Network Pharmacology-Based Investigation into the Mechanisms of Qibangyishen Formula for the Treatment of Diabetic Kidney Disease

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Research

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Abstract

Background Diabetic kidney disease is the main microvascular complication of diabetes, and new treatment strategies are needed. We investigated the multi-component, multi-target, and multi-path mechanism of Qibangyishen formula for the treatment of diabetic kidney disease by network pharmacology methods.

Methods We collected the active ingredients and targets of Qibangyishen formula and examined diabetic kidney disease-related genes by searching the ETCM, TCMID, and DisGeNet databases. We constructed and analyzed the genetic network through Cytoscape software and used the STRING platform for pathway enrichment analysis.

Results We uncovered 421 active ingredients of Qibangyishen formula, corresponding to 748 targets. A network analysis screen revealed 47 hub-node targets, and 13 of these targets were diabetic kidney disease-related disease genes. Further functional analysis identified 26 targets acting on 11 pathways related to the development of diabetic kidney disease, including PI3K-Akt, thyroid hormone, neurotrophin, Wnt, chemokine, and osteoclast differentiation signaling pathways.

Conclusions This study suggests that Qibangyishen formula regulates multiple genes and biological processes related to diabetic kidney disease and provides a foundation for further research and clinical applications.

Background

Diabetic kidney disease (DKD) is a chronic disease caused by diabetes and has a complicated pathogenesis [1–3]. The clinical features include continuously increasing excretion of albuminuria and/or glomerular filtration rate (GFR) less than 60 ml/(min·1.73m²) for more than 3 months, which can eventually develop into end-stage renal disease (ESRD). Diabetic kidney disease leads to about 30–50% ESRD cases worldwide [4, 5] and is the leading cause of ESRD in middle-aged and elderly people in China [6, 7].

There are many clinical treatments for diabetic kidney disease [2, 8, 9], including life management [10, 11], blood sugar control [12, 13], blood pressure control [14, 15], blood lipid regulation [16, 17], uric acid control [18, 19], and proteinuria regulation [20]. These treatments have various degrees of efficacy, but many patients with DKD continue to progress to dialysis. Traditional Chinese medicine has also been widely used to treat diabetic kidney disease. Chinese medicine may improve kidney and immune function and elicit therapeutic effects [21–23]. Diabetic kidney disease has no precise definition in ancient Chinese medical literature, but according to etiology and pathogenesis, diabetic kidney disease can be attributed to "edema" and "guange" secondary to Xiaoke. Huang et al. [24] found that QufengTongluo Formula and YiqiHuayu Formula delay renal fibrosis and reduce urine protein in DKD rats, which may be related to enhanced PTEN expression, inhibition of PI3K/Akt signaling, and reduced transforming growth factor-β (TGF-β) expression. Hong et al. [25] showed that Jiangtang Formula reduces the level of advanced

glycosylation products in KK-Ay mice and increases the phosphorylation of PI3K and Akt, which reduces inflammatory responses in DKD rats.

Qibangyishen Formula (QBYSF) is composed of DI HUANG (*Rehmannia glutinosa* Libosch.), HUANG QI (*Astragalus membranaceus*(Fisch.)Bge.), SAN QI (*Panax notoginseng*(Burk.)F. H. Chen), NIU BANG ZI (*Arctium lappa* L.), BAI SHAO (*Paeonia lactiflora* Pall.) and HEI DOU (*Glycine max*(L.)Merr.). QBYSF has been clinically used to treat diabetic kidney disease, and ingredients within QBYSF have been shown to have beneficial effects. Specifically, DI HUANG reduces blood sugar, serum triglycerides, uric acid, and the 24-hour urine albumin excretion rate, increases high density lipoprotein, interferes with inflammation, significantly improves serum creatinine and urea nitrogen, and protects patients' renal function [26, 27]. HUANG QI reduces blood sugar, uric acid, urea nitrogen, and blood creatinine, improves proteinuria, and has a protective effect on the kidneys [28–30]. SAN QI regulates sugar metabolism, has anti-fibrosis, anti-oxidation and anti-inflammatory effects, improves kidney function, and delays kidney damage [31, 32]. Previously, we found that HUANG QI combined with SAN QI reduces urinary protein excretion, decreases renal pathological changes, and improves apoptosis and shedding of kidney podocytes in DKD rats [33]. NIU BANG ZI extract reduces podocyte damage and proteinuria symptoms of DKD mice by enhancing PP2A activity in podocytes and protects kidney function [34]. NIU BANG ZI extract also significantly reduces blood sugar in DKD mice and reduces the damage to the kidney [35]. Total glycosides is the main component of the BAI SHAO and reduces serum hs-CRP, TNF- α , and MCP-1 levels in patients with DKD, thereby protecting the kidneys [36]. Peony total glucosides prevent renal tubular interstitial damage in rats with diabetic nephropathy and delay the development of diabetic nephropathy [37]. HEI DOU reduces blood sugar, blood lipids, serum creatinine, and blood urea nitrogen in streptozotocin (STZ)-induced diabetic rats [38], and long-term low-dose HEI DOU protects diabetic renal insufficiency [39]. Although, the effects of individual components of QBYSF have been examined in diabetic murine models and in patients, the mechanism of QBYSF on diabetic kidney disease is not clear yet.

This study uses network pharmacology to screen the main active ingredients, targets, and pathways of QBYSF to analyze its mechanism on the treatment of diabetic kidney disease.

Materials And Methods

Collection of active ingredients and potential targets of QBYSF.

QBYSF is composed of six herbs: DI HUANG (*Rehmannia glutinosa* Libosch.), HUANG QI (*Astragalus membranaceus*(Fisch.)Bge.), SAN QI (*Panax notoginseng*(Burk.)F. H. Chen), NIU BANG ZI (*Arctium lappa* L.), BAI SHAO (*Paeonia lactiflora* Pall.) and HEI DOU (*Glycine max*(L.)Merr.).Based on the pinyin name of each herb, we searched ETCM [40] and TCMID [41] databases to identify the active ingredients of QBYSF. In addition, we searched the ETCM database for the names of traditional Chinese medicines and compounds that are potential targets of the compounds contained in QBYSF.

Collection of targets for diabetic kidney disease.

Using "Diabetic Kidney Disease" as a keyword, we searched DisGeNet [42] to find genes and targets related to diabetic kidney disease.

Constructing a sub-network affected by diabetic kidney disease.

In November 2019, we downloaded all high-quality binary protein-protein interactions from a high quality proteomics database HINT (High-quality INteractomes) [43] and used Cytoscape [44] software to construct a genome-wide protein-protein interaction network in humans. This network is named the HINT network, which contains 12933 nodes and 60672 edges. We mapped all disease genes from diabetic kidney disease to the HINT network and extracted all nodes, neighbor nodes, and edges between all nodes related to diabetic kidney disease, but only retained the largest connected components to construct the diabetic kidney disease sub-network.

Constructing an association network between compound herbal medicines and important targets.

We used Cytoscape software to perform topology analysis on the diabetic kidney disease sub-network. We calculated the degree for each node and kept all nodes with a degree greater than twice the average degree for the network's hub nodes. The targets corresponding to the hub nodes were defined as important targets of QBYSF for the treatment of diabetic kidney disease. Cytoscape software was used to construct an association network between targets and corresponding herbs.

Pathway enrichment analysis

We entered the target gene ID into the STRING [45] platform for pathway enrichment analysis.

Results

Active ingredients and potential targets of QBYSF.

In the ETCM and TCMID databases, the herbs of QBYSF were searched, and 421 active ingredients of QBYSF were obtained (Supplementary Table 1), corresponding to 748 targets (Supplementary Table 2). The number of compounds and targets of each herbal medicine is shown in Table 1, and the intersection between herbal targets is shown in Fig. 1A.

Table 1

The number of compounds and corresponding potential targets contained in the herbal medicine of QBYSF

Herb Latin name	Herb Pinyin name	Number of compounds	Number of targets
<i>Rehmannia glutinosa</i> Libosch.	DI HUANG	67	393
<i>Astragalus membranaceus</i> (Fisch.)Bge.	HUANG QI	73	557
<i>Panax notoginseng</i> (Burk.)F. H. Chen	SAN QI	168	290
<i>Arctium lappa</i> L.	NIU BANG ZI	28	93
<i>Paeonia lactiflora</i> Pall.	BAI SHAO	67	345
<i>Glycine max</i> (L.)Merr.	HEI DOU	43	257

Genes related to diabetic kidney disease.

We searched the DisGeNet database to identify diabetic kidney disease-related target genes. We obtained 559 diabetic kidney disease-related genes (Supplementary Table 3), of which 66 disease genes were potentially targeted by QBYSF (Fig. 1B).

The diabetic kidney disease sub-network.

The diabetic kidney disease sub-network had 3467 nodes and 23661 edges and included genes related to diabetic kidney disease and neighboring genes in the human protein-protein interaction network. We mapped QBYSF targets to this network, identified 219 targets, and found 52 related to diabetic kidney disease (Fig. 2).

Identification of QBYSF targets.

We calculated the degree for each node in the diabetic kidney disease sub-network, and the average degree for the network was 13.6. The nodes with a degree greater than 27 were labeled hub nodes for the sub-network. There were 444 hub nodes in total, 47 were QBYSF targets, and 13 QBYSF targets were related to diabetic kidney disease.

The correlation network between the 47 QBYSF targets and QBYSF ingredient herbs is shown in Fig. 3A. HUANG QI (*Astragalus membranaceus*(Fisch.)Bge.) and DI HUANG (*Rehmannia glutinosa* Libosch.) had many common targets, and BAI SHAO (*Paeonia lactiflora* Pall.), NIU BANG ZI (*Arctium lappa* L.), SAN QI (*Panax notoginseng*(Burk.)F. H. Chen), and the adjuvant HEI DOU (*Glycine max*(L.)Merr.) also shared many common targets.

In general, a natural compound's effect on a target is lower than that of a drug because a drug's structure is designed to increase its binding affinity to the target. Although a single natural compound may have small effect on a target in isolation, targeting the same protein by multiple compounds by multiple compounds may synergistically increase the effect on the target, thereby producing a therapeutic effect. We defined a protein target score by the number of herb-compound pairs that act on a protein. There were 43 of 47 QBYSF targets with a score equal or greater than two, which suggests that QBYSF may regulate these targets.

Enrichment analysis of QBYSF targets

We examined 219 QBYSF targets including the 47 hub-node targets in the diabetic kidney disease sub-network using the STRING platform for functional enrichment analysis. We used an FDR < 0.0001 to identify KEGG pathways significantly enriched in QBYSF targets and selected the top 20 signal pathways significantly regulated by QBYSF (Figure 4).

The signal pathways regulated by the two target sets include PI3K-Akt, thyroid hormone, neurotrophin, and osteoclast differentiation signal pathways (Figure 4A, B). The intersection of the two sets in Figure 4A and 4B includes 11 signal pathways, which include 26 hub-node targets (Figure 5).

Discussion

The main characteristics of Chinese medicine are a "holistic concept" and "symptom differentiation and treatment", and network pharmacology research methods are similar to this "holistic concept". Network pharmacology for Chinese medicine is an emerging and rapidly developing cross-disciplinary field, and includes databases, network servers, and software to study TCM network pharmacology [46, 47].

In this study, we used network pharmacology to study the mechanism of Qibangyishen formula for the treatment of diabetic kidney disease. Based on TCM databases, 421 active ingredients in QBYSF were identified, corresponding to 748 targets. There were 559 diabetic kidney disease-related genes obtained from the DisGeNet database. Network analysis revealed 47 QBYSF targets, and 13 of these were diabetic kidney disease-related disease genes. Pathway enrichment analysis found that 26 of the 47 targets were regulated in 11 pathways related to endocrine and renal functions, including PI3K-Akt signaling, thyroid hormone signaling, estrogen signaling, insulin signaling, osteoclast differentiation, and Wnt signaling.

The phosphatidylinositol 3'-kinase (PI3K)-protein kinase B (Akt) signaling pathway regulates the cell cycle, transcription, translation, proliferation, growth, and survival in response to extracellular signals such as toxins. Abnormal PI3K/AKT signaling can cause cancer [48–50], diabetes [51–53], and other diseases. PI3K-Akt signaling is closely related to the pathogenesis of DKD and is a common target in many traditional Chinese medicine compounds. Huang et al. [24] found that enhancing the expression of PTEN, inhibiting the PI3K/Akt signaling pathway, and reducing TGF- β expression can delay renal fibrosis and reduce urine protein in DKD rats. Hong et al. [25] showed that the Chinese medicine Jiangtang

reduces the level of advanced glycosylation products in KK-Ay mice and increases the phosphorylation of PI3K and Akt, thereby reducing the inflammatory response of DKD. Increased activation of PI3K-Akt signaling can also aggravate Tubulointerstitial Fibrosis (TIF) [54].

The Wnt signaling pathway, highly conserved in various species, is a signal transduction pathway that includes proteins that pass signals through cell surface receptors, and is essential in developmental processes. Continuous activation of Wnt signaling induces fibroblast proliferation, which can lead to renal fibrosis, which can then be reversed by inhibiting Wnt signaling [55]. Wnt signaling triggers the pathogenesis of podocyte dysfunction and proteinuria [56–58]. Targeted inhibition of Wnt / β -catenin signaling transmission can preserve podocyte integrity and is used in animal models [59, 60]. Diabetes can cause overactivation of Wnt1/ β -catenin signaling, induces renal fibrosis and podocyte damage, and inhibition of Wnt1/ β -catenin signaling improves DKD progression [61, 62].

Insulin is the only hormone in the body that lowers blood sugar. Inadequate insulin secretion causes high blood sugar and may lead to diabetes. The regulatory effect of insulin on metabolism is mainly mediated by the PI3K signaling pathway [63]. Podocyte insulin sensitivity is critical to renal function, and dysregulated podocyte insulin response can result in podocyte damage [64]. Intracellular lipids are the main determinants of podocyte insulin signal transduction and contributes to the pathogenesis of DKD [65]. Sadi et al. found that repairing the components of the insulin signaling pathway improves kidney oxidative stress and inflammation caused by diabetes [66].

Thyroid hormones are produced and released by the thyroid gland. Thyroid hormones have an important role in kidney physiology, which is manifested in the growth, development, and maintenance of kidney homeostasis [67, 68]. Chemokines also affect DKD, and inhibiting chemokine secretion has anti-inflammatory and anti-fibrotic effects, which delays DKD progression [69].

Conclusion

In summary, our network pharmacological study suggests that QBYSF protects the kidneys through 26 targets that regulate 11 pathways involved in the progression of diabetic kidney disease, including PI3K-Akt signaling, Wnt signaling, insulin signaling, and chemokine signaling, which delays the progression of diabetic kidney disease.

Abbreviations

DKD: Diabetic kidney disease; GFR: Glomerular Filtration Rate; ESRD: End-Stage Eenal Disease; QBYSF: Qibangyishen Formula; HINT: High-quality INTeractomes; TIF: Tubulointerstitial Fibrosis.

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

Not applicable

Availability of data and materials

Relevant data associated with the study are available in the Supplementary Materials of this paper.

Competing interests

The authors declare that they have no competing financial interests.

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Authors' Contributions

Zhi Wang, Guihua Jian: conception and design of the study, and generation and collection of data. Wang Zhi: assembly, analysis, and interpretation of data, drafting and revision of the manuscript. All authors approved of the final version of the manuscript.

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Figures

Figure 1

QBYSF target analysis. (A) The intersection between potential targets of the six herbs in QBYSF. (B) The intersection between potential QBYSF targets and diabetic kidney disease genes.

Figure 2

The diabetic kidney disease sub-network. Red and pink nodes are QBYSF targets, and red nodes are related to diabetic kidney disease genes and target proteins.

(A)

(B)

Figure 3

QBYSF targets. (A) Association network between QBYSF ingredient herbs (triangles) and QBYSF targets (circles). Red nodes are related to diabetic kidney disease. (B) Target scores for diabetic kidney disease-related genes.

Figure 4

KEGG signaling pathways regulated by QBYSF. (A) Signal pathways regulated by the 219 targets included in the diabetic kidney disease sub-network. (B) Signal pathways regulated by the 47 hub-node targets.

Figure 5

The association between QBYSF hub-node targets (circles) and signal pathways (boxes). Red nodes are genes related to diabetic kidney disease.

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