltiorrhiza, and the yellow nodes represent the intersection targets. The larger the area, the higher the degree value.

3.4 GO Function and KEGG Pathway Enrichment Analysis Results

3.4.1 GO functional enrichment analysis results

GO functional enrichment analysis was performed using the Metascape database to further clarify the possible role of intersection targets. According to the number and significance of gene enrichment, the

top 10 genes were selected. See Figure 4 for details. Regulation of transferase activity in enzyme-linked receptor protein signaling pathway; Cellular components were mainly involved in membrane rafts, membrane microdomains, cell membrane caveolae, plasma membrane rafts, euchromatin, etc. The molecular functions are mainly involved in kinase binding, nitric oxide synthase regulatory activity, nuclear receptor activity, phosphatase binding, protein kinase activity, etc.

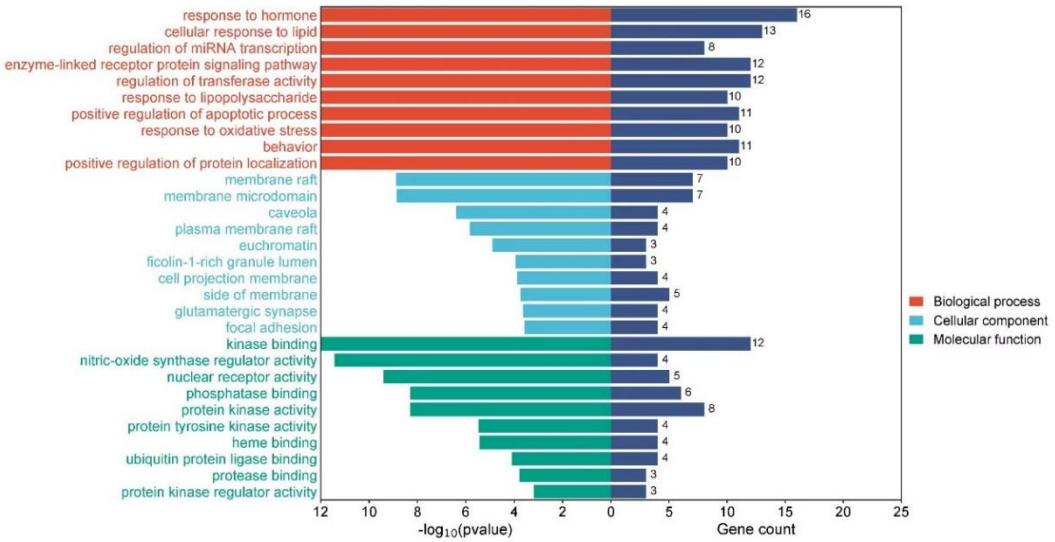

Figure 4: Three in one histogram of the core target GO function of Salvia miltiorrhiza-Tripterygium wilfordii medicine in the treatment of DKD

3.4.2 KEGG pathway enrichment analysis results

Using KEGG Pathway enrichment analysis in the Metascape database, a total of 123 signaling pathways were obtained according to the targets related to the treatment of diabetic nephropathy and the corresponding P values, and 20 pathways with higher scores were selected. At the same time, bubble diagram was drawn through the wechat website for visualization. See Figure 5 for details. The pathway enrichment analysis results showed that: It is mainly involved in cancer-related pathways, lipids and atherosclerosis, IL-17 signaling pathway, AGE/RAGE signaling pathway in diabetic complications and so on.

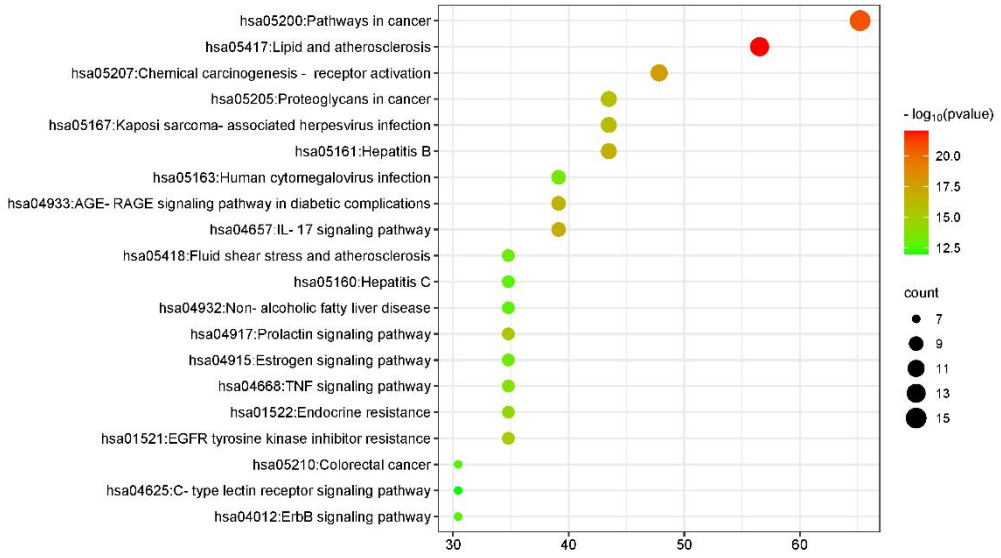

Figure 5: Enrichment analysis of the core target KEGG pathway in the treatment of DKD using

miltiorrhiza-Tripterygium wilfordii medicine

3.5 Analysis of Molecular Docking Results

According to the Degree value, luteolin, kaempferol were the main active ingredients The binding energy of Ydro-3H--2-one and TNF, AKT1, PPARG, SRC, The results are shown in Table 1, were all lower than -7kcal/mol, indicating that the main active ingredient had good stability with the key protein receptors. The partial molecular docking mode diagrams drawn are shown in Figures 6 and 7.

Table 1: The minimum binding energy between the main active ingredients and key target proteins(kcal/mol)

Active	AKT1	TNF	PPARG	SRC
luteolin	-9.8	-8.9	-7.9	-8.9
kaempferol	-8.8	-8.9	-7.4	-8.0

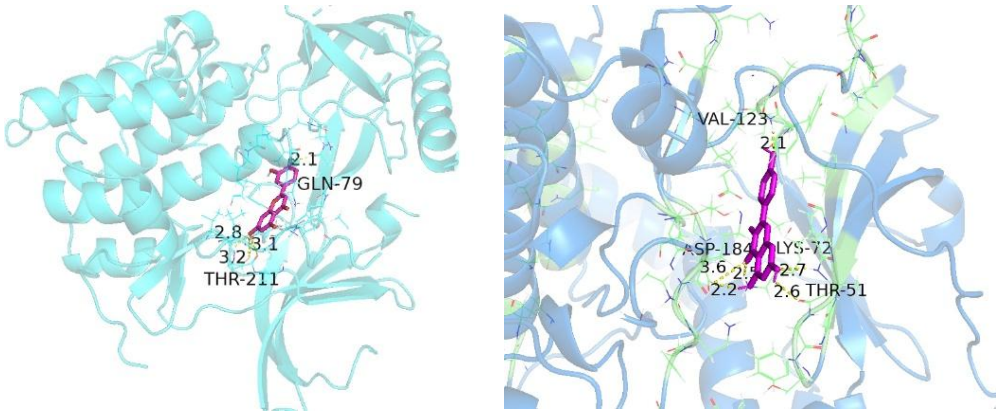

Figure 6: From left to right are the molecular docking diagrams of luteolin, kaempferol, and AKT1

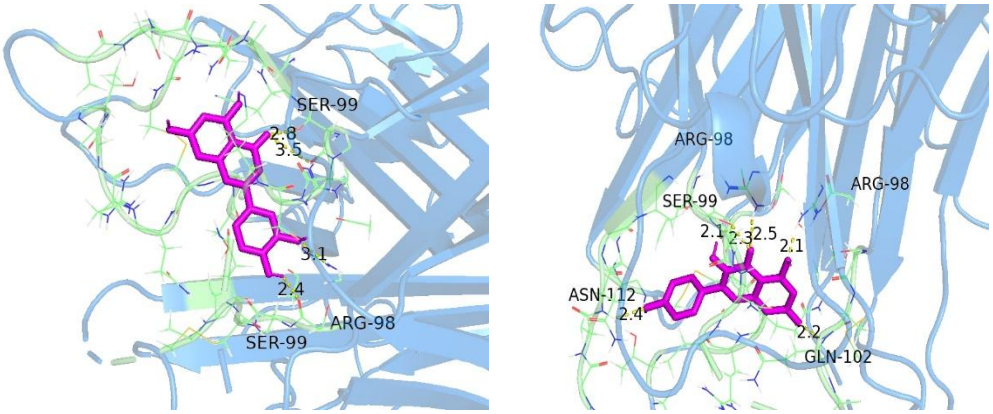

Figure 7: From left to right are the molecular docking diagrams of luteolin, kaempferol, and TNF

4. Discussion

The mechanisms of action of traditional Chinese medicine therapies are complex, with multiple components and targets. Analyzing the mechanisms of action of Chinese herbs becomes even more challenging when the pathophysiology is not fully elucidated. Network pharmacology, which combines systematic network analysis and pharmacology, allows for the systematic study of the active ingredients, targets, and pathways of drugs at the molecular level, enhancing our understanding of the interactions between components, targets, and pathways.

This study primarily employs network pharmacology and molecular docking to explore the

mechanism of action of the combination of Danshen (Salvia miltiorrhiza) and Lei Gong Teng (Tripterygium wilfordii) in the treatment of diabetic nephropathy (DN). Based on the network analysis of active components, targets, and DN for Danshen-Lei Gong Teng, the most significant active ingredients were identified as luteolin and kaempferol. Studies have shown that kaempferol has an inhibitory effect on oxidative stress and apoptosis in human renal glomerular endothelial cells under high glucose conditions [11], and it reduces kidney damage in diabetic or high glucose states by inhibiting the activation of the RhoA/Rock pathway and lowering the expression of oxidative stress and pro-inflammatory cytokines (TNF-α, IL-1β) [12]. Luteolin is a natural flavonoid compound widely present in various herbal medicinal plants and has multiple pharmacological effects such as anti-tumor, antitussive, expectorant, antibacterial, anti-inflammatory, and antioxidant activities [13]. Modern research indicates that luteolin can prevent and treat diabetes by improving insulin resistance, regulating lipid metabolism, inhibiting intestinal sugar and lipid absorption, and suppressing oxidative stress and inflammation [14], and in a study on the kidneys of STZ-induced diabetic rats, luteolin was found to protect the kidneys through its antioxidant effects and by reducing the protein expression of renal TGF-β1 and PAI-1 [15].

Through protein-protein interaction (PPI) network analysis, TNF, AKT1, PPARG, and SRC were identified as core targets, suggesting that these four targets may play an important role in the process of treating DN with Danshen-Lei Gong Teng. Research indicates that AKT1, also known as protein kinase B, is an important target of the downstream insulin signaling pathway that can prevent the dephosphorylation of the insulin receptor and control glucose transport pathways [16]. The activation of AKT1 promotes cell proliferation and inhibits apoptosis, making it a significant participant in the immunoinflammatory mechanism of diabetic nephropathy [17]. PPARG controls the peroxisome-proliferator-activated receptor-gamma pathway of fatty acid oxidation and is a key regulator of adipocyte differentiation and glucose homeostasis; its genetic polymorphisms are significant independent risk factors for DN patients [18]. Tumor necrosis factor TNF is an important target in the study of diabetic retinopathy and is heavily involved in the physiological and pathological processes of type 2 diabetes; the overexpression of TNF is positively correlated with the degree of insulin resistance (IR) [19]. In vivo experimental results show that the level of Src activation is positively correlated with podocyte mitochondrial damage, podocyte apoptosis, and the degree of renal function damage in db/db mice. In vitro experiments have found that inhibiting the activity of Src can reduce mitochondrial damage [20]. Therefore, it can be speculated that as the main active components, luteolin and kaempferol may delay the progression of DN by reducing oxidative stress, inhibiting the expression of inflammatory mediators, regulating lipid metabolism, and improving insulin resistance.

KEGG pathway enrichment analysis showed that Salvia miltiorrhiza and Tripterygium wilfordii treatment of DN mainly involved in cancer-related pathways, lipid and atherosclerosis, IL-17 signaling pathway, diabetic complications AGE/RAGE and other signaling pathways. Lipids and atherosclerosis are the main factors of cardiovascular risk in renal disease [21]. Studies have shown that AGE/RAGE signaling pathway can promote the expression of NF-κB [22], up-regulate TGF-β1, VEGF [23], activate NADPH oxidase, induce the expression and release of inflammatory factors and adhesion factors, increase vascular permeability, increase the expression of connective tissue growth factor, enhance oxidative stress, and thus increase proteinuria. It promotes renal fibrosis, leading to the onset and development of DN. In a study on the mechanism of traditional Chinese medicine intervention of AGEs-RAGE signaling pathway to improve diabetic nephropathy, it was found [24] that down-regulating the level of AGE/RAGE could effectively delay the pathological changes of renal fibrosis. IL-17 signaling pathway can regulate blood glucose by activating the MAPK pathway [21] and play a regulatory role in lipid metabolism by inhibiting HMG-CoA reductase [25]. Based on the above

multiple pathways, it is speculated that Salvia miltiorrhiza and tripterygium wilfordii can delay the progression of DN and protect renal function by participating in oxidative stress, inflammatory response, lipid metabolism and other processes.

To further explore the potential molecular mechanism of salvia miltiorrhiza and tripterygium wilfordii in the treatment of DN, we performed molecular docking studies on four targets closely related to DN using luteolin and kaferol, the main active components, as ligands. The results showed that the four potential targets had good binding ability to the main active ingredient, indicating that the main active ingredient had good stability with the key protein receptors.

In conclusion, Salvia miltiorrhiza and tripterygium wilfordii drug pair may act on TNF, AKT1, PPARG, SRC and other targets through effective active ingredients such as luteolin and kaferol, and interfere with cancer-related pathways, lipids and atherosclerosis, IL-17 signaling pathway, aging signaling pathway in diabetic complications and other signaling pathway mechanisms. To achieve the purpose of treating DN. In this study, we used network pharmacology and molecular docking to investigate the chemical constituents and targets of the salvia-Tripterygium wilfordii drug pair and the mechanism of DN. The results show that the action on a variety of components, targets and pathways is the advantage of salvia-Tripterygium wilfordii drugs in the treatment of DN, and also provides ideas and theoretical basis for subsequent cell and animal research and new clinical drug development and application. However, there are few reports on the regulation of diabetic nephropathy by salvia-tripterygium wilfordii drug pair by affecting these signaling pathways. At the same time, the current network information technology is not comprehensive, the accuracy and real-time update of database data need to be improved, and the biological processes and signaling pathways are jointly involved or regulated by multiple gene targets. Therefore, experimental mechanisms are needed to verify the complex multi-target, multi-pathway and synergistic interactions involved in the therapeutic effects of Salvia miltiorrhiza-Tripterygium wilfordii.

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