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Study on the mechanism of warming yang and reducing turbidity decoction in the treatment of diabetic kidney disease based on network pharmacology

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Abstract

This study aimed to investigate the mechanism of warming yang and reducing turbidity decoction in the treatment of diabetic kidney disease (DKD) by network pharmacology. The active components and corresponding targets of warming yang and reducing turbidity decoction were screened through the Traditional Chinese Medicine Systems Pharmacology database, DKD-related targets were obtained from Genecard and Online Mendelian Inheritance in Man databases, and drug-disease common targets were screened through Venny online website. Then we used STRING and Cytoscape software to analyze and perform protein–protein interaction network, and used CytoNCA plug-in to perform topological analysis to screen out the core target. We used RStudio to performed gene ontology (GO) functional enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. One hundred one active components in warming yang and reducing turbidity decoction participated in the regulation of the body's response to foreign bodies, lipopolysaccharides, metal ions, ketone bodies, hypoxia and oxidative stress by regulating 186 targets related to DKD, and played a role in the treatment of DKD by interfering with pathways such as interfered with lipids and atherosclerosis, PI3K-Akt, fluid shear stress and atherosclerosis, AGE-RAGE and cell senescence. It was implied that warming yang and reducing turbidity decoction had the features of multi components, multi targets and multi pathways in the treatment of DKD, which might create methods and directions for further verification of the molecular mechanism of warming yang and reducing turbidity decoction.

Abbreviations: AGEs = advanced glycation end products, BP = biological process, DKD = diabetic kidney disease, FDR = false discovery rate, GO = gene ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes, TCM = traditional Chinese medicine.

Keywords: active components, diabetic kidney disease, network pharmacology, warming yang and reducing turbidity decoction

1. Introduction

With changes in human behavior and lifestyle, diabetes has become one of the major diseases in the world in the 21st century.[1] According to the ninth edition of the International Diabetes Federation Diabetes Atlas, approximately, the number of patients with diabetes worldwide was 463 million in 2019 and will probably rise to about 700 million by 2045.[2] One third of patients will develop diabetic kidney disease (DKD).[3] DKD is the primary factor which causes end-stage renal disease[4,5] and brings a lot of pressures on individuals and society. The currently recognized pathogenesis of DKD include renal hemodynamic changes, oxidative stress, renal ischemia and inflammation, excessive activation of the renin-angiotensin-aldosterone system, genetic and epigenetic effects, mitochondrial dysfunction,[6] and podocyte autophagy.[7] Nowadays, the common ways of prevention and treatment of DKD are changing lifestyle, controlling blood sugar, blood pressure, and blood lipids, and the use of renin-angiotensin-aldosterone system inhibitors, sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor, etc, but the progression of DKD cannot be completely blocked, and finally, some patients will develop into end-stage renal disease. With the development of researches on traditional Chinese medicine (TCM), it is particularly important to use TCM to delay or even block the progression of DKD on the basis of western medicine treatment.

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Not applicable, because TCMSP, PubChem, Uniprot, RCSB PDB, Gene Cards, OMIM, Venny2.1.0, STRING database, and Cytoscape 3.7.1. belongs to public databases, the patients involved in the database have obtained ethical approval and informed consent, users can download relevant data for free for research and publish relevant articles, and our study is based on open-source data, and the Second Affiliated Hospital of Soochow University do not require research using publicly available data to be submitted for review to their ethics committee, so there are no ethical issues and other conflicts of interest.

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In the opinion of TCM, DKD is named as "nephropathy secondary to wasting-thirst disease," and its etiology and pathogenesis include congenital insufficiency, being invaded by exogenous pathogens, eating disorders, emotional disorders, physical fatigue and internal injuries, which caused dysfunction of zang-fu organs.[8] DKD is related to the dysfunction of spleen and kidney fluid metabolism and distinguishing turbidity. Warming yang and reducing turbidity is one of the treatment methods of TCM. Warming yang and reducing turbidity decoction is composed of Alisma (Zexie), Epimedium (Yinyanghuo), Baked Astragalus (Huangqi), Poria (Fuling), Polygonatum (Huangjing), Lycium barbarum (Gouqi), Cinnamon twig (Guizhi), dried ginger (Ganjiang), dogwood (Shanzhuyu), and Polyporus (Zhuling). Meta-analysis showed that combined with western medicine, TCM for warming yang and reducing turbidity was more effective in reducing serum creatinine, urine protein, and blood urea nitrogen in patients with DKD than using TCM alone, and western medicine combined with warming yang and lowering turbidity TCM was more effective in improving renal function than Western medicine combined with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers.[9] Many clinical studies have shown[10–13] that warming yang and reducing turbidity decoction has a significant effect on reducing the level of serum creatinine, urine protein, and blood urea nitrogen in DKD patients. On our present research, we used network pharmacology analysis to explore relationship between the main chemical components and core targets of warming yang and reducing turbidity decoction and DKD, thereby providing new ideas and theoretical basis for further clarifying the mechanism of warming yang and reducing turbidity decoction in treatment of DKD.

2. Materials and Methods

2.1. Databases and software

Sources of databases, analysis platforms and software involved in the full text included Traditional Chinese Medicine System Pharmacology (http://www.tcmspw.com/tcmsp.php),[14] PubChem (https://pubchem.ncbi.nlm.nih.gov/), Uniprot (http://www.uniprot.org), RCSB PDB (http://www.rcsb.org), Gene Cards, (https://www.genecards.org/), OMIM (http://www.Omim.org/), Venny2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/), STRING database (https://string-db.org/), and Cytoscape 3.7.1 (http://cytoscape.org/).

Screening active components acquisition and targets of warming yang and reducing turbidity decoction.

In the Traditional Chinese Medicine System Pharmacology database, we entered "Alismatis," "Epimedium," " Baked Astragalus," "Poria," " Polygonatum," " Lycium barbarum," "Cinnamon twig," "Dried Ginger," " dogwood," and " Polyporus" to do the retrieving, and screened the active components under the conditions of oral bioavailability ≥ 30% and drug-like ≥ 0.18, and target information of each active component was searched in this database, the results of which were entered into Uniprot in order to obtain corresponding gene symbols of the target genes.

2.2. Screening disease-related targets

We used "diabetic Nephropathy" and "diabetic kidney disease" as keywords to search Genecards and OMIM databases, respectively, thereby screening disease-related targets. Then, we integrated these targets. The large target score means that relationship between the target and disease was closer. So, the target which score ≥ 10 was taken to be screening criteria, and combined targets in 2 databases to establish targets set of diabetic nephropathy.

2.3. Core targets screening and network construction and analysis

Potential targets of active components in warming yang and reducing turbidity decoction and the DKD-related targets were entered into the Venny online tool to screen the predictive targets in DKD, and a Venn diagram was drawn. We uploaded predictive targets to STRING database, and limited species to "human" to select data with moderate confidence and a scoring condition more than 0.95, which hided isolated proteins in graph to obtain a visualized protein–protein interaction network at the end. At the same time, it was imported into Cytoscape 3.8.0, and the CytoNCA plug-in was used to further obtain the core targets.

2.4. Gene ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis

For further find out signaling pathway of warming yang and reducing turbidity decoction in the treatment of DKD, "clusterProfiler" package of RStudio 4.1.2 software was used to convert the target gene symbol of warming yang and reducing turbidity decoction in the treatment of DKD into entrez ID. Then the packages such as "enrichplot" and "org.Hs.e.g..db" were used to run "enrichGO function" and "enrichKEGG function," respectively, thereby performing GO function analysis and KEGG signaling pathway enrichment analysis in active components in warming yang and reducing turbidity decoction in the treatment of DKD. Then multiple comparisons (Benjamini & Hochberg) was performed to do the false discovery rate (FDR) correction, with FDR-adjusted P value [p(FDR)} ≤ .05, and those meeting this criteria were regarded as significant enrichment, thereby predicting the mechanism of action of the active components in warming yang and reducing turbidity decoction.

3. Results

3.1. Active components and their targets of warming yang and reducing turbidity decoction

Under screening condition of oral bioavailability ≥ 30% and drug-like ≥ 0.18, 168 active components of warming yang and reducing turbidity decoction, including 15 from Poria, 5 from dried ginger, 45 from Lycium barbarum, 7 from Cinnamon twig, 12 from Polygonatum, 20 from Baked Astragalus, 20 from dogwood, 23 from Epimedium, 10 from Alisma, and 11 from Polyporus. After removal of duplicate active components, a total of 147 active components were obtained. After conversion, 30 target genes of Poria, 22 of dried ginger, 357 of Epimedium, 437 of Lycium barbarum, 149 of Polygonatum, 474 of Astragalus, 130 of Cornus, 9 of Alisma, and 10 of Polyporus were obtained. After removal of the duplicate target genes, we obtained 265 target genes.

3.2. Disease-related targets

3204 DKD-related genes were obtained from Genecards database, and 188 DKD-related genes were obtained from the OMIM database. After removal of the duplicate DKD-related genes, we obtained 3236 DKD-related genes, as shown in Figure 1A. The intersection of DKD-related genes and target genes of warming yang and reducing turbidity decoction was obtained, as shown in Figure 1B, and 186 common targets were obtained.

3.3. Disease–TCM–component-common targets network

Cytoscape3.8.0 software was used to construct a disease-TCM–compound-common targets network, as shown in Figure 2. There were 287 nodes in this network, including 101 compounds and 186 target genes, and their interactions were represented by lines. Cytoscape style plug-in was used to analyze the network, the results of which showed that the top 3 components were luteolin, stigmasterol and isorhamnetin.

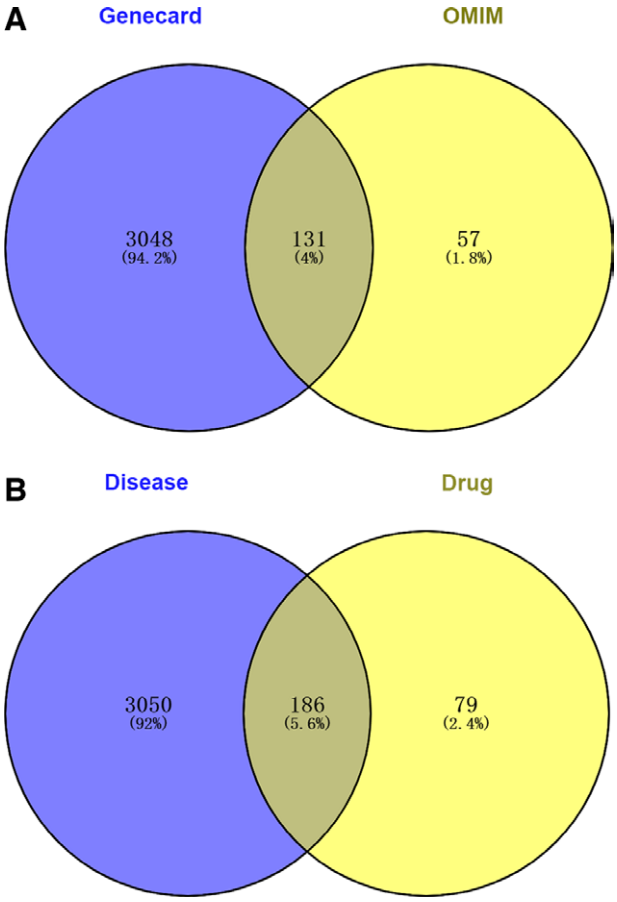

Figure 1. Venn diagram of disease- and drug- related genes. (A) A total of 3236 diabetic kidney disease (DKD)-related genes were obtained from Genecard and Online Mendelian Inheritance in Man (OMIM) databases; (B) the intersection of DKD-related genes and target genes of warming yang and reducing turbidity decoction was obtained.

3.4. Protein–protein interaction network

The target genes of warming yang and reducing turbidity decoction in the treatment of DKD were imported into String 11.5 database for analysis, and the relationship score was > 0.98. PPI network was shown in Figure 3. There are 121 proteins, and 245 relationships among these 121 proteins. Then, the PPI network was imported into Cytoscape3.8.0 software, and the CytoNC plug-in, with the medians of "Betweenness," "Closeness," "Degree," "Eigenvector," "LAC," "Network" 6.612235912, 0.034752389, 3, 0.038255922, 0.5, 0.666666667 as the screening criteria, was used to screen out 31 nodes and 140 edges (Fig. 4A). Then, the CytoNC plug-in, with the medians of "Betweenness," "Closeness," "Degree," "Eigenvector," "LAC," "Network" 255.1088143, 0.035325287, 7, 0.151431516, 2.285714286 and 3.85 as the screening criteria, was used again to screen out 4 key nodes and 24 edges, as shown in Figure 4B.

3.5. GO functional enrichment analysis

R packages such as "enrichplot" and "org.Hs.e.g..db" were used to perform GO enrichment analysis on 186 common target genes, *P* values were calculated and FDR correction was performed under threshold in *P* value ≤ .05. GO items that met this requirement were considered as significantly enriched, and finally 3017 GO items are obtained, including 2732 items in biological process (BP), 94 items in composition process, and 188 items in molecular function. The top 10 items in BP, composition process, and molecular function were showed in Figure 5. The BP involved mainly included responses to xenobiotic stimulus, wound healing, and response to metal ion, oxidative stress, and lipopolysaccharide. The X-axis in the figure represented the gene enrichment degree of each entry, and the adjusted *P* value was represented by the color of bubble. The redder the color indicted that smaller adjusted *P* value. The Y-axis was the GO-enriched entry name.

3.6. KEGG pathway enrichment analysis

Using "enrichKEGG" function to analyze the enrichment and annotation of the KEGG pathway on common target genes.

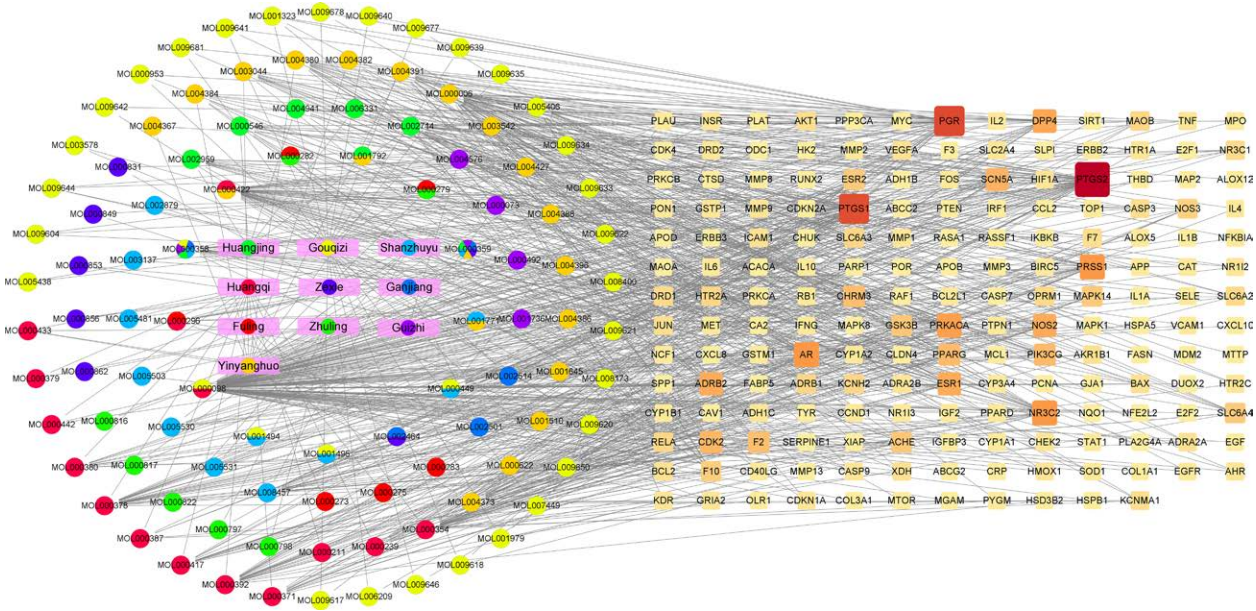

Figure 2. Disease–traditional Chinese medicine (TCM)–component-common targets network. The circles on the left represented components which were linked to the corresponding drugs filled with different colors. The squares on the right side represented the targets, and the shade of color, and the size of the square represented the degree.

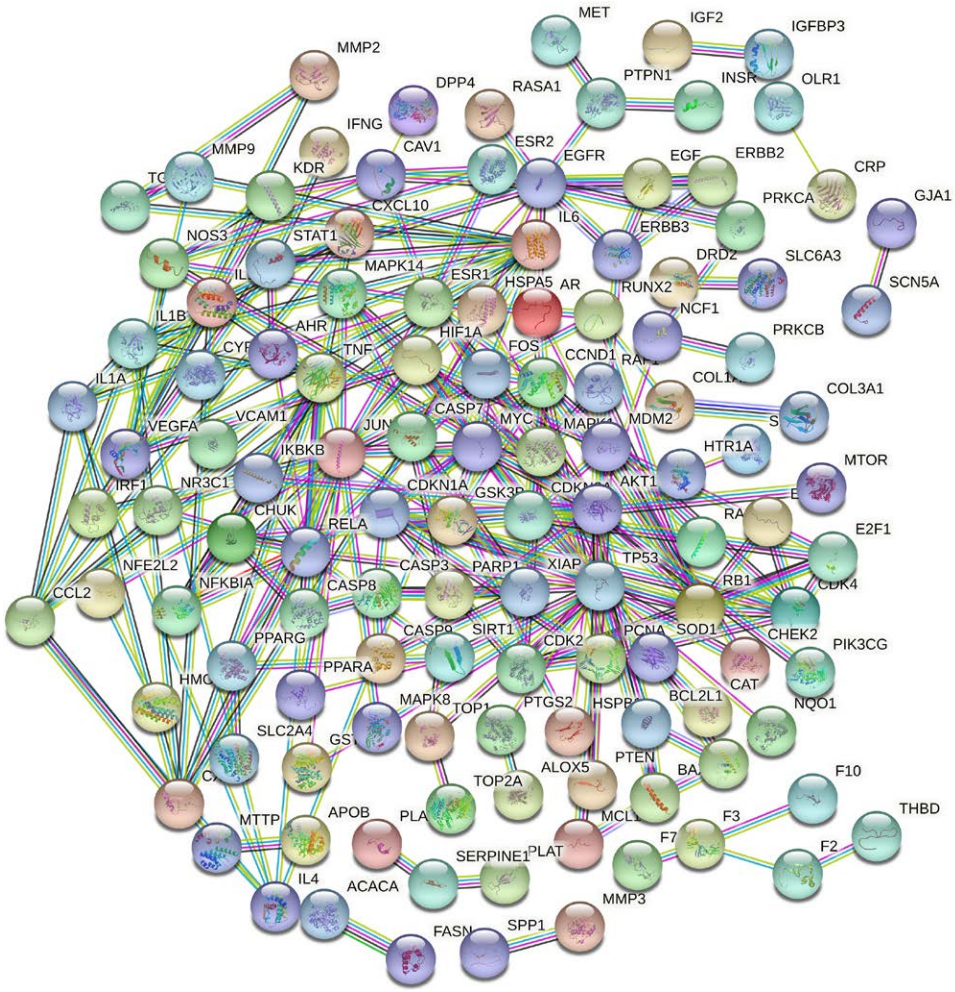

Figure 3. Protein–protein interaction network.

P values were calculated and FDR correction was performed, with *P* value ≤ .05 as the threshold. Two hundred seventy-four pathways that met this condition were obtained, which was visualized in the Figure 6. After excluding pathways without association with diabetes, the top 5 pathways were the receptor for AGEs (RAGE)-advanced glycation end product (AGEs) signaling pathway (Fig. 7), TNF signaling pathway, lipid and atherosclerosis, fluid shear stress and atherosclerosis, and cellular senescence. The abscissa axis (Gene Ratio) in the figure represented the gene enrichment degree of each entry, and the adjusted *P* value was represented by the color of the column. The smaller the adjusted *P* value was, the redder the color was. The Y-axis was the KEGG pathway-enriched entry name.

4. Discussion

Warming yang and reducing turbidity decoction is one of the prescriptions for the treatment of DKD, especially stage IV DKD. At present, there are few studies on the overall effect of warming yang and reducing turbidity decoction in the treatment of DKD. The pathogenesis of DKD is not fully elucidated and the composition of warming yang and reducing turbidity decoction is complex. Therefore, in order to fully understand the mechanism of warming yang and reducing turbidity decoction in the treatment of DKD, our present study used network pharmacology analysis to reveal the synergistic mechanism of warming yang and reducing turbidity decoction.

Our present study screened out 147 active components in warming yang and reducing turbidity decoction, constructed a component-target network, and identified 101 active compounds and 186 potential targets for the treatment of DKD. Luteolin, stigmasterol and isorhamnetin have the most corresponding targets, which may be the main active components of warming yang and reducing turbidity decoction. Luteolin,[15–17] stigmasterol[18] and isorhamnetin[19] have been proved to have protective effects on the kidneys of diabetic animal models. However, due to the low content of these 3 components in warming yang and reducing turbidity decoction, whether they are the main components to exert the curative effect needs further experimental verification.

In our present study, it was found that the curative effects of warming yang and reducing turbidity decoction on DKD were mainly achieved by the 4 key genes, including RELA, CDKN1A, CCND1, and TNF, regulating AGE-RAGE signaling pathway, lipid and atherosclerosis pathway, fluid shear stress and atherosclerosis, TNF signaling pathway, and cellular senescence pathway.

Glucose provides the carbonyl groups for the glycosylation reaction, so the generation and accumulation of AGE is very easy in the diabetic state, thereby promoting the expression of receptor for AGEs.[20] Activation of the AGE-RAGE pathway leads to increased production of reactive oxygen species, and amplify the inflammatory response, and this leads to a chronic inflammatory state in the kidneys, thereby damaging renal structure and function.[21] AGE-RAGE can activate multiple signaling pathways like NF-kB,[22] PI3K/Akt/mTOR,[23] and MAPK/ERK,[24] causing adverse effects on the kidneys.

The kidney is actively involved in the lipid metabolism, and renal insufficiency can lead to changes in lipid metabolism, thereby

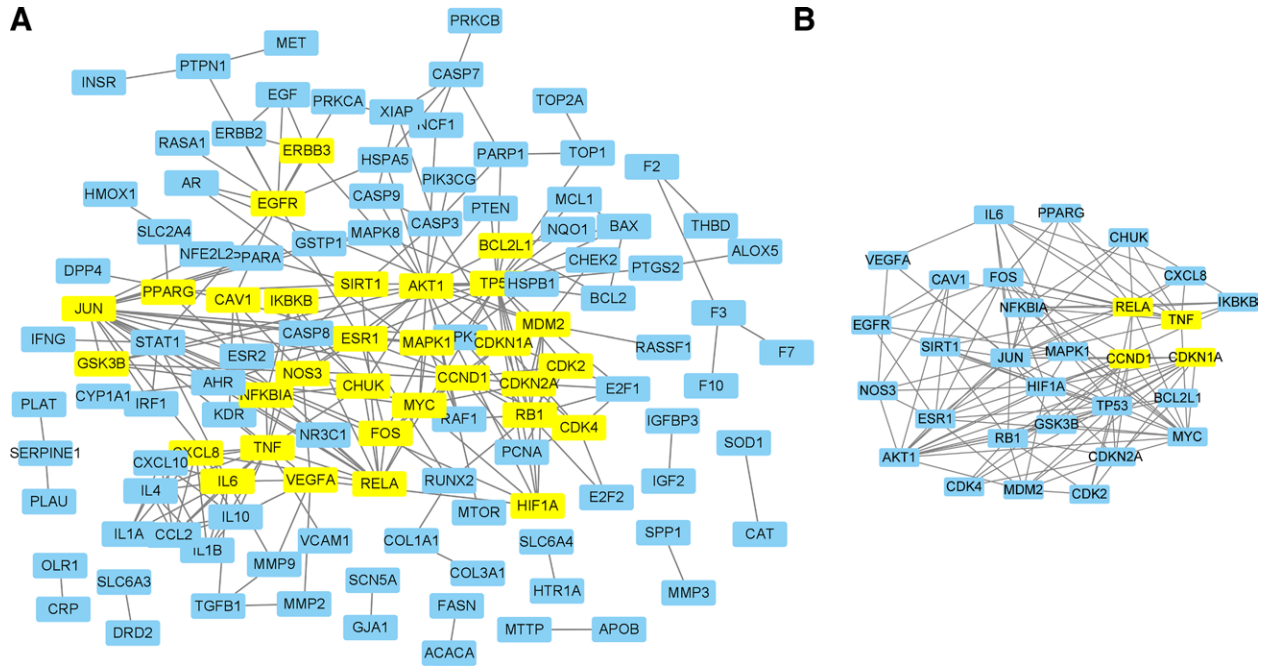

Figure 4. (A) The CytoNC plug-in, with the medians of "Betweenness," "Closeness," "Degree," "Eigenvector," "LAC," "Network" 6.612235912, 0.034752389, 3, 0.038255922, 0.5, 0.666666667 as the screening criteria, was used to screen out 31 nodes and 140 edges; (B) the CytoNC plug-in, with the medians of "Betweenness," "Closeness," "Degree," "Eigenvector," "LAC," "Network" 255.1088143, 0.035325287, 7, 0.151431516, 2.285714286 and 3.85 as the screening criteria, was used again to screen out 4 key nodes and 24 edges.

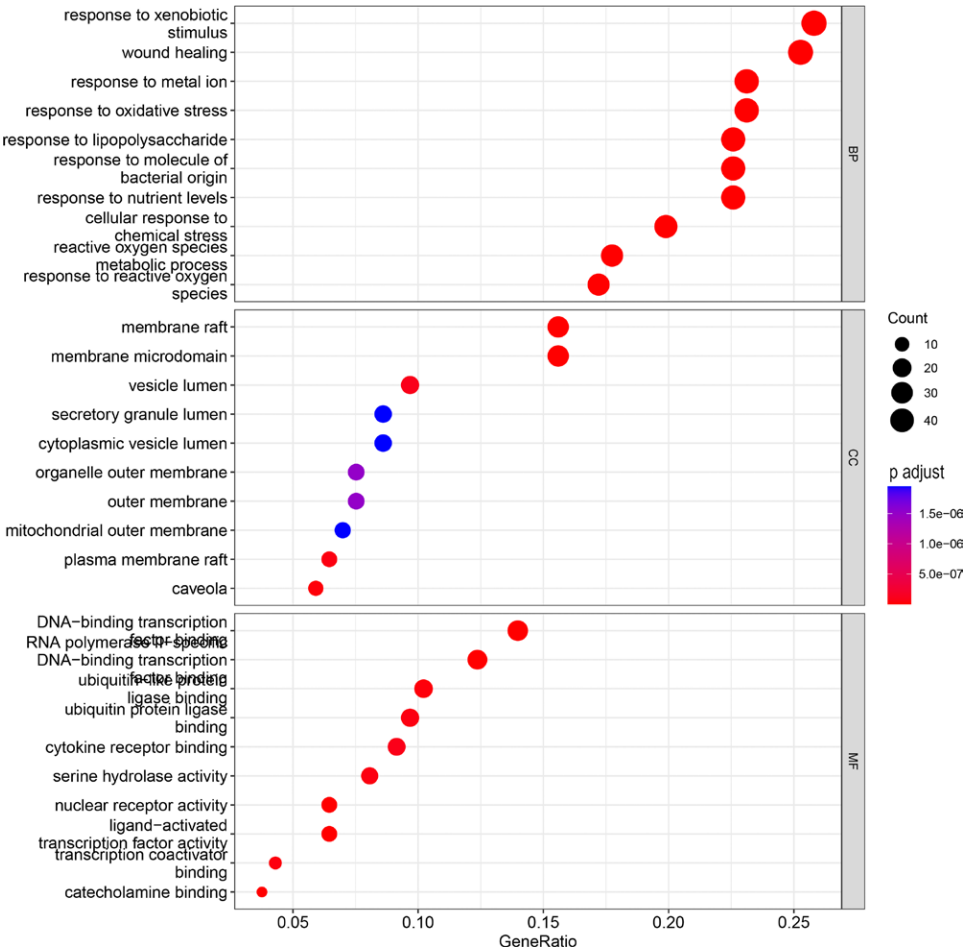

Figure 5. Gene Ontology (GO) functional enrichment analysis.

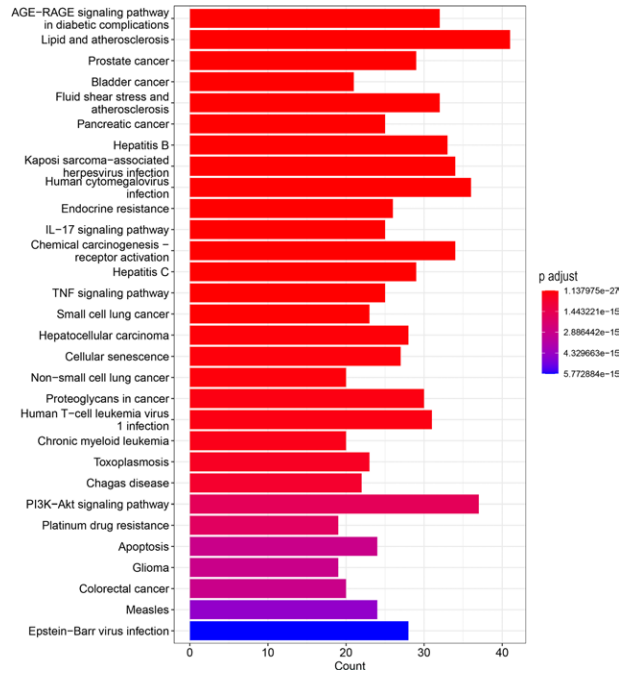

Figure 6. Kyoto Encyclopedia of Genes and Genomes (KEGG) signaling pathway enrichment analysis.

leading to atherosclerotic dyslipidemia.[25] At the same time, renal lipid deposition can also lead to aggravated renal damage, especially diabetic nephropathy. As advanced glycation end products (AGEs) not only impair the antioxidant capacity of high-density lipoprotein particles,[26] but also specific high-density lipoprotein subsets are also associated with high levels of inflammatory markers.[27,28] High glucose exacerbates renal lipid deposition by altering the molecular expression of lipid uptake or efflux, leading to renal extracellular matrix accumulation and fibrosis.[29–31] Abnormal renal hemodynamics is one of the important mechanisms of the pathogenesis of DKD. Our present study implied that warming yang and reducing turbidity decoction might reduce renal lipid deposition caused by high glucose through regulating lipid metabolism, and improving dyslipidemia caused by abnormal renal function.

In the early stage of DKD, glomerular hyperfiltration occurs before the occurrence of renal damage. Podocyte glycocalyx changes due to increased fluid flow shear stress mediated by glomerular ultrafiltration may alter podocyte-glomerular adhesion.[32] Increased flow shear stress activates ERK2, a key molecule of epithelial-mesenchymal transition, and induces renal tubular epithelial cell apoptosis by activating reactive oxygen species.[33] Our present study implied that warming yang and reducing turbidity decoction might reduce renal fluid shear stress, protect residual nephrons, and delay renal failure. In addition to mediating inflammation, TNF[34] can also cause hemodynamic changes, reduce glomerular blood flow and filtration rate, damage the glomerular barrier, recruit inflammatory cells, and induce apoptosis. Cellular aging or cellular senescence is a key factor in the aging process. DKD is a manifestation of premature aging. Hyperglycemia can directly lead to senescence of mesangial cells and tubular epithelial cells.[35–37] On the one hand, senescent cells lose their ability to repair and renew themselves.[38] On the other hand, renal senescent cells produce pro-inflammatory factors and matrix-synthesizing cytokines, which aggravates kidney damage and fibrosis. Warming yang and reducing turbidity decoction might block the activation of AGE-RAGE pathway in DKD, regulate renal lipid metabolism, reduce flow shear stress, inhibit TNF activation, and delay renal cell aging, which has profound significance in protecting renal function.

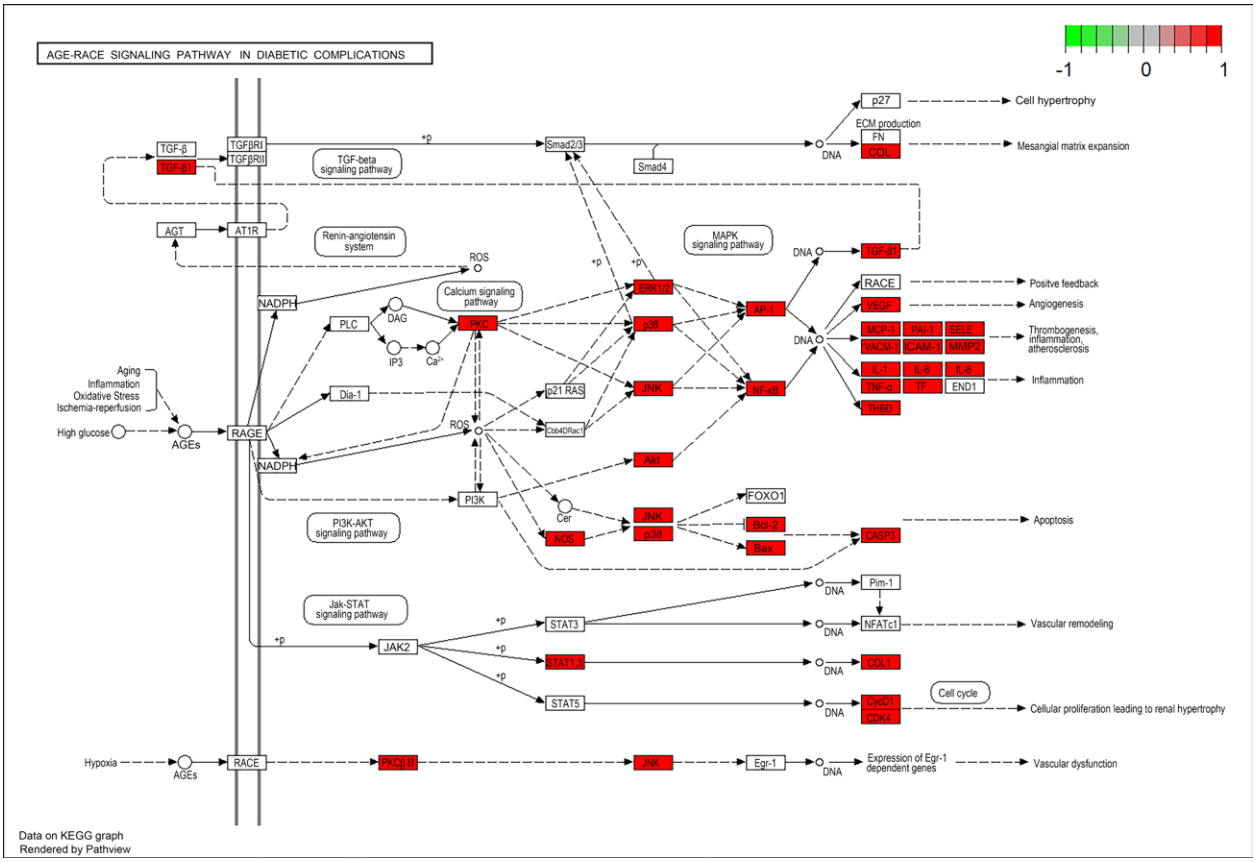

Figure 7. AGE-RAGE signal pathway. AGE = advanced glycation end product.

In conclusion, warming yang and reducing turbidity decoction might treat DKD with multiple pathways. Combination of chemical analysis and network pharmacology analysis was used to comprehensively study the pharmacological effects of warming yang and reducing turbidity decoction, which might provide the theoretical basis for further development and application of this formula. Due to the complex pathogenesis of DKD and the limitations of the network pharmacology analysis method, the predicting outcomes of our present study still need further experimental validation and exploration.

Author contributions

Quan-Qing Cui, Substantial contributions to the conception and design of the work; And Quan-Qing Cui, Xian-Min Li, the acquisition, analysis, and interpretation of data for the work; And Quan-Qing Cui, drafting the work; AND Quan-Qing Cui, Xian-Min Li, Ying Xie, revising it critically for important intellectual content; AND Quan-Qing Cui, Xian-Min Li, Ying Xie, final approval of the version to be published; AND Quan-Qing Cui, Xian-Min Li, Ying Xie, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Conceptualization: Ying Xie.
Data curation: Quan-Qing Cui, Xian-Min Li, Ying Xie.
Formal analysis: Quan-Qing Cui, Xian-Min Li, Ying Xie.
Investigation: Quan-Qing Cui, Xian-Min Li, Ying Xie.
Methodology: Ying Xie.
Resources: Quan-Qing Cui.
Software: Xian-Min Li.
Supervision: Xian-Min Li.
Validation: Quan-Qing Cui, Ying Xie.
Writing – original draft: Ying Xie.
Writing – review & editing: Quan-Qing Cui, Xian-Min Li, Ying Xie.

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