

Exploring New Therapeutic Directions for Diabetic Kidney Disease Using High-Throughput Sequencing

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Abstract: Objective: To screen for miRNAs and mRNAs with target-binding relationships, DKD-related signaling pathways, and potential therapeutic agents for diabetic kidney disease (DKD), so as to explore novel therapeutic directions for DKD at the gene, signaling pathway, and drug levels. **Methods:** Differential miRNAs and mRNAs associated with DKD were screened from high-throughput sequencing datasets downloaded from the GEO database using R. The TargetScan database was used to further filter miRNAs and mRNAs with target-binding interactions. The DSigDB database was employed to identify drug components targeting proteins encoded by differentially expressed mRNAs, and molecular docking was performed to validate their binding stability. **Results:** In total, 17 miRNAs with >4-fold change, 68 mRNAs with >2-fold change, and 7 mRNAs with >4-fold change were retrieved from the GEO database. KEGG enrichment analysis revealed several key DKD-associated signaling pathways, including the IL-17, NF- κ B, TGF- β , and TNF signaling pathways. TargetScan further identified 7 miRNAs and 26 mRNAs with reciprocal target-binding interactions. Using DSigDB, 51 drug components with potential therapeutic effects against DKD (e.g., acetovanillone, ademetonine, beta-carotene, pterostilbene) and their five corresponding target proteins OLR1, IL1B, SERPINB2, CXCL3, and ALAS2 were identified. Molecular docking confirmed stable binding between these drug components and their target proteins. **Conclusion:** Hsa-miR-142-5p, hsa-miR-1225-3p, hsa-miR-513a-5p, along with mRNAs encoding OLR1, IL1B and ALAS2, may serve as key targets for DKD prevention and treatment. The IL-17, NF- κ B, TGF- β , and TNF signaling pathways exert critical regulatory functions during DKD pathogenesis and represent core pathways for therapeutic intervention. Moreover, natural active compounds including acetovanillone, ademetonine, beta-carotene, and pterostilbene exhibit promising therapeutic potential for DKD. These findings provide a theoretical basis and novel insights for exploring DKD pathogenesis and developing targeted preventive and therapeutic strategies, and help improve clinical prognosis and slow DKD progression in patients.

Keywords: High-Throughput Sequencing; Diabetic Kidney Disease; MiRNA; Molecular Docking

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Diabetic Kidney Disease (DKD) is a severe complication of diabetes. Over the past two decades, its morbidity and mortality have risen rapidly, accompanied by poor prognosis^[1]. It is the leading cause of kidney failure and end-stage renal disease, responsible for ~50% of all cases, and contributes to 34%-36% of deaths related to chronic kidney disease^[2]. DKD is defined by renal structural and functional abnormalities, including interstitial expansion, thickening of glomerular and tubular basement membranes, and glomerulosclerosis^[3]. As disease advances, patients gradually develop proteinuria and progressive

renal function loss. Many eventually require hemodialysis, peritoneal dialysis or kidney transplantation for survival, imposing substantial care-related and economic burdens on families. Furthermore, DKD patients frequently suffer comorbidities including cardiovascular disease and hypertension; their risk of cardiovascular events is 2-4-fold higher than that of patients with uncomplicated diabetes, further increasing mortality risk. DKD therefore represents a major global public-health challenge^[4].

In molecular biology and bioinformatics, the Gene Expression Omnibus (GEO) database hosts abundant disease-related gene-expression datasets, offering critical resources for screening and functional analysis of differentially expressed genes. In addition, bioinformatics-driven drug-repositioning approaches are emerging to discover candidate therapeutic agents by interrogating interactions between differentially expressed genes and known drugs^[5]. In this study, we screened differentially expressed genes between DKD patients and healthy controls using GEO datasets and performed pathway-enrichment analysis to identify drug components targeting these genes. Molecular docking was applied to validate binding interactions and stability between drug candidates and target proteins, generating theoretical evidence supporting potential clinical translation. Comprehensive analysis of GEO-derived DKD data facilitates identification of disease-associated genes, proteins, signaling pathways and candidate therapeutics, and helps elucidate relationships between DKD and other comorbid disorders. It further provides novel insights for developing precision-diagnostic tools and optimizing targeted therapeutic strategies. This work carries important scientific and clinical significance for improving early DKD detection, slowing disease progression and optimizing patient outcomes, and lays groundwork for advancing precision nephrology medicine.

1. Materials and Methods

1.1 Screening of DKD-Related Differential Genes and Candidate Targeted Therapeutic Agents

DKD-associated miRNAs and mRNAs were retrieved from the GEO database, and a “miRNA-mRNA” regulatory network linked to DKD pathogenesis was constructed. KEGG enrichment analysis of differentially expressed mRNAs was conducted to characterize DKD-relevant signaling pathways. A “drug-target gene” regulatory network was built using the DSigDB database, and molecular docking validated binding between drug moieties and target proteins.

1.2 Screening for Differential Genes

MiRNA and mRNA datasets for DKD patients were downloaded from GEO using the search term “Diabetic kidney disease”, with species set to Homo sapiens. Differences in miRNA and mRNA expression between groups were analysed using the Limma package in R software (R version 4.4.1, <https://www.r-project.org>). Differentially expressed mRNAs were filtered with thresholds of $|\log FC| > 1$ (≥ 2 -fold change), $|\log FC| > 2$ (≥ 4 -fold change) and $P < 0.05$. Clustering heatmaps of differentially expressed genes were generated accordingly.

1.3 KEGG Enrichment Analysis

KEGG pathway enrichment for mRNAs with $|\log FC| > 1$ was implemented using the KEGG package in R, supplemented with manual annotation via the KEGG web portal, to identify DKD-associated signaling pathways.

1.4 Construction of “MiRNA-mRNA-DKD” Regulatory Network

TargetScan was used to retrieve mRNAs predicted to bind miRNAs with $|\log FC| > 2$. These target mRNAs were intersected with mRNAs satisfying $|\log FC| > 1$. Only miRNA-mRNA pairs exhibiting inverse expression patterns (up-regulated miRNAs paired with down-regulated mRNAs; down-regulated miRNAs paired with up-regulated mRNAs) were retained. The “miRNA-mRNA-DKD” regulatory network was visualised using Cytoscape software.

1.5 Identification of Drug Components Targeting Differentially Expressed Genes

The DSigDB database was queried to retrieve chemical compounds targeting proteins encoded by $|\log FC| > 2$ differentially expressed genes defined in section 1.1. The “drug-target gene” interaction network was constructed with Cytoscape.

1.6 Molecular Docking

SDF files of drug molecular structures were downloaded from PubChem. Chem3D software was applied to compute minimum-energy conformers, which were saved in mol2 format. Target protein structures were retrieved from the PDB database. Water molecules, small organic molecules, pro-ligands, crystallization additives and contaminating moieties were removed using PyMOL. AutoDockTools was used to define protein active-site pockets and configure docking parameters.

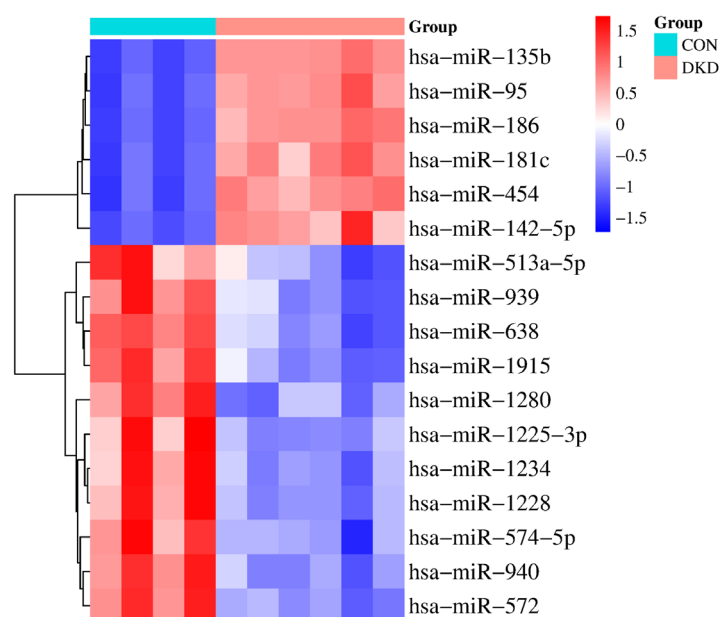
Docking simulations between target proteins and drug compounds were performed; binding interactions were analysed using the PLIP web server and visualised in PyMOL.

2. Results

2.1 Differential Genes

Considering sample size and publication year, dataset GSE51674 was selected for miRNA analysis, containing miRNA expression profiles from four healthy controls and six patients with DKD. Seventeen miRNAs exhibited >4-fold expression change (11 down-regulated and 6 up-regulated; Figure 1). Dataset GSE142153 was chosen for mRNA analysis, covering profiles from 10 healthy controls and 23 DKD patients. Sixty-eight mRNAs showed >2-fold expression change (22 down-regulated, 46 up-regulated; Figure 2A). Seven mRNAs had >4-fold expression change (1 down-regulated and 6 up-regulated; Figure 2B).

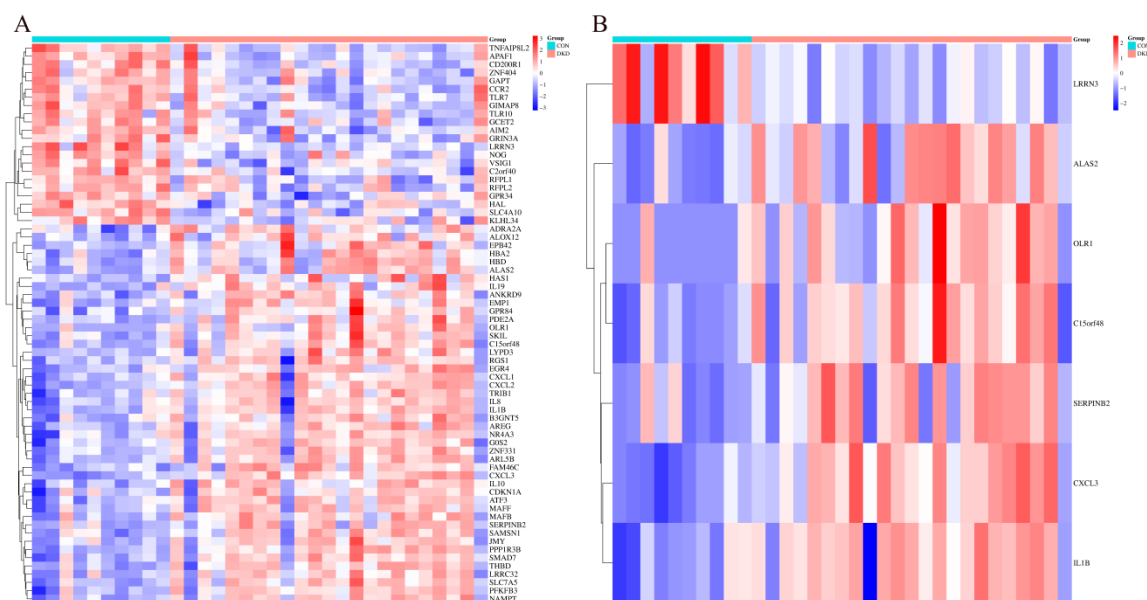
Figure 1: Heatmap of differentially expressed miRNAs. Con: control group; DKD: diabetic kidney disease group.



Note: Red represents up-regulated transcripts, blue represents down-regulated transcripts. Color intensity corresponds to magnitude of expression difference.

Figure 2: Heatmaps of differentially expressed mRNAs. A: mRNAs with >2-fold change; B: mRNAs with >4-fold change.

Con: control group; DKD: diabetic kidney disease group.

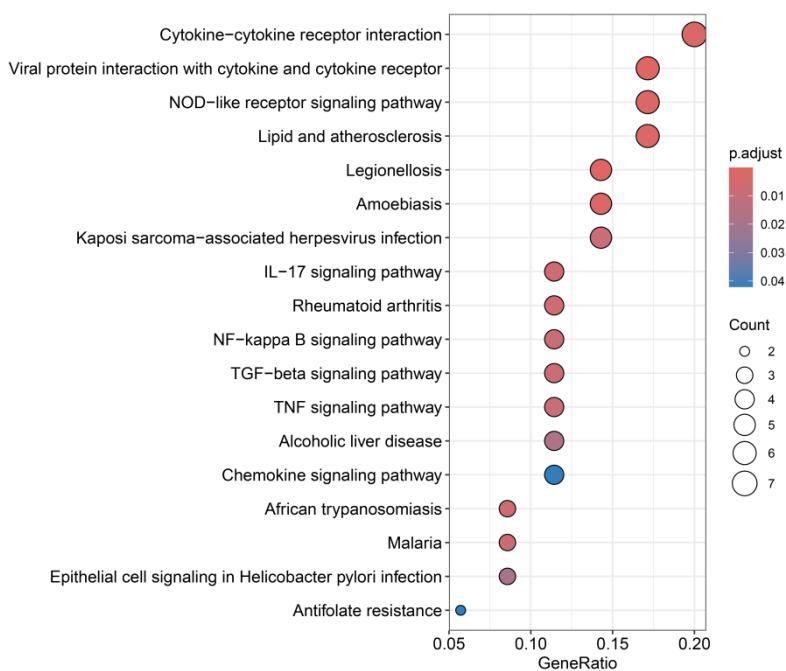


Note: red indicates up-regulated genes and blue indicates down-regulated genes. The darker the color, the greater the difference.

2.2 KEGG Analysis

KEGG enrichment identified multiple enriched pathways including IL-17, NF- κ B, TGF- β and TNF signaling pathways (Figure 3).

Figure 3: Bubble plot of KEGG pathway enrichment results.

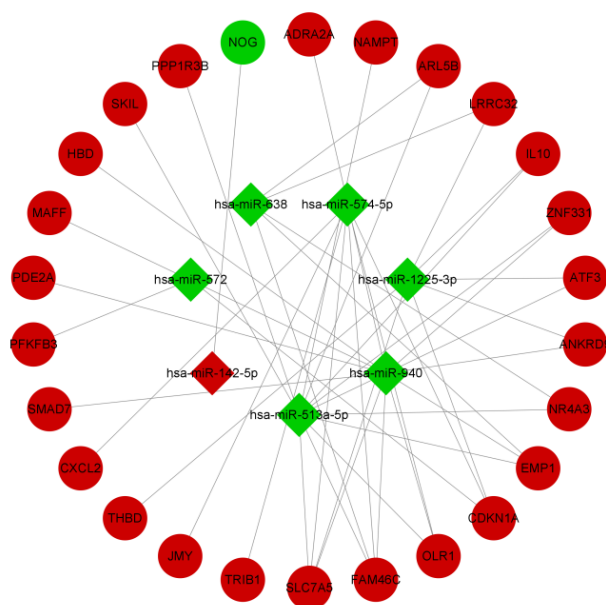


Note: Larger bubbles indicate higher gene counts within the pathway. Darker colour denotes greater statistical significance.

2.3 “MiRNA-mRNA-DKD” Regulatory Network

Seven miRNAs and 26 predicted target mRNAs were obtained from the network. Among these miRNAs, one was up-regulated and six were down-regulated. Twenty-five of the 26 target mRNAs were up-regulated and one was down-regulated (Figure 4).

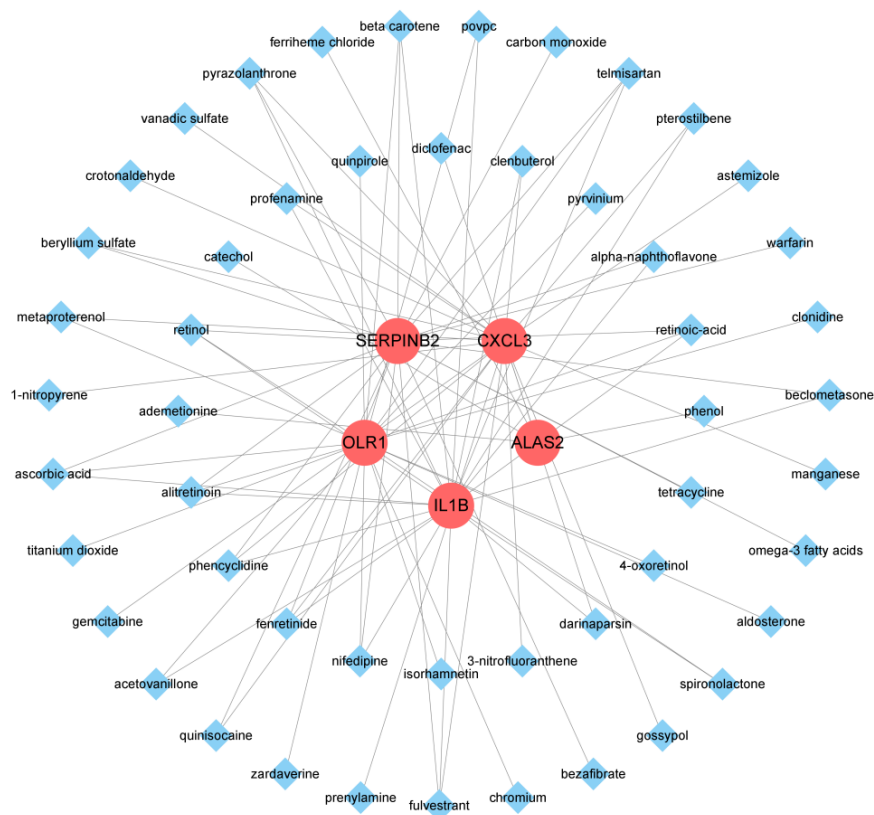
Figure 4: The “miRNA-mRNA-DKD” regulatory network. Diamonds represent miRNAs; circles represent mRNAs. Red: up-regulated; green: down-regulated.



2.4 Candidate Compounds Targeting Differentially Expressed Genes

The “drug-target gene” interaction network was constructed in Cytoscape (Figure 5). Five target genes (IL1B, OLR1, SERPINB2, CXCL3, ALAS2) are shown as red circles; the 51 candidate drug compounds, including acetovanillone, ademetonine, beta-carotene and pterostilbene, are represented as blue diamonds.

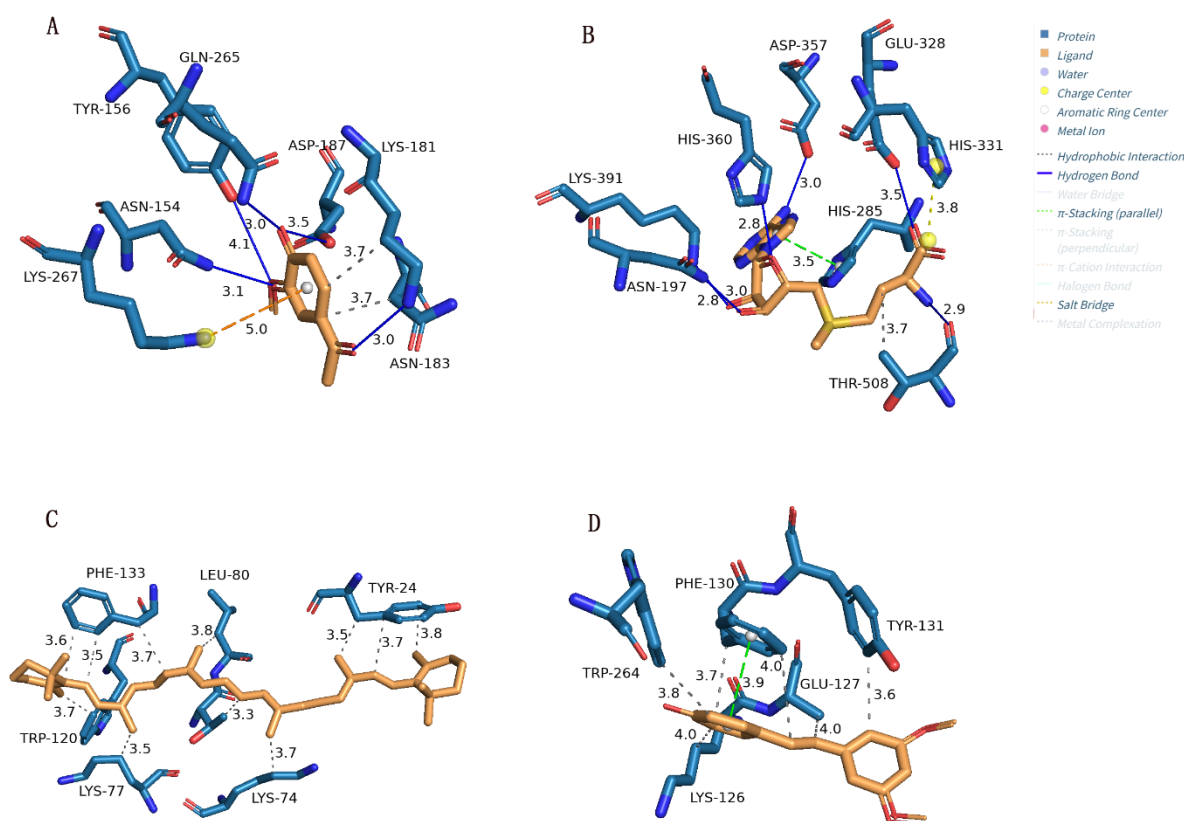
Figure 5: Drug-target gene interaction network. Blue diamonds denote drug compounds; red circles denote target genes; connecting lines represent predicted binding interactions.



2.5 Molecular Docking

Molecular docking simulations between candidate compounds and their corresponding target proteins revealed favourable, stable target-binding interactions (Figure 6). Panel A: acetovanillone docked to OLR1; Panel B: ademetonine docked to ALAS2; Panel C: beta-carotene docked to IL1B; Panel D: pterostilbene docked to CXCL3. The molecular docking results indicated stable binding between these small-molecule compounds and target proteins. Among them, the docking score of acetovanillone with OLR1 was -5.0 kcal/mol, indicating that acetovanillone could bind to OLR1. The hydrogen-bond distances between acetovanillone and amino acid residues GLN-265, ASP-187, LYS-181, ASN-154, and TYR-156 were 3.0, 3.5, 3.0, 3.1, and 4.1 Å, respectively. The hydrophobic-interaction distances with residues LYS-181 and ASN-183 were both 3.7 Å, and the π -stacking interaction distance between the charge centre of LYS-267 and the aromatic-ring centre of OLR1 was 5.0 Å. The docking score of ademetonine with ALAS2 was -7.2 kcal/mol. The hydrogen-bond distances for residues HIS-360, ASP-357, GLU-328, THR-508, ASN-197, and LYS-391 of ALAS2 were 2.8, 3.0, 3.5, 2.9, 3.0, and 2.8 Å, respectively. The hydrophobic-interaction distance for residue THR-508 was 3.7 Å; salt-bridge distances for HIS-331 and HIS-285 were 3.8 Å and 3.5 Å, respectively. The docking score of beta-carotene with IL1B was -7.5 kcal/mol. The interaction was predominantly hydrophobic. Hydrophobic-interaction distances were 3.6, 3.5, and 3.7 Å for PHE-133; 3.8 Å for LEU-80; 3.5, 3.7, and 3.8 Å for TYR-24; 3.7 Å for LYS-74; 3.5 Å for LYS-77; and 3.7 Å for TRP-120. The docking score of pterostilbene with CXCL3 was -7.7 kcal/mol, and its binding was mainly maintained by hydrophobic interactions. The hydrophobic-interaction distances were 3.7 Å and 4.0 Å for PHE-130; 3.6 Å for TYR-131; 4.0 Å for GLU-127; 4.0 Å for LYS-126; and 3.8 Å for TRP-264. In addition, a π -stacking interaction of 3.9 Å was observed with the aromatic-ring centre of PHE-130.

Figure 6: Molecular docking visualisation. Yellow structures represent drug compounds; blue structures represent amino-acid residues. Panel A: acetovanillone-OLR1; Panel B: ademetonine-ALAS2; Panel C: beta-carotene-IL1B; Panel D: pterostilbene-CXCL3.



3. Discussion

DKD is a multifactorial disorder. Cumulative evidence indicates that miRNAs and mRNAs participate in DKD onset and progression and may serve as candidate therapeutic targets for clinical translation. Previous work reported that hsa-miR-142-5p correlates strongly with type 2 diabetes mellitus (T2DM) severity and may act as a novel diagnostic biomarker for T2DM and its complications [6]. Hsa-miR-1225-3p and hsa-miR-513a-5p are expressed at low levels in DKD. High-throughput sequencing confirms their significant expression differences relative to healthy controls, ranking them among the top-10 differentially expressed miRNAs [7,8]. Hsa-miR-572 is closely related to DKD ferroptosis, which is a key pathological mechanism driving tubular atrophy, interstitial fibrosis, and deterioration of renal function in DKD [9]. Hsa-miR-574-5p production is differential in human umbilical cord mesenchymal stem cell after advanced glycation end products intervention, and hsa-miR-574-5p may contribute to the differentiation of human umbilical cord mesenchymal stem cell by combating cell damage under high glucose environment, which may provide a theoretical basis for the development of advanced glycation end products, inhibition of glycolysis and so on ameliorates diabetic injury [10]. Compared with healthy controls, the serum levels of miR-638 in T2DM and DKD patients were significantly reduced. High expression of miR-638 could reduce the level of pro-inflammatory factors and proliferation ability induced by high glucose, and the mechanism was related to the regulation of proliferation and inflammation, miR-638 may serve as a diagnostic marker for DKD [11]. Hsa-miR-940 has not yet been reported in the literature on DKD, which is worthy of further study.

Acetovanillone can reduce the generation of superoxide anion in kidney podocytes, thereby alleviating proteinuria and water and sodium retention in animal models of nephropathy, suggesting a therapeutic effect of acetovanillone on DKD [12]. Ademetonine, a key metabolite in the regulation of cysteine and methionine metabolic pathways, attenuates oxidative stress and inflammation in DKD renal tissue [13]. Beta-carotene exerts renal protection against streptozotocin-induced diabetic

nephropathy and histopathology by alleviating hyperglycemia, alleviating inflammation, activating AMPK/SIRT1/autophagy pathway, and inhibiting apoptosis^[14]. Pterostilbene is used to treat diabetes and has been shown to control blood glucose levels in diabetic animals and to ameliorate acute renal ischemia-reperfusion injury^[15].

OLR1 is a critical receptor mediating renal injury induced by oxidised low-density lipoprotein. It exerts prominent pro-pathogenic effects in DKD by driving inflammation, oxidative stress, podocyte damage and renal fibrosis. Suppression of renal OLR1 expression can mitigate renal injury^[16]. Patients with DKD have significantly higher levels of IL1B, which is positively correlated with fasting plasma glucose, and IL1B is closely related to the occurrence and development of DKD^[17]. 5-aminophenylpropionic acid (ALA) synthase (ALAS)-catalyzed ALA deficiency leads to impaired glucose tolerance and insulin resistance in aged mice and is accompanied by reduced mitochondrial function, and ALAS has two isoenzymes, which are responsible for the impairment of insulin resistance in aged mice, encoded by different chromosomes, namely ALAS1 and ALAS2, respectively. ALAS2 has been implicated in the development of diabetes^[18]. CXCL3, as a key chemokine ligand, interacts with its receptors to mediate cascade amplification of inflammatory and fibrotic signals, thereby accelerating renal fibrosis, and represents a potential therapeutic target for preventing and treating renal fibrosis and related renal-injury disorders^[19]. Inflammatory states such as obesity downregulate SERPINB2 expression in macrophages, leading to enhanced mitochondrial oxidative phosphorylation, decreased glutathione levels, and a massive release of pro-apoptotic cytochrome c from mitochondria to the cytosol, which may promote inflammatory responses in macrophages and ultimately trigger macrophage apoptosis, thereby aggravating impaired glucose tolerance with insulin resistance, suggesting an important role for SERPINB2 in the maintenance of insulin sensitivity^[20].

IL-17 signaling pathway plays a key pro-inflammatory role in the progression of DKD, which can be activated by high glucose environment to mediate renal inflammation, mesangial proliferation and fibrosis. Clinical and animal studies have shown that elevated levels of IL-17 in renal tissue and peripheral blood are positively associated with the degree of renal impairment in DKD patients^[21]. High glucose can abnormally activate NF- κ B signaling pathway in kidney and mediate inflammation and fibrosis gene expression. The excessive activation of this pathway promotes the secretion of inflammatory factors, induces inflammatory injury in renal tissue, aggravates glomerular mesangium hyperplasia, tubulointerstitial fibrosis, and podocyte destruction, amplifies oxidative stress and inflammatory cascades, and increases the risk of inflammation, promote glomerulosclerosis and disease progression^[22]. TGF- β signaling pathway mediates renal tubular epithelial cell apoptosis and mesenchymal transition, promotes abnormal accumulation of extracellular matrix, drives renal fibrosis, and leads to structural destruction and functional decline of renal tissue^[23]. TNF- α has a significant effect on glomerular endothelial permeability and podocyte apoptosis. Clinical and animal experiments have confirmed that TNF- α and its receptor are abnormally expressed in the kidney tissue and peripheral circulation of diabetic nephropathy, it is closely related to the severity of renal function injury and proteinuria. Inhibition of TNF- α signaling pathway can significantly reduce renal injury and improve renal function^[24].

In summary, this study delineates regulatory crosstalk among candidate drugs, key genes, signalling pathways and DKD pathogenesis, providing a theoretical foundation for DKD research. We have identified key therapeutic targets and candidate pharmacological agents for DKD intervention: miRNAs such as hsa-miR-142-5p, hsa-miR-1225-3p, hsa-miR-513a-5p and mRNAs such as OLR1, IL1B and ALAS2 were key regulatory genes for the pathogenesis and intervention of DKD; IL-17, NF- κ B, TGF- β , TNF and other signaling pathways are important pathways to mediate the occurrence and development of DKD; natural active compounds including acetovanillone, ademetionine, beta-carotene and pterostilbene represent promising candidate therapeutics for DKD. It is of great research value and clinical significance to clarify the internal regulatory network of drugs, genes, signaling pathways and diseases. It can not only systematically reveal the molecular pathogenesis of DKD, but also effectively promote the in-depth mining and innovative breakthrough of disease-targeted therapeutic mechanisms, to provide a new theoretical basis, research direction and treatment ideas for the precise prevention and treatment of clinical DKD, disease intervention and patient pain relief, and effectively supplement clinical treatment strategies, it also provides an important reference value for the optimization of clinical diagnosis and treatment of DKD and the development of new drugs.

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Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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