A Network Pharmacology Approach to Understanding the Mechanisms of Action of Traditional Medicine: *Rheum L.* for Diabetic Kidney Disease

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Research

Keywords: Rheum L., Network pharmacology, Diabetic kidney disease

Posted Date: October 14th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-76167/v1>

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Abstract

Background

Rheum L. (Da-huang in pinyin, *Radix Rhei Et Rhizome* in pharmaceutical name), a classic Chinese herb, has been extensively used to treat diabetic kidney disease in clinical practice in China for many years. However, the pharmacological mechanisms of *Rheum L.* remain elusive. To decrypt the underlying mechanisms of *Rheum L.* in the treatment of diabetic kidney disease using a systems pharmacology approach.

Methods

A network pharmacology-based strategy was proposed to elucidate the underlying multi-component, multi-target, and multi-pathway mode of action of *Rheum L.* against diabetic kidney disease. We collected putative targets of *Rheum L.* and a network of the interactions among the putative targets of *Rheum L.* and known therapeutic targets of diabetic kidney disease was built. The major hubs were imported to the Database to perform a pathway enrichment analysis.

Results

A total of 6 active ingredients and 271 targets of *Rheum L.* were picked out. 11 cellular biological processes and 18 pathways of *Rheum L.* mostly associated with inflammatory response, apoptosis, fibrosis, and peripheral circulation.

Conclusions

Rheum L. could alleviate diabetic kidney disease via the molecular mechanisms predicted by network pharmacology.

1. Background

Diabetic kidney disease (DKD) is one of the most common and serious complications of diabetes mellitus. Pathological changes in renal cells of DKD patients include glomerular hypertrophy, mesangial expansion, and tubulointerstitial fibrosis due to the accumulation of extracellular matrix (ECM) proteins, thickening of basement membrane, and podocyte dysfunction¹. DKD is now the main cause of CKD worldwide and the leading cause of end-stage-renal disease (ESRD) requiring renal replacement therapy. Approximately 20–40% of diabetic patients suffer from DKD in China, which is the main cause of CKD and end-stage renal failure in patients with diabetes². DKD is a major but under-recognized contributor to the global burden of disease. Between 1990 and 2012, the number of deaths attributed to DKD rose by 94%³. This dramatic rise is one of the highest observed for all reported chronic diseases⁴. Early medical research has shown that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), the first-line treatment for DKD, can reduce proteinuria and have a certain effect on

delaying the progress of renal dysfunction⁵. However, the side effects of ACEI/ARB, such as dry cough, hypotension, hyperkalemia, and angioedema, limit the application of these drugs. Evidence-based medical studies have shown that these agents have not significantly reduced DKD vascular event rate and mortality⁶. Therefore, it is urgent to discover potential therapeutic targets and develop new therapeutic strategies for the treatment of DKD.

Traditional Chinese Medicine (TCM) is a branch of traditional oriental medicine, characterized by its systematic and holistic philosophy, which has been widely used in Asian countries⁷. TCM have multiple ingredients that contain a variety of advantages, such as synergy, minor side effects, and improvement of adaptive resistance⁸. TCM network pharmacology not only confirms and optimizes multiple targets interventions by modeling signaling pathways and precise processes, but also estimates the efficacy of drugs, especially multi-target drugs^{9,10}. Based on the theory of traditional Chinese herbal medical science, TCM can offer a treatment for the prevention and treatment of DKD in a systematic way. As a traditional medicinal plant, *Rheum L.* has satisfactory drug efficacy for the alleviation of DKD, which indicates the existence of certain pharmacological components in *Rheum L.*¹¹. In clinical practice, we discovered that some formulas, which contained *Rheum L.*, could effectively decrease 24-hour urinary protein level, increase glomerular filtration rate in type 2 DKD patients with macroalbuminuria, and ameliorate diabetic kidney injury^{12,13}. However, the pharmacological mechanisms of *Rheum L.* are still vague.

The aim of our study was to screen the related ingredients of *Rheum L.* using multiple databases and acquire the potential targets by target fishing. Then, we aimed to screen the related targets of DKD by consolidation of a multi-source database. Based on the matching results between *Rheum L.* potential targets and DKD targets, we aimed to build a protein-protein interaction (PPI) network to analyze the interactions among these targets and screen the hub targets based on topology. Moreover, using The DAVID bioinformatics resources, we aimed to obtain the enrichment analysis of the GO-BP and KEGG. This study is necessary to investigate how *Rheum L.* alleviates DKD via the molecular mechanisms predicted by network pharmacology and how the network pharmacology approach can be an effective tool to reveal the mechanisms of TCM. The flowchart of the experimental procedures of our study is shown in Fig. 1.

2. Methods

2.1 Ingredients in *Rheum L.* and its targets

To collect the ingredients in *Rheum L.*, we used the Traditional Chinese Medicine System Pharmacology Database¹⁴ (TCMSP, <http://lsp.nwu.edu.cn/tcmsp.php>, 2020.2.28). Ninety-two herbal ingredients were recorded in this process. Retrieving the small molecular structure information of the active ingredients in *Rheum L.* on the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) and the Swiss Target Prediction webserver (<http://www.swisstargetprediction.ch/index.php>).

2.2 Disease targets database building

We collected DKD targets from four source databases. The databases used in our study were: the DrugBank database (<http://www.drugbank.ca/>, version 4.3, 2020.2.28), Online Mendelian Inheritance in Man (OMIM) database¹⁵ (<http://www.omim.org/>, 2020.2.28), Therapeutic Target Database (<http://db.idrblab.org/ttd>, 2020.2.28), and Genetic Association Database¹⁶ (<https://www.geneticassociationdb.nih.gov/>, 2020.2.28). The targets were then processed by String (<https://string-db.org/>, 2020.3.3) to draw the data of PPI.

2.3 Network construction

1. Compound-target network (C-T network);
2. *Rheum L.* target-DKD target interactional network (T-T network);
3. Target-pathway network (T-P network). The pathway information of targets was screened from the result of KEGG pathway enrichment. Cytoscape3.6.0 (<http://www.cytoscape.org/>, 2020.3.3).

2.4 Enrichment analysis

We used DAVID¹⁷ (<https://david.ncifcrf.gov/>, v6.8, 2020.3.3) for GO enrichment analysis and KEGG¹⁸ (<http://www.kegg.jp/>, 2020.3.3) for pathway enrichment analysis.

3. Results

3.1 Active compounds in *Rheum L.*

Retrieved from TCMSP, there were 92 related components in the whole formula in total. According to the active ingredient screening thresholds of $OB \geq 30\%$ and $DL \geq 0.18$, 16 active ingredients were selected.

3.2 Target prediction and analysis

We conducted target fishing on the 16 active ingredients based on chemical similarity, obtaining 271 related targets. The 16 active compounds that were obtained are listed in Table 1.

Table 1
The list of active ingredients of *Rheum L.*

ID	Compound	OB (%)	DL
MOL002235	EUPATIN	50.8	0.41
MOL002251	Mutatochrome	48.64	0.61
MOL002259	Physciondiglucoside	41.65	0.63
MOL002260	Procyanidin B-5,3'-O-gallate	31.99	0.32
MOL002268	rhein	47.07	0.28
MOL002276	Sennoside E_qt	50.69	0.61
MOL002280	Torachrysone-8-O-beta-D-(6'-oxayl)-glucoside	43.02	0.74
MOL002281	Toralactone	46.46	0.24
MOL002288	Emodin-1-O-beta-D-glucopyranoside	44.81	0.80
MOL002293	Sennoside D_qt	61.06	0.61
MOL002297	Daucosterol_qt	35.89	0.70
MOL002303	palmidin A	32.45	0.65
MOL000358	beta-sitosterol	36.91	0.75
MOL000471	aloe-emodin	83.38	0.24
MOL000554	gallic acid-3-O-(6'-O-galloyl)-glucoside	30.25	0.67
MOL000096	(-)-catechin	49.68	0.24

Twenty three targets that matched the related targets of *Rheum L.* on DKD were collected as related targets for the effect of *Rheum L.* on DKD (Fig. 2 and Fig. 3).

3.3 GO biological process and KEGG pathway enrichment analysis

In the String database, the PPI network of the 23 targets was established. The details are shown in Fig. 4. There were 23 nodes and 65 edges in total. The threshold values were degree ≥ 5.9 and closeness ≥ 0.51 and the results settled at 23 hub nodes and 65 edges. The details are shown in Fig. 5, which includes Caspase-3 (CASP3) (degree = 14), Cyclooxygenase-2 (PTGS2) (degree = 12) Angiotensin-converting enzyme (ACE) (degree = 11), Peroxisome proliferator-activated receptor gamma (PPARG) (degree = 9), Insulin-like growth factor I receptor (IGF1R) (degree = 9), Glycogen synthase kinase-3 beta (GSK3B) (degree = 8), Beta amyloid A4 protein (APP) (degree = 8), Androgen Receptor (AR) (degree = 7), Thrombin (F2) (degree = 6), Plasminogen activator inhibitor-1 (SERPINE1) (degree = 6), Hepatocyte growth factor receptor (MET) (degree = 6), and Hepatocyte nuclear factor 4-alpha (HNF4A) (degree = 6).

represent the degree, as the scale indicates. The size of the circle also indicates the degree.

3.3.1 GO biological process enrichment analysis

DAVID v6.8 was used for enrichment analysis of the 23 targets. The screening threshold was $P < 0.01$ and 11 GO items were retrieved. We selected 18 KEGG pathways for analysis. The details are shown in Fig. 6.

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Figure 6. The main 18 pathways enriched by major hubs from the DAVID database.

3.3.2 KEGG pathway enrichment analysis

The 11 biological processes were mainly involved in inflammatory response, apoptosis, fibrosis, and peripheral circulation. The details are shown in Fig. 7. The processes were, in the aspect of cell proliferation: positive regulation of transcription from RNA polymerase II promoter (GO:0045944), positive regulation of cell proliferation (GO:0008284), transmembrane receptor protein tyrosine kinase signaling pathway (GO:0007169), and transcription, DNA-templated (GO:0006351); in the aspect of protein metabolism: negative regulation of protein binding (GO:0032091) and positive regulation of protein binding (GO:0032092); in the aspect of inflammatory response: response to oxidative stress (GO:0006979); in the aspect of apoptosis: negative regulation of extrinsic apoptotic signaling pathway (GO:2001237); and in the aspect of peripheral circulation regulation: glucose homeostasis (GO:0042593), regulation of blood pressure (GO:0008217), and blood coagulation (GO:0007596). Based on these five main aspects, a complex multi-path synergetic effect may be the cause of the effect of *Rheum L.* on DKD.

4. Discussion

4.1 Inflammatory response

It is known that PTGS2 is often called cyclooxygenase 2 (COX-2), several inflammatory cytokines contribute to DKD pathogenesis, including COX-2, inflammatory parameters in patients with type 2 diabetes at an early stage of nephropathy are independently associated with urinary albumin excretion (UAE)¹⁹. High glucose activates protein kinase C (PKC) to increase the permeability of Glomerular endothelial cells (GECs), which up-regulates the COX-2 in endothelial cells and COX-2 up-regulation is associated with an imbalance in eicosanoids profile, with an increase in vasoconstricting thromboxane B₂ and a decrease in vasodilatory 6-keto-prostaglandin F α ²⁰. These changes lead to renal hemodynamic changes, which may participate in glomerular hyperfiltration observed in early DKD. In addition, increased ROS production upregulates COX-2 gene transcription and modifies the production of prostanoids^{21, 22} which control vascular reactivity of the renal glomerular arterioles and deteriorate the glomerular endothelial surface layer²³. In mice, diabetes-induced endothelial injury, albuminuria, podocyte loss, and glomerulosclerosis are ameliorated by scavenging of mitochondrial ROS prevent endothelial mitochondrial oxidative stress²⁴.

Adiponectin exerts favorable effects in anti-inflammatory, antifibrotic, antioxidant effects, and potentially stimulates ceramidase activity. Low circulating adiponectin levels in obese patients who have a risk of insulin resistance, type 2 diabetes, and cardiovascular diseases, and increased adiponectin expression in the state of albuminuria suggest a protective and compensatory role for adiponectin in mitigating further renal injury during the development of overt DKD. Enhancing the AMPK/PPAR α pathway and ceramidase activity alleviate renoprotective role against lipotoxicity and oxidative stress²⁵. Moreover, a study demonstrated that peroxisome proliferator-activated receptor γ (PPAR γ) coactivator-1 α (PGC-1 α) participates in mitochondrial biogenesis in tissues with high energy consumption, as a key nuclear factor in energy and oxidative stress²⁶. PGC-1 α is highly expressed in the kidney²⁷, and is reported to protect against several kidney diseases. PGC-1 α upregulation has been demonstrated to alleviate mitochondrial dysfunction in acute kidney injury and an adriamycin nephrosis model^{28, 29}.

IGF1 is a powerful regulatory factor in various cell types, including glomerular and tubular cells³⁰. It is an important growth factor for keeping the nephritic structure and function. It also plays a key role in the pathological process of DKD³¹. Inhibition of IGF1R could alleviate inflammation in DKD more efficiently³². Li J et al³³ found that inhibition of IGF1R was a more effective choice for inflammation treatment than insulin in diabetic kidney disease (DKD). The IGF1R inhibitor blocked pathological changes induced by the over-expression of IGF1 in DKD without up-regulating SOCS2 protein levels.

4.2 Apoptosis

Apoptosis, which programmed cell death, plays an essential role in the development and homeostasis of metazoans. Deregulation of apoptosis leads to a variety of pathologic disorders, including cancer, autoimmune diseases, and neurodegenerative disorders. Caspases, part of the cysteine protease family, are central to the initiation and execution of apoptosis, acting to specifically cleave the C-terminal side of an aspartate residue in substrates. The apoptotic caspases are generally classified into initiator and executioner caspases, and one of the principal executioner caspases is Caspase-3^{34, 35}. Researchers have found that apoptosis had an indispensable role in renal ischemia-reperfusion injury and contrast-induced acute kidney injury^{36, 37}. Markers of apoptosis have repeatedly been linked with DKD³⁸. Wang et al³⁹ showed that GSDME could switch Caspase-3-dependent non-inflammatory and immunologically silent apoptosis to a terminal phase, namely secondary necrosis. Wen et al⁴⁰ found that Caspase-3 could promote renal injury and fibrosis in DKD through gasdermin E-mediated progression to secondary necrosis during apoptosis.

IGF-I is synthesized in renal glomeruli and distal tubules. IGF-I raises GFR through reducing arteriolar resistance and increasing LpA. IGF-I has been associated with the initiation of hypertrophy in models of compensatory renal growth and may contribute to the accumulation of extracellular matrix proteins in the nephron in chronic renal diseases. IGF-1 can promote sclerosis by either increasing synthesis, or decreasing the degradation of glomerular extracellular matrix (ECM), suggesting that IGF-1 could be a major contributor to the development of diabetic glomerulosclerosis^{41, 42}. In addition, insulin and IGF-1

are major anti-apoptotic hormones, as well as metabolic and growth hormones. Their effects are mediated through activation of the insulin and IGF-1R and the consequent activation of the PI3K-Akt (phosphatidylinositol 3-kinase to Akt) and the Ras-Raf-MEK-ERK (Ras to Raf to mitogen-activated or extracellular signal-regulated protein kinase to extracellular signal-regulated protein kinase) pathways^{43, 44}. In brown preadipocytes in the basal state, the presence of insulin or IGF-1 receptors plays a permissive role in apoptosis, which is blocked either by ligand binding or by deletion of both receptors, revealing the apoptosis that is independent of their kinase activity⁴⁵.

4.3 Fibrosis

PPAR γ belongs to the ligand-activated type II nuclear receptor superfamily and predominantly expressed in adipose tissues⁴⁶. In the kidney, PPAR γ is mainly located in the medullary collecting duct, and glomeruli and proximal tubules were also expressed in small amounts⁴⁷. Activated PPAR γ delayed the progress of DKD by improving insulin resistance⁴⁸, lowering blood pressure⁴⁹, ameliorating inflammation⁵⁰, reversing cell cycle arrest⁵¹, increasing adiponectin⁵², improving oxidative stress⁵³, and other mechanisms. On the other hand, the study has shown that PPAR γ single nucleotide polymorphism (SNP) is associated with the risk of diabetic kidney disease⁵⁴. All of these indicated that PPAR γ signal pathway plays a protective role in DKD⁵⁵. Moreover, The PPAR γ agonist may induce PGC-1 α expression to maintain mitochondrial function and to reduce ROS generation, and it may ameliorate podocyte impairment, GBM thickening and kidney fibrosis to aid in the prevention of DKD occurrence and progression⁵⁶.

IGF-1 participates in multiple biological metabolic pathways of DKD. Dong et al⁵⁷ discovered that IGF-1R inhibitor could ameliorate urinary albumin excretion and kidney histological changes due to diabetes, including amelioration of glomerulomegaly, inflammatory infiltration, and tubulointerstitial fibrosis. Activation of IGF-1 in diabetic kidneys induces fibrogenesis through Snail1 upregulation. The diabetes-related histological and functional changes, as well as fibrogenesis, can be attenuated by IGF-1/IGF-1R inhibition.

4.4 Peripheral circulation regulation

In type 1 diabetes (T1D), adjuvant treatment with inhibitors of the renin-angiotensin-aldosterone system (RAAS), which dilate the efferent arteriole, is associated with prevention of progressive albuminuria and renal dysfunction. In the setting of chronic hyperglycemia, overactivation of the RAAS is strongly implicated in the initiation and progression of DKD^{58, 59}. Angiotensin II (Ang II) is the major peptide of RAS, and is formed under the action of the angiotensin converting enzyme (ACE). Ang II shows increased activity under high glucose conditions that causes hypertrophy of various renal cells and has a pressor effect on arteriolar smooth muscles, thereby resulting in increased vascular pressure⁶⁰. The ACE gene is composed of 26 exons and 25 introns, with a length of 21 kb. Recently, many researchers have demonstrated that the ACE I/D polymorphism is related to diabetic microangiopathy, and that the D allele

might be a susceptibility factor for patients with DKD ^{61–63}. The ACE I/D polymorphism was suggested to be strongly associated with the development of DKD, and using valsartan in DKD patients could significantly decrease the excretion of urinary albumin ⁶⁴.

4.5 *Rheum L.*

Rheum L., one of the most popular traditional Chinese medicines used to control various diseases for thousands of years, there are several studies that demonstrate that *Rheum L.* can effectively reduce inflammation, apoptosis, antioxidant stress, and blood pressure.

4.5.1 Glycolipid metabolism

Cheng et al. ⁶⁵ found that the fasting blood glucose (FBG), total cholesterol (TC), and triglyceride (TG) levels in the serum of rats in the purified anthraquinone-Glycoside from *Rheum palmatum L.* treatment groups were significantly decreased. The expression of Fas ligand (FasL), cytochrome C (Cyt-c), and Caspase-3 in pancreatic tissue was obviously decreased, and the pathological damage to the liver, kidney, and pancreas was improved, which indicated that PAGR can reduce oxidative stress in rats with diabetes mellitus by improving blood lipid metabolism and enhancing their antioxidant capacity, thereby regulating the mitochondrial apoptotic pathway to inhibit β -cell apoptosis and improve β -cell function. Furthermore, PAGR could activate the GLP-1/cAMP pathway to decrease glycated serum protein (GSP), insulin concentration and HOMA-IR index, increase GLP-1 concentrations, ameliorate insulin resistance, and restore the gut microbiota ⁶⁶.

4.5.2 Improving renal function

The changes in mean blood glucose levels, normalized kidney weight, urinary albumin excretion, serum creatinine levels and tubulointerstitial injury index (TII) scores of the rats with DN were significantly attenuated by emodin. Furthermore, treatment with emodin significantly inhibited inflammation-related factors and oxidative stress, suppressed the expression of intercellular adhesion molecule 1 (ICAM-1) and B-cell lymphoma 2-associated X protein (Bax), increased phosphorylated Akt and phosphorylated-glycogen synthase kinase 3 (p-GSK-3 β) expression and inhibited caspase-3 activity in diabetic rats⁶⁷. Li et al⁶⁸ discovered that using *Rheum L.* anthraquinones extract decreased the serum creatinine (SCr), blood urea nitrogen (BUN) and urine protein (UP) values in diabetic nephropathy rats, which suggested that it displayed certain therapeutic and preventive effects against the diabetic nephropathy. Moreover, administration of *Rheum L.* inhibited increase of BUN and serum creatinine in cases with chronic renal failure and was effective for the reduction of uremic substances, which can retard the introduction-period of hemodialysis and inhibit deterioration of the disease ⁶⁹. Gentamicin increased the level of urinary glucose and protein, and increased malondialdehyde while it decreased thiol in kidney tissue, and increased the concentration of urea and creatinine in the serum. However, hydroalcoholic extract of *Rheum turkestanicum* was able to improve gentamicin toxicity, it has positive effects in the attenuation of gentamicin-induced nephrotoxicity ⁷⁰.

4.5.3 Delaying renal fibrosis

Shui et al ⁷¹ found that Dahuang Fuzi Decoction could attenuate renal fibrosis and ameliorates mitochondrial dysfunction in chronic aristolochic acid nephropathy. Besides, Dahuang Fuzi Decoction could alleviate adenine-induced tubular epithelial apoptosis and renal damage in vivo, presumably through the suppression of TGF- β 1-JNK pathway activation ⁷². Chinese researchers believed that Niaoduoqing particles safely and effectively delayed CKD progression in patients with stage 3b-4 CKD. This traditional Chinese medicine may be a promising alternative medication for patients with moderate-to-severe renal dysfunction ⁷³. As the main active ingredient of *Rheum L.*, emodin regulates lipopolysaccharide-induced toll-like receptor 4 and reduces the expression of tumor necrosis factor alpha and interleukin 6, all three being synthesized by renal tubular epithelial cells ⁷⁴. Emodin acts as an anti-inflammatory agent by inhibiting the differentiation and maturation of dendritic cells and increasing the number of regulatory T-cells ⁷⁵. It also can bring high blood pressure down, decrease blood lipids and improve microcirculation, protect kidney ⁷⁶. Tu et al ⁷⁷ discovered that rhein could inhibit autophagy in rat renal tubular cells by the regulation of the AMPK/mTOR, p38/Erk MAPKs and Akt-independent signaling pathways, which may explain the therapeutic mechanisms of *Rheum L.* and rhein in treating CKD patients.

Advances in traditional herbal medicine suggest Chinese herbal remedies can be considered promising agents in the prevention and treatment of DKD. However, the clinical application of Chinese herbal medications is pretty limited, due to the following concerns and barriers (1) Lacking of high-quality animal studies, focusing on the role of herbal medicine on DKD. (2) The potential side effects associated with herbal medicine may be underrecognized and underreported. (3) The screened active ingredients may be inconsistent with the actual absorbed components in the blood of patients with DKD. (4) The interaction relationships between the nodes in the network construction methods are still unclear. Therefore, further experimental verification of the potential active ingredients is needed to verify this theoretical prediction.

5. Conclusion

This study used a scientific approach to decipher the pharmacological mechanisms of *Rheum L.* in the treatment of DKD. We discovered that the effects may be associated with inflammatory response, apoptosis, fibrosis, and peripheral circulation. Among these crucial biological functions, twelve targets were identified as key active factors involved in the related pathways. This research suggests that *Rheum L.* can alleviate DKD via the molecular mechanisms predicted by network pharmacology and that the network pharmacology approach can be an effective tool to reveal the mechanisms of TCM. However, to improve the reliability of the results, further experimental experiments are needed to validate these results.

Abbreviations

DKD, diabetic kidney disease; TCM, traditional Chinese medicine; TCMSP, Traditional Chinese Medicine Systems Pharmacology Database; OB, Oral Bioavailability; DL, Drug-likeness; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PPI, protein-protein interaction; DAVID, Database for Annotation, Visualization and Integrated Discovery; OMIM, Online Mendelian Inheritance in Man; TTD, Therapeutic Target Database; GAD, Genetic Association Database; C-T, compound-target; T-T, target-target; T-P, target-pathway.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The data and materials generated or analyzed during this study are available from the corresponding author on reasonable request.

Funding

This work was supported by the 2015 Traditional Chinese Medicine Scientific Research (grant number: 201507001-11) and The National Natural Science Foundation of China (grant number: 81973813).

Authors' Contributions

Conceptualization, J.L., C.P. and D.J.; Methodology, D.J.; Software, C.P.; Validation, J.L., C.P., D.J. and X.Z.; Formal Analysis, J.L. and C.P.; Investigation, L.W.; Resources, F.L. and X.T.; Data Curation, J.L.; Writing-Original Draft Preparation, J.L.; Writing-Review & Editing, C.P.; Visualization, J.L. and C.P.; Supervision, F.L. and X.T.; Project Administration, F.L. and X.T.; Funding Acquisition, F.L. and X.T.

Acknowledgement

Not applicable.

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Figures

Figure 1

The flowchart of the experimental procedures

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Figure 3

The T-D network that consists of 267 nodes and 271 targets. Pink and blue nodes denote the diseases and targets, respectively.

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The T-D network that consists of 267 nodes and 271 targets. Pink and blue nodes denote the diseases and targets, respectively.

Figure 4

The 23 matching targets of the related targets in Rheum L. on DKD.

Figure 4

The 23 matching targets of the related targets in Rheum L. on DKD.

Figure 5

PPI network of 23 nodes and 65 edges established in the String database.

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PPI network of 23 nodes and 65 edges established in the String database.

Figure 6

The main 18 pathways enriched by major hubs from the DAVID database.

Figure 6

The main 18 pathways enriched by major hubs from the DAVID database.

Figure 7

Main 11 GO biological process by major hubs from the DAVID database

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Main 11 GO biological process by major hubs from the DAVID database