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Explore a New Direction for the Treatment of Diabetic Nephropathy by High-Throughput Sequencing

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Abstract: Objective: To screen out miRNAs and mRNAs with targeted binding relationship, DKD-related signaling pathways and potential therapeutic drugs related to diabetic kidney disease (DKD), and to explore new directions for DKD treatment from the gene, signaling pathway and drug levels. **Methods:** Using the R language, diff erential miRNAs and mRNAs related to DKD were screened from the high-throughput sequencing data set of the GEO database. DKD-related signals were obtained by KEGG analysis. TargetScan database was used to further screen out miRNAs and mRNAs with targeted interaction. The DSigDB database was used to fi nd out the drug components that had targeted eff ects on the proteins corresponding to the diff erential mRNA, and the binding stability of the two was verifi ed by molecular docking. **Results:** A total of 17 miRNAs with a diff erence of more than 2 times, 68 mRNAs with a diff erence of more than 1.5 times, and 7 mRNAs with a diff erence of more than 4 times were obtained from the GEO database. KEGG analysis showed that DKD-related signaling pathways were IL-17 signaling pathway, NF-κB signaling pathway, TGF-β signaling pathway, TNF signaling pathway, etc. The TargetScan database further screened 7 miRNAs with targeted interaction and 26 mRNAs with targeted interaction. Through the DSigDB database, 51 drug components with potential treatment of DKD, such as acetovanillone, ademetionine, betacarotene, pterostilbene, and 5 corresponding target gene proteins were obtained : OLR1, IL1B, SERPINB2, CXCL3, ALAS2. Molecular docking showed that the drug components were stable in binding to the target gene protein. **Conclusion:** Hsa-miR-142-5p, hsa-miR-1225-3p, hsa-miR-513a-5p and OLR1, IL1B, ALAS2 mRNA can be used as key targets for the prevention and treatment of DKD. IL-17, NF-κB, TGF-β, TNF and other signaling pathways play an important regulatory role in the pathological process of DKD, and are the core related pathways for intervening DKD. In addition, natural active ingredients and compounds such as vanillone, adenosylmethionine, β-carotene, and pterostilbene showed good potential therapeutic value for DKD. The above research results can provide theoretical basis and new ideas for the exploration of the mechanism of DKD, targeted intervention and the development of new prevention and treatment strategies, and lay a research foundation for improving the clinical prognosis and alleviating the progression of DKD patients.

Keywords: High-Throughput Sequencing ; Diabetic Nephropathy ; MiRNA ; Molecular Docking
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Diabetic Kidney Disease (DKD) is a serious complication of diabetes, and in the past two decades, the morbidity and mortality of this Disease have increased rapidly and the prognosis is poor[1]. DKD is the leading cause of kidney failure and end-stage renal disease, accounting for approximately 50% of cases, and DKD accounts for 34%-36% of all chronic

kidney disease deaths[2]. DKD is characterized by structural and functional changes in the kidney with significant structural changes, including interstitial dilatation, glomerular and tubular basement membrane thickening, and glomerulosclerosis[3]. With the progression of the disease, patients will gradually develop proteinuria and progressive decline in renal function, and eventually need to rely on hemodialysis, peritoneal dialysis or kidney transplantation to maintain life, it also brings heavy care pressure and economic burden to the family. In addition, patients with DKD are often accompanied by complications such as cardiovascular disease and hypertension, and the incidence of cardiovascular events is 2-4 times higher than that of ordinary diabetic patients, which further aggravates the risk of death from the disease, it has become a major challenge to be overcome in the field of global public health[4].

In the field of molecular biology and bioinformatics, Gene Expression Omnibus (GEO) database provide a large number of Gene Expression data about diseases, which provide important resources for screening and functional analysis of differential genes. In addition, Drug repositioning studies based on bioinformatics methods are also gradually emerging to find potential therapeutic drugs by analyzing the interaction of differential genes with known drugs[5]. We screened the differential genes between patients with diabetic nephropathy and healthy people through GEO database and performed pathway enrichment analysis to find out the drug components that are targeted to the differential genes, so as to provide a theoretical basis for the development of drugs targeting the differential genes, the molecular docking between the drug components and the protein molecules of the differential genes verifies the binding relationship and stability, and provides a theoretical basis for clinical application.

In-depth study of GEO Database and DKD not only helps to clarify the disease-related genes, proteins, signaling pathways, therapeutic drugs, but also helps to clarify the relationship between DKD and other diseases, it can also provide new ideas for the research and development of precise diagnostic technologies and the optimization of targeted treatment strategies. It has important scientific value and clinical significance for improving the early detection rate of DKD, delaying the progression of disease and improving the prognosis of patients, and lays a foundation for promoting the development of precision medicine in kidney disease.

1. Materials and Methods

1.1 Screening of DKD Differential Genes and Targeted Therapeutic Agents

The DKD-related miRNAs and mRNAs were screened out by GEO database, and the“miRNA-mRNA” regulatory network related to DKD pathogenesis was established. KEGG analysis of differential mRNAs was performed to clarify the DKD-related signaling pathways. The“Drug-target Gene” regulatory network was established by DSigDB database, and the binding relationship between drug components and target gene proteins was verified by molecular docking.

1.2 Screening for Differential Genes

The miRNA and mRNA datasets of patients with DKD were downloaded from the GEO database with the search term“Diabetic kidney disease” and the species selected“Homo Sapiens”. MiRNA and mRNA expression levels were compared between groups by the Limma package in R software (R version 4.5.1, https://www.r-project.org) . MRNAs with thresholds | logFC | > 1(1.5-fold or more differences in genes between the two groups) , | logFC | > 2(4-fold or more differences in genes between the two groups) were plotted with p-value < 0.05 as the screening criterion and a heat map of differential gene clustering was plotted.

1.3 KEGG Analysis

KEGG analysis of | logfc | > 1 mRNA was performed by R language software“KEGG” package and by KEGG website to clarify DKD-related signaling pathways.

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

The mRNAs with a targeted binding relationship with miRNAs of | LogFC | > 2 were screened through the TargetScan database and intersected with mRNAs of | LogFC | > 1, retaining miRNAs and mRNAs with a targeted binding relationship and regulation in the opposite direction, while the mRNAs with a targeted binding relationship and regulation in the opposite direction were selected, that is, up-regulated miRNAs and down-regulated mRNAs, down-regulated miRNAs and up-regulated mRNAs, the“miRNA-mRNA-DKD” regulatory network was constructed by Cytoscape software.

1.5 Search for Drug Components That Bind Differential Genes

DSigDB database is used to search the chemical composition of the differential genes with | LogFC | > 2 in 1.1, and Cytoscape software is used to make the"Drug-target gene" network.

1.6 Molecular Socking

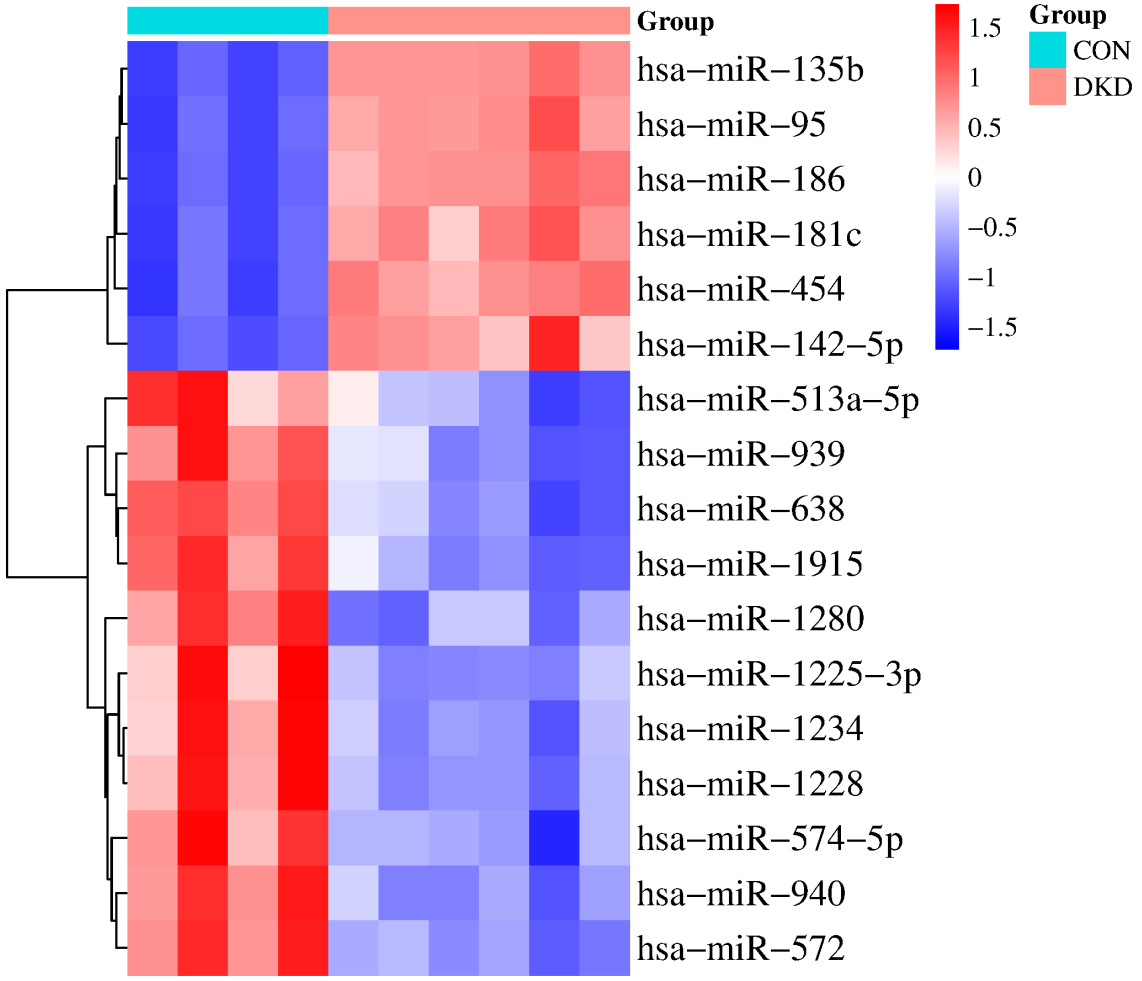
Download the SDF format of drug molecular structure from pubchem. By Chem3D software, the lowest free energy was calculated and saved as mol2 format. The protein structure was obtained through the PDB website, and the water molecules, organic small molecules, protoligands, crystallization additives, impurities, etc. were removed by Pymol software. The active pocket of molecular protein was determined by AutoDockTools, and the docking parameters were determined. The protein was docked with the drug components by PLIP website and Pymol Software.

2. Results

2.1 Differential Genes

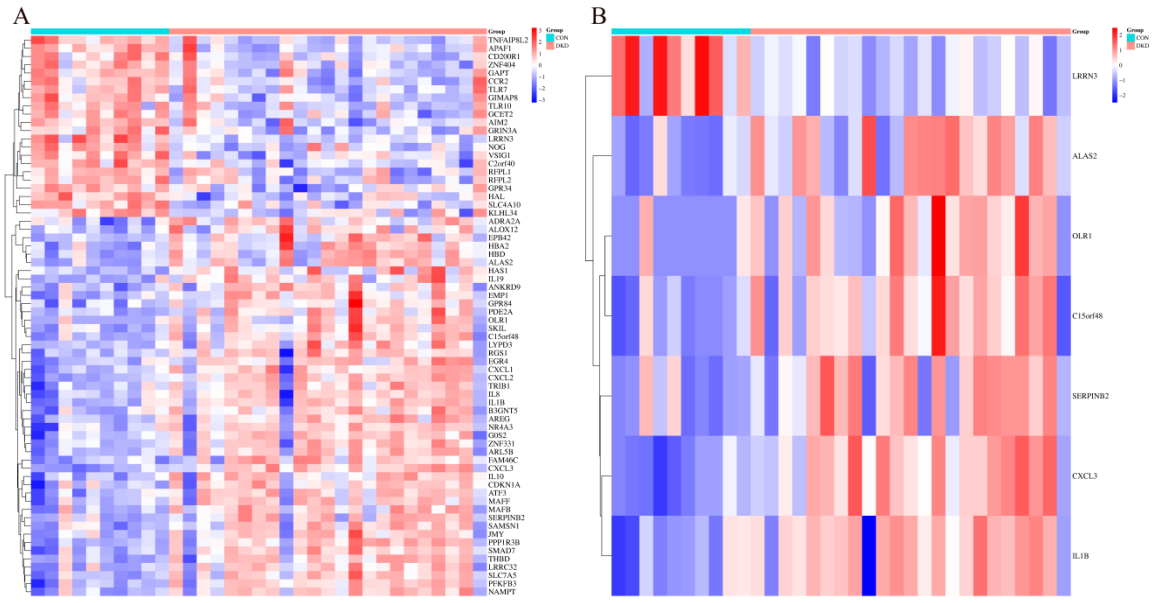
Combining sample size and year, the selected miRNA dataset was GSE51674, which included miRNA expression profiles of 4 healthy controls and 6 DKD patients. A total of 17 miRNAs with more than 4-fold difference, including 11 downregulated miRNAs and 6 upregulated miRNAs, are shown in Figure 1. The data set of selected miRNAs was GSE142153, which included the mRNA expression profiles of 10 healthy controls and 23 DKD patients. The results showed a total of 68 mRNAs that differed by more than 1.5-fold, of which 22 were down-regulated and 46 were up-regulated, as shown in figure 2a. A total of 7 mRNAs differed by 2-fold or more, including 1 down-regulated and 6 up-regulated, as shown in Figure 2B.

Figure 1: Differential mirnas. Con: control group, DKD: diabetic nephropathy group.



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

Figure 2: Differential mirnas. A: more than 1.5-fold difference, b: more than 4-fold difference. Con: control group, DKD: diabetic nephropathy group.

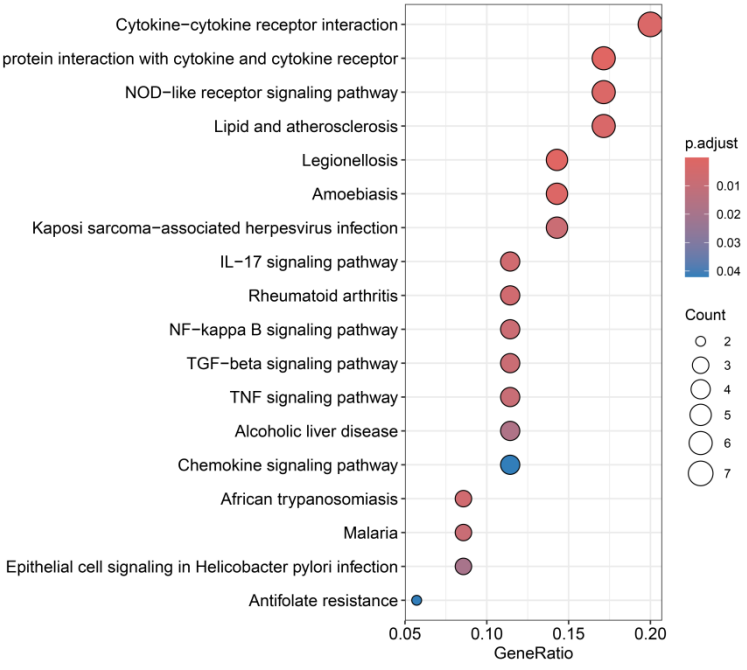


Note: red indicates up-regulated genes and blue indicates down-regulated genes. The darker the color, the greater the difference.

2.2 KEGG Analysis

The results show that Il-17 signaling pathway, NF-κb signaling pathway, TGF-β signaling pathway, TNF signaling pathway and so on are involved, see Figure 3.

Figure 3: Enrichment results of KEGG signaling pathway.

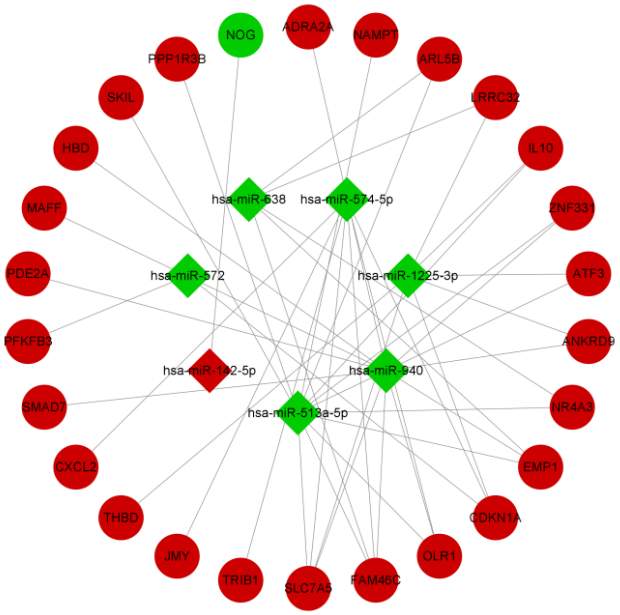


Note: the larger the bubble, the more genes involved in the corresponding pathway. The darker the color, the higher the significance.

2.3 "MiRNA-mRNA-DKD" Regulatory Network

A total of seven miRNAs were obtained, of which one was up-regulated and six were down-regulated. Of the 26 mRNAs with a targeted binding relationship, 25 were up-regulated and 1 was down-regulated, as shown in Figure 4.

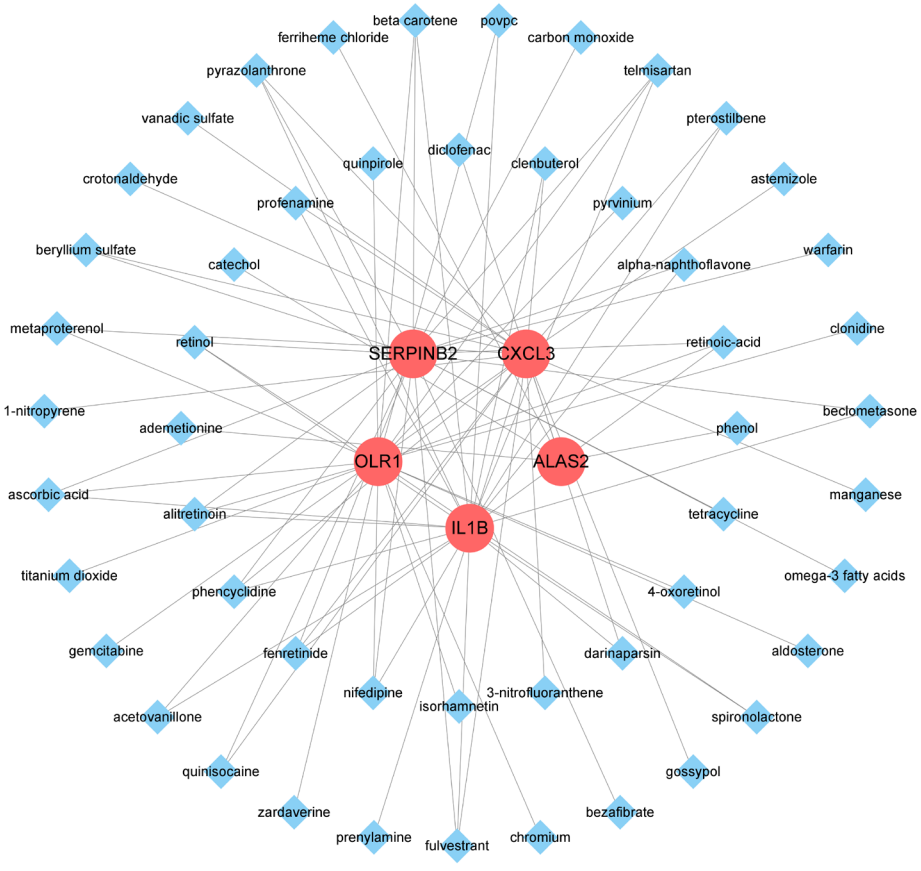
Figure 4: "MiRNA-mRNA-DKD" regulatory network. Diamond: MiRNA, Circle: mRNA. Red: upregulated, Green: downregulated.



2.4 Chemical Components That Bind Differential Genes

The "Drug-target Gene" action network was created by Cytoscape software, as shown in Figure 5. Among them, 5 target genes are indicated by red circle pattern, which are IL1B, OLR1, SERPINB2, CXCL3 and ALAS2; 51 drug components are indicated by blue diamond pattern, they are acetovanillone, adenosylmethionine, beta-carotene, pterostilbene, etc.

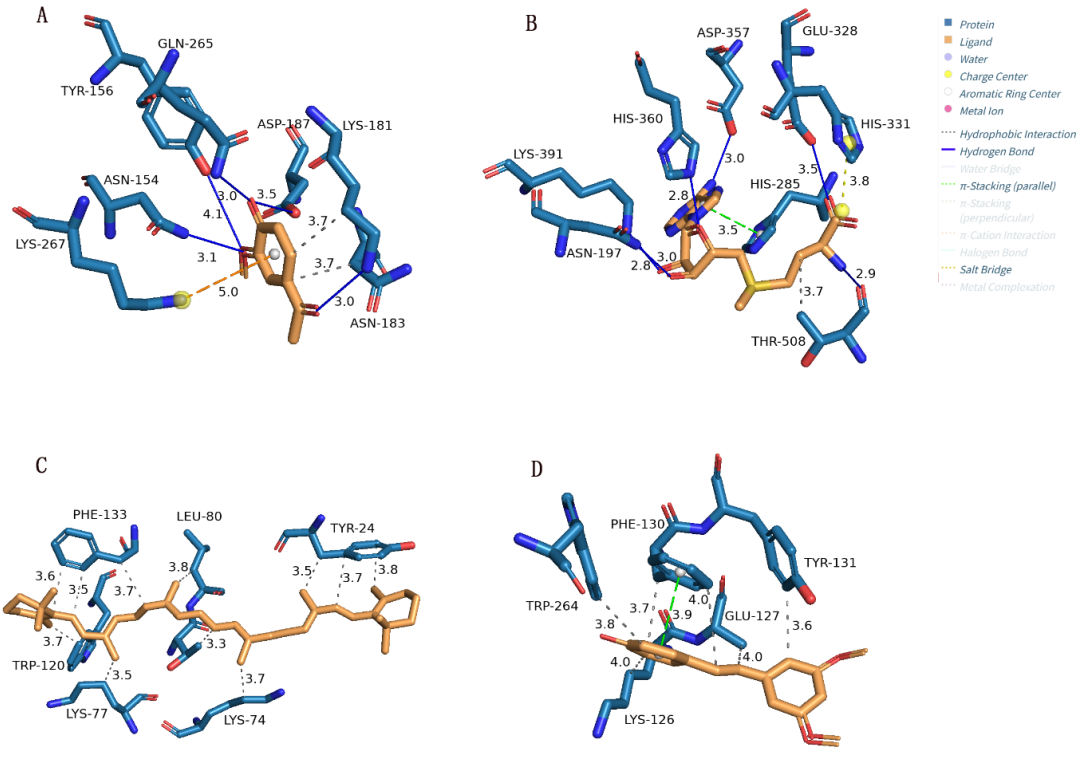
Figure 5: Drug-target gene "Interaction Network. Blue diamond pattern indicates drug components, red circle pattern indicates target genes, and lines indicate binding relationships."



2.5 Molecular Docking

Molecular docking of the obtained chemical components with the corresponding gene protein showed that it had a targeted binding relationship and the binding was stable. See Figure 4. A is the docking of vanillin and OLR1, B is the docking of adenosylmethionine and Alas2, c, Beta-carotene and IL1B, D, pterostilbene and CXCL3. The results of molecular docking showed that the binding of drug components and gene proteins was stable. Among them, the docking score of vanillin ethyl ketone with OLR1 was -5.0 kcal/moL, which indicated that vanillin ethyl ketone could bind to OLR1, the hydrogen bond distances between vanillin and amino acid residues GLN-265, ASP-187, LYS-181, ASN-154, Tyr-156 of OLR1 were 3.0,3.5,3.0,3.1,4.1 Å, respectively, and the hydrogen bond distances between vanillin and amino acid residues GLN-265, ASP-187, LYS-181, ASN-154, TYR-156 were 3.0,3.5,3.0,3.1,4.1 Å, respectively, the hydrophobic interaction distances with the amino acid residues LYS-181 and ASN-183 are both 3.7 Å and the π-cation interaction distance between the charge centre of LYS-267 and the aromatic ring centre of OLR1 is 5.0 Å. The docking score of adenosylmethionine with Alas2 was -7.2 kcal/moL, and the binding distance was 5.0 Å, the hydrogen bond distances linked to the amino acid residues HIS-360, ASP-357, GLU-328, THR-580, ASN-197, LYS-391 of Alas2 were 2.8,3.0,3.5,2.9,3.0,2.8 Å, respectively, and the hydrogen bond distances linked to the amino acid residues HIS-360, ASP-357, GLU-328, THR-580, ASN-197, Lys-391 of Alas2 were 2.8,3.0,3.5,2.9,3.0, the hydrophobic interaction distance linked to the amino acid residue THR-580 is 3.7 Å, to the salt bridge of HIS-331 is 3.8 Å, and to HIS-285 is 3.5 Å. The docking score of beta-carotene with Il1b was-7.5 kcal/moL, which was mainly connected by hydrophobic interaction, and the hydrophobic interaction distance with the amino acid residue PHE-133 of IL1B was 3.6,3.5,3.7 Å, respectively, the hydrophobic interaction distance was 3.8 Å for the connection with LEU-80,3.5,3.7,3.8 Å for the connection with TYR-24, and 3.7 Å for the connection with LYS-74, respectively, the hydrophobic interaction distance is 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, which was mainly connected by hydrophobic interaction distance, and the hydrophobic interaction distance with amino acid residues PHE-130 was 3.7,4.0 Å, and the hydrophobic interaction distance with TYR-131 was 3.6 Å, respectively, the hydrophobic interaction distance is 4.0 Å with GLU-127,4.0 Å with LYS-126,3.8 Å with TRP-264, and 3.9 Å with π-cations in the aromatic ring centre of PHE-130.

Figure 6: Molecular docking. The blue diamond represents the drug component, the red circle represents the target gene, and the line represents the binding relationship. A for vanillin ethyl ketone and OLR1 docking, B for adenosylmethionine and Alas2 docking, C for Beta-carotene and IL1B docking, D for pterostilbene and CXCL3 docking.



3. Discussion

DKD is a multifactorial disease. In recent studies, mirnas and mrnas are closely related to the occurrence and development of DKD disease, which can be used as potential therapeutic targets for clinical application. Studies have found that has-miR-142-5p is highly associated with the severity of type 2 diabetes mellitus (T2DM) and may serve as a novel diagnostic biomarker for T2DM and its associated complications[6]. HSA-MIR-1225-3P and hsa-miR-513a-5p were lowly expressed in DKD and found to be significantly different from the expression of healthy people by high-throughput sequencing and were among the top 10 differential 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]. Has-mir-574-5p production is differential in human umbilical cord mesenchymal stem cell after advanced glycation end products intervention, and has-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.

Vanillin 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 vanillin on DKD[12]. Adenosylmethionine, 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 key receptor mediating oxidative low-density lipoprotein injury to the kidney and plays an important pro-injury role in DKD, promoting the occurrence and progression of DKD through inflammation, oxidative stress, podocyte injury, and fibrosis, and promoting the development and progression of DKD, by reducing the expression of OLR1 in kidney tissues, it can alleviate kidney 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, can promote the progression of renal fibrosis by interacting with its receptors to mediate the cascade amplification of inflammatory and fibrotic signals, which in turn promotes the progression of renal fibrosis, it provides a potential therapeutic target for the prevention and treatment of renal fibrosis and related kidney injury diseases[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 contribute to inflammation in macrophages, it eventually triggers 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-KB 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 clarifies the regulatory association between drugs, key genes, signaling pathways and DKD disease, and provides a theoretical basis for the development of DKD, therefore, the key targets and potential drugs for the treatment of DKD were screened: 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-κb, TGF-β, TNF and other signaling pathways are important pathways to mediate the occurrence and development of DKD; natural active substances such as vanillin, adenosylmethionine, beta-carotene, pterostilbene, etc. , can be used as potential therapeutic candidates 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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