Exploring the molecular mechanism of action of curcumin for the treatment of diabetic retinopathy, using network pharmacology, molecular docking, and molecular dynamics simulation

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Competing interests
The authors declare no conflicts of interest.

Acknowledgments
This work was supported by the Hubei Province Research Innovation Team Project (T2021022), and Scientific Research Projects of Hubei Health Commission (WJ2023M119).

Peer review information
Integrative Medicine Discovery thanks Yu-Feng Zhang and anonymous reviewers for their contribution to the peer review of this paper.

Abbreviations
DR, diabetic retinopathy; CUR, curcumin; VEGF, vascular endothelial growth factor; TCM, traditional Chinese medicine; TNF-α, tumor necrosis factor-alpha; MD, molecular dynamics; OMIM, Online Mendelian Inheritance in Man; CTD, Comparative Toxicogenomics Database; GEO, Gene Expression Omnibus; DAVID, Database for Annotation, Visualization and Integrated Discovery; PPI, protein-protein interaction; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; ALB, albumin; AGF, advanced glycation endproducts.

Abstract
Background: Based on network pharmacology and molecular docking, the present study investigated the mechanism of curcumin (CUR) in diabetic retinopathy treatment. Methods: Based on the DisGeNET, Swiss TargetPrediction, GeneCards, Online Mendelian Inheritance in Man, Gene Expression Omnibus, and Comparative Toxicogenomics Database, the intersection core targets of CUR and diabetic retinopathy were identified. The intersection target was imported into the STRING database to obtain the protein-protein interaction map. According to the Database for Annotation, Visualization and Integrated Discovery database, the intersected targets were enriched in Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes pathways. Then Cytoscape 3.9.1 is used to make the drug-target-disease-pathway network. The mechanism of CUR and diabetic retinopathy was further verified by molecular docking and molecular dynamics simulation. Results: There were 203 intersecting targets of CUR and diabetic retinopathy identified. 1320 GO entries were enriched for GO functions, which were primarily involved in the composition of cells such as identical protein binding, protein binding, enzyme binding, etc. It was found that 175 pathways were enriched using Kyoto Encyclopedia of Genes and Genomes pathway enrichment methods, which were mainly included in the lipid and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, pathways in cancer, etc. In the molecular docking analysis, CUR was found to have a good ability to bind to the core targets of albumin, IL-1B, and IL-6. The binding of albumin to CUR was further verified by molecular dynamics simulation. Conclusion: As a result of this study, CUR may exert a role in the treatment of diabetic retinopathy through multi-target and multi-pathway regulation, which indicates a possible direction of future research.

Keywords: curcumin; diabetic retinopathy; network pharmacology; molecular docking; molecular dynamics simulation

Citation

Executive editor: Xin-Yun Zhang.
Received: 02 January 2024; Accepted: 14 March 2024.
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**Introduction**

Diabetic retinopathy (DR) refers to a highly specific neurovascular complication caused by diabetes, and is currently the most common microvascular complication in diabetic patients worldwide, with a positive correlation between incidence and disease duration [1]. Studies have shown that 50% of patients who have had diabetes for more than seven years suffer from DR [2]. Chronic hyperglycemia and altered blood composition in diabetic patients disrupt the blood-retinal barrier, causing peripapillary cell necrosis and endothelial dysfunction in the retina, leading to leakage of intravascular fluid components into the retinal space. As a result, the retina undergoes a series of changes, including hemorrhage, edema, exudation, and ischemia [3]. The pathogenesis of DR is highly complex, and it is mainly believed to be caused by inflammation, oxidative stress, apoptosis, retinal vascular endothelial cells and neoangiogenesis [4]. It has become common practice in clinical to use laser therapy or intravitreal injections of vascular endothelial growth factor antibody. However, due to the high cost of treatment, many adverse reactions, and long treatment time, the application of this method is limited [5]. In addition to damage to vision, DR also causes an increased risk of systemic vascular complications, including kidney, heart, and nervous system.

Curcumin (CUR) is a low-toxicity, widely available and inexpensive yellow phenolic pigment derived from the rhizomes of turmeric, tulip and other ginger plants in the family *Curcuma longa*, which has numerous clinical applications and prospects [6]. A wide range of pharmacological properties have been attributed to CUR, including antioxidant, anti-inflammatory, antimutagenic, etc [7]. Researchers found that CUR had a beneficial effect on the expression of vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF-α), and pro-inflammatory cytokines in the retina of diabetic rats [8]. Diabetic macular edema can lead to visual impairment in DR [9]. In an investigation reported by Mazzolani et al., they found that curcumin-phospholipid lecithin formulation was able to improved visual acuity and retinal thickness in most patients with chronic diabetic macular edema [10]. In addition, CUR has also been demonstrated to have the capability of slowing down or even reversing the progression of certain fundus diseases [11], making it a new option for the treatment of retinal diseases.

Traditional Chinese medicine (TCM), as a non-invasive therapy, has gained attention for its unique advantages in the treatment of diabetic retinopathy, including TCM formulas, single drugs and monomers. Using the theory of systems biology, network pharmacology enables us to analyze potential mechanisms of drug treatment of disease from multiple perspectives by creating a “drug-target-disease-pathway” network. By simulating the interaction between drug and target proteins and predicting docking mode and binding affinity for drug ligands and protein receptors, molecular docking will provide a new approach to Chinese medicine. Molecular dynamics (MD) simulations were conducted in order to further verify the reliability of docking results using GROMACS software. It provides a research strategy for the exploration of multi-component and multi-target drug action mechanisms [12]. The potential therapeutic targets of CUR for the treatment of DR were investigated in the context of network pharmacology, molecular docking, and MD simulation. A flowchart of the specific process is shown in Figure 1.

**Materials and methods**

**Software and databases**


![Figure 1 A flowchart illustrating the overall design of this study.](https://www.tmrjournals.com/im)

PPI, protein-protein interaction; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.
Predicted targets of action associated with CUR and diabetic retinopathy

The chemical structure and molecular weight of CUR were obtained by searching “curcumin” in PubChem database [13]. CUR-related targets were predicted by CTD database and Swiss TargetPrediction database [14]. The input “diabetic retinopathy” was analyzed in DisGeNET database, GeneCards database and OMIM database, and set the filtering condition as “Homo Sapiens” to obtain the relevant targets [15]. The data from GSE221521 were downloaded and processed using the online analysis tool GEO2R in GEO database [16]. In order to obtain genes from the DR group, \( P < 0.05 \) and \( \log_{2}\text{FoldChange} \leq -1 \) were used as the criteria for gene screening [17]. Then de-duplicated all the obtained target informations and organized the collection.

Core targets for screening CUR and diabetic retinopathy

Through InteractVenn, CUR and DR targets were intersected, those targets were the core targets of CUR in the treatment of DR [18].

Functional classification of potential core CUR targets for diabetic retinopathy treatment

Based on the Panther classification system, functional annotations and classifications were conducted on the intersecting core targets that were screened, and the screening condition was “Homo Sapiens” for protein classification [19].

Constructing a protein–protein interaction (PPI) network of core targets for CUR treatment of diabetic retinopathy

The core targets were inputted into STRING data analysis platform to construct a protein interactions model, and the species was set as “Homo Sapiens” with the interaction scores \( > 0.7 \), the independent nodes in the network were hidden, and the rest of the nodes were set to the default values to obtain the interactions among the targets [20]. Cytoscape 3.9.1 was used to visualize the target interactions, and the topological parameters of the nodes in the network were analyzed by setting degree, betweenness, and closeness greater than their respective thresholds in the plug-incentiscape 2.2 to create a network diagram of PPI protein interactions [21].

Gene Ontology (GO) functional enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis of core targets for CUR treatment of diabetic retinopathy

The core targets were inputted into DAVID database, set as “Official Gene Symbol, Homo Sapiens”, and select biological process, cell component, molecular function terms in GO and KEGG enrichment analysis, set significance \( P < 0.05 \) [22]. The results were imported into the Weishengxin platform to display bubbles and bar charts [23].

“Drug-target-disease-pathway” network

Using the screened intersecting core targets, we created drug-target-disease network files, node attribute files and KEGG pathway-related files, and imported them into Cytoscape 3.9.1 software to construct the “drug-target-disease-pathway” network of CUR and DR [24].

Molecular docking

The top 5 proteins with the highest degree were selected for molecular docking. The 3D structures of compounds and proteins were obtained from PubChem and PDB databases respectively [25]. Using the protein visualization software PyMOL, the receptor proteins are separated from ligands and water and the interconnection process is undertaken by AutoDock [26]. The conformation with the highest score was selected from the docking results for further mapping analysis.

MD simulation

MD simulations of the protein-ligand complex were performed to explore the interaction between the receptors and ligands by using GROMACS 2019.6 [27]. Albumin (ALB) and CUR were selected for MD simulation. For the generation of the parameters and topology of proteins and ligands, we utilized the amber99sb-ildn force field as well as the general Amber force field. Setting the size of the simulation box so that the distance between each atom of the protein and the box was greater than 1 nm. Filling the box with an explicit solvent-simple point charge model (SPC216 water molecules) and replacing the water molecules with Na\(^+\) and Cl\(^-\) counterions to make the simulation system electrically neutral. Through the steepest descent method, the entire system has been optimized in order to reduce unreasonable contact or atom overlaps. To achieve sufficient pre-equilibration of the simulation system, the canonical ensemble and the constant-temperature ensemble were performed for 100 ps at 300 K and 1 bar, respectively. Subsequently, the MD simulation of 50 ns was performed with periodic boundary conditions, and the V-rescale method and the Parrinello-Rahman method were used for regulating the temperature (300 K) and pressure (1 bar), respectively [28]. The Newton equation of motion was calculated using the leapfrog integration with the time step of 2 fs. The long-range electrostatic interaction was calculated by the particle mesh Ewald method using Fourier spacing of 0.16 nm, and the linear constraint solver method was used to constrain all bond lengths. The visual molecular dynamics 1.9.3 and PyMOL 2.5 were used to display, analyze, and animate trajectories visually [29]. In order to determine the binding free energy of the compound, gmx MMPBSA was used [30].

Statistical analysis

In GEO database, GEO2R analysis tool uses the Wald test for comparing 2 groups of samples, set \( P < 0.05 \) [31]. In DAVID database, KEGG pathway and GO enrichment analysis were obtained by functional annotation chart tool. This tool provides enrichment analysis using a modified Fisher Exact Test to identify the most overrepresented annotation terms associated with a gene list, set \( P < 0.05 \) [32]. In STRING database, the score is computed by combining the probabilities from the different evidence channels and corrected for the probability of randomly observing an interaction [33].

Results

Potential core targets of CUR for diabetic retinopathy treatment

The chemical structure of CUR was retrieved from PubChem with a molecular weight of 368.3799 (Figure 2A). The Swiss TargetPrediction database and CTD database were searched for CUR targets, and the total number of targets was determined to be 1031 after the elimination of duplicates. Following the deletion of duplicates in GeneCards, OMIM, DisGeNET, and GEO database, 816 action targets for diabetic retinopathy were identified. From the intersection of CUR and DR targets of action, 203 core targets of CUR for diabetic retinopathy were obtained (Figure 2B).

Panther functional classification

As a result, the Panther classification system was applied to 203 intersecting targets, which were grouped into seven categories for classification according to the function of their proteins: protein modifying enzymes, gene-specific transcriptional regulator, metabolite interconversion enzyme, intercellular signal molecule, transmembrane signal receptor, protein-binding activity modulator and other in Figure 2C.

PPI network construction and screening key targets

The STRING database was used to establish a PPI network graph for diabetic retinopathy treatment based on 203 intersecting targets, and the PPI network graph was obtained by adjusting the interaction score between the two points to \( > 0.7 \) and hiding the free targets (Figure 3). The graph contained a total of 198 interconnected nodes with 6382 connecting lines, and the node average degree value was 64.5. Using the plugin centiscape 2.2 in Cytoscape 3.9.1 software to set degree-betweenness centrality and closeness centrality greater than their respective thresholds. Based on the topological parameters of the network nodes, 47 nodes with node degree values greater than the
average degree (64.5) were screened out as core targets. In terms of the degree of significance, AKT1, IL-6, and TNF have the highest degrees (Figure 4). The results of the top 10 core targets and the network node characteristic parameters are shown in Table 1. As a result of the interactions among these core targets, CUR action in DR is likely to be driven by the interaction between these targets.

Figure 2 Network pharmacology of DR-related targets treated with CUR. (A) CUR basic chemical structure infographic. (B) Venn diagram of the core target at the intersection of CUR and DR. (C) Functional classification map of the intersection target of CUR and DR by Panther. DR, diabetic retinopathy; CUR, curcumin.

Figure 3 PPI plot of key targets of CUR for DR. PPI, protein-protein interaction; CUR, curcumin; DR, diabetic retinopathy.

Figure 4 Bar chart of targets with the top 10 degrees. ALB, albumin.
Table 1 CUR acts on the node characteristic parameters of the core targets network of diabetic retinopathy

<table>
<thead>
<tr>
<th>Target</th>
<th>Degree</th>
<th>Betweenness centrality</th>
<th>Closeness centrality</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKT1</td>
<td>171</td>
<td>0.035070450</td>
<td>0.883408072</td>
</tr>
<tr>
<td>IL-6</td>
<td>168</td>
<td>0.027783758</td>
<td>0.871681416</td>
</tr>
<tr>
<td>TNF</td>
<td>166</td>
<td>0.025281437</td>
<td>0.864035088</td>
</tr>
<tr>
<td>IL-1B</td>
<td>158</td>
<td>0.021887891</td>
<td>0.834745763</td>
</tr>
<tr>
<td>ALB</td>
<td>154</td>
<td>0.038433467</td>
<td>0.820833333</td>
</tr>
<tr>
<td>INS</td>
<td>153</td>
<td>0.019693076</td>
<td>0.817427386</td>
</tr>
<tr>
<td>STAT3</td>
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<td>0.80737049</td>
</tr>
<tr>
<td>HIF1A</td>
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<td>0.017613706</td>
<td>0.800813008</td>
</tr>
<tr>
<td>EGFR</td>
<td>145</td>
<td>0.023339973</td>
<td>0.791164659</td>
</tr>
<tr>
<td>CASP3</td>
<td>144</td>
<td>0.012874166</td>
<td>0.780000000</td>
</tr>
</tbody>
</table>

CUR, curcumin; ALB, albumin; INS, insulin.

Enrichment analysis of GO and KEGG in intersection targets of CUR and diabetic retinopathy

After 203 intersecting targets were imported into DAVID database, the enrichment analysis of GO functions led to 1320 entries, of which 1042 were biological process entries, 110 were cellular component entries, and 168 were molecular function entries. As shown in Figure 5A–5C, the top 10 entries based on *P* < 0.05 were selected for GO function enrichment analysis on the Weishengxin online mapping platform. In these bubble maps different color levels represent the size of *P* value and the circle size represents the number of genes that have been enriched. Based on the results, it appeared that these targets are mainly involved in the positive regulation of gene expression, inflammatory response and other biological processes. These targets are mainly enriched in the extracellular space, extracellular region, and cell surface are involved in identical protein binding, protein binding, enzyme binding and other molecular functions. The KEGG enrichment analysis identified 175 pathways that may be related to CUR in diabetic retinopathy treatment. Among the top 10 entries mapped on the Weishengxin online mapping platform (Figure 5D), two pathways related to inflammation were identified: the AGE-RAGE signaling pathway in diabetic complications and the PI3K-Akt signaling pathway. Additionally, there are pathways involved in cancer, lipids and atherosclerosis, and TNF signaling.

“Drug-target-disease-pathway” network analysis

To demonstrate a clearer and more intuitive connection between the main KEGG pathways and the intersection targets. Data was organized and visualized by Cytoscape 3.9.1 to obtain the “drug-target-disease-pathway” network diagram (Figure 6). Further visualization analysis yielded 134 nodes and 390 edges, and the connecting lines indicated the interactions between the core targets and KEGG pathways, and the greater the value, the darker the node corresponding to the target.

Molecular docking

Combined with PPI network and Cytoscape 3.9.1 visualization analysis, core targets AKT1, IL-1B, IL-6, ALB, and TNF-α (note: TNF-α was selected for TNF target) were screened to bind to CUR, respectively, and molecular docking and visualization were performed using Autodock and PyMOL to validate the network pharmacology by virtual evaluation of the predicted results (Figure 7). Previous studies have shown that if the ligand-receptor binding energy ≤ −5 kcal/mol, the ligand-receptor can bind, and if the binding energy ≤ −7 kcal/mol good affinity activity is indicated [34]. Table 2 shows the binding energy values and molecular docking shows that ALB, IL-1B, IL-6, TNF-α, and AKT1 binding energies are −7.8, −6.5, −6.1, and −5.8 kcal/mol, respectively.

MD simulation

The root-mean-square deviation is applied to measure protein stability. When the root-mean-square deviation value of a system is smaller, it generally indicates that it is more stable [35]. During the dynamic simulation, ALB-CUR fluctuated slightly after 25 ns, but remained stable at 0.3–0.4 nm (Figure 8A). The root-mean-square function curve represents the fluctuations in the amino acid residues of the protein [36]. As can be seen from Figure 8B, there is a greater degree of flexibility in the middle region of this protein as compared to other regions. In addition, radius of gyration and solvent accessible surface area were used to evaluate the tightness of the protein structure. During the MD simulation, the radius of gyration and solvent accessible surface area of the ALB-CUR complex decreased, indicating an increase in density and stability (Figure 8C, 8D). It can be seen from Figure 8E that ARG117, PRO118, ARG186, LYS137, and LEU115 are the main five amino acids that protein interacts with small molecules. Hydrogen bonding is a major interaction in complex formation and stability, which can verify the mechanism and determine the stability of protein-ligand binding. Figure 8F shows the hydrogen bond interaction in ALB-CUR complex. These results suggest that CUR can stably bind ALB, which may be a potential mechanism for the pharmacological effects of CUR.

**Discussion**

The mechanism of diabetic retinopathy is very complex, mainly characterized by ocular microangiopathy, and the abnormalities of retinal vascular endothelial cells accompany the whole process of diabetic retinopathy, CUR may be a potential therapeutic drug for diabetic retinopathy. Multitarget research for diabetic retinopathy is of great importance since it explains the occurrence and progression of diabetic retinopathy, which is the result of interactions between multiple targets. The target of diabetic retinopathy and CUR were retrieved and analyzed in multiple databases using network pharmacology in this study, to further clarify the key aspects and characteristic targets of CUR’s therapeutic effects on diabetic retinopathy. This study utilized the techniques and concepts of network pharmacology to predict the mechanism of CUR in diabetic retinopathy. In the interaction network analysis of CUR therapeutic diabetic retinopathy targets constructed based on the STRING database, it was found that the top 5 targets with degree values were AKT1, IL-1B, IL-6, ALB, and TNF-α, hypothesizing that these targets may play a vital role in CUR therapeutics for diabetic retinopathy. We molecularly docked ALB, IL-1B, IL-6, TNF-α and AKTI with the structure of CUR, respectively, in which the data showed better docking results for ALB, IL-1B and IL-6, further suggesting the possible important role of CUR with this three targets. The binding stability of ALB and CUR was further found by MD simulation.
Figure 5 Core targets of GO and KEGG enrichment analysis. (A) Top 10 terms of BP in GO enrichment analysis of key targets of CUR for DR. (B) Top 10 terms of CC in GO enrichment analysis of key targets of CUR for DR. (C) Top 10 terms of MF in GO enrichment analysis of key targets of CUR for DR. (D) Top 10 KEGG pathway enrichment bar graph of key targets of CUR for DR. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; DR, diabetic retinopathy; BP, biological process; CC, cellular component; MF, molecular function.

Figure 6 CUR-target-DR-pathway diagram. CUR, curcumin; DR, diabetic retinopathy.
Figure 7 Molecular docking diagram of CUR-AKT1, CUR-IL-1B, CUR-IL-6, CUR-ALB and CUR-TNF-α. (A) CUR-AKT1; (B) CUR-IL-1B; (C) CUR-IL-6; (D) CUR-ALB; (E) CUR-TNF-α. CUR, curcumin; ALB, albumin.

<table>
<thead>
<tr>
<th>Target</th>
<th>PDB ID</th>
<th>Binding energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALB</td>
<td>1AO6</td>
<td>-7.8 kcal/mol</td>
</tr>
<tr>
<td>IL-1B</td>
<td>1HIB</td>
<td>-6.5 kcal/mol</td>
</tr>
<tr>
<td>IL-6</td>
<td>1ALU</td>
<td>-6.1 kcal/mol</td>
</tr>
<tr>
<td>TNF-α</td>
<td>1A8M</td>
<td>-6.0 kcal/mol</td>
</tr>
<tr>
<td>AKT1</td>
<td>1UNP</td>
<td>-5.8 kcal/mol</td>
</tr>
</tbody>
</table>

CUR, curcumin; ALB, albumin; PDB, Protein Data Bank.
Figure 8 MD simulation analysis of CUR-ALB. (A) The RMSD of CUR-ALB. (B) The RMSF of CUR-ALB. (C) The Rg of CUR-ALB. (D) The SASA of CUR-ALB. (E) The contribution energy of CUR-ALB. (F) The number of hydrogen bonds of CUR-ALB. MD, molecular dynamics; CUR, curcumin; ALB, albumin; RMSD, root-mean-square deviation; RMSF, root-mean-square function; Rg, radius of gyration; SASA, solvent accessible surface area; H-bond, hydrogen bond.

Several factors contribute to the pathogenesis of diabetic retinopathy, including oxidative stress, hypoxia, and inflammation [37]. Moore et al. found that treatment of retinal microvascular endothelial cells with advanced glycation endproducts (AGE)-ALB led to an increase in the regulation of the NF-κB signaling pathway and leukocyte adherence with blood-retinal barrier dysfunction [38], and Treins et al. demonstrated that AGE-ALB stimulated VEGF expression through an ERK-dependent pathway and played an essential role in the development of actinic DR [39]. Activation of AKT1 increases microvascular permeability, which is closely associated with diabetic retinopathy pathogenesis, and decreases nitric oxide synthase phosphorylation in the vascular endothelial cells [40]. There are several proteins encoded by these genes that are involved in the regulation of glucose inflammatory pathways (IL-1B, IL-6, TNF), angiogenesis (IL-1B, IL-6, TNF, EGFR), and several other processes as well [41]. Diabetes-induced complications in mice increase several inflammatory mediators such as IL-6, TNF-α, and IL-1B, they also play a role in activating chemo-kinase production, infiltrating inflammatory cells into the retina, and damaging tissues [42]. Pro-inflammatory cytokines chemotaxis inflammatory cells to adhere to retinal capillaries. By releasing free radicals and proinflammatory cytokines, the blood-retinal barrier is disrupted and vascular permeability increases [43]. Diabetes-related retinopathy is associated with IL-6, which is an important part of the inflammatory process, inducing increased capillary permeability and exacerbating vascular pathology.

Some studies have found that IL-6 can interact with insulin and participate in insulin resistance thus affecting the development of type 2 diabetes [44], as well as IL-6 may be involved in diabetic microangiopathy and found that the level of IL-6 in diabetic retinopathy vitreous was elevated, suggesting that IL-6 is involved in the onset and progression of diabetic retinopathy [45]. TNF-α, a target protein of TNF, is widely expressed in retinal pigment epithelial cells in humans, choroidal vascular endothelial cells, and other ocular retinal basement membranes, TNF-α plays a crucial role in diabetic retinopathy pathogenesis. In conditions of high glucose, TNF-α is released via Miller cells, activating the EGFR/p38/NF-κB/p62 pathway, increasing mitosis and apoptosis of retinal pigment epithelial cells, and accelerating the pathogenesis of diabetic retinopathy [46]. In addition, TNF-α enhances the synthesis of reactive oxygen species as well as the expression of IL-6, adhesion molecules in vascular endothelial cells, which promotes the infiltration of leukocytes from the bloodstream into the retina, aggravates the inflammatory response within the retina, and induces endothelial cell damage [47].

Core targets of CUR for diabetic retinopathy were mainly located in the extracellular space, cytoplasm, extracellular region, and other regions, as determined by GO function enrichment analysis, also involving the cellular response to the drug, the positive regulation of cell proliferation and other biological processes, which mainly regulate such as protein binding, enzyme binding, etc. The KEGG...
enrichment analysis revealed that the AGE-RAGE signaling pathway and PI3K/Akt signaling pathway in diabetic complications are closely related to CUR treatment of diabetic retinopathy. There is a strong correlation between late glycosylation end products and diabetic complications in the pathophysiology of diabetes. The persistent hyperglycemic state of diabetes leads to a series of non-enzymatic glycosylation reactions of proteins, lipids, and nucleic acids, which results in the production of advanced glycosylation end products [48]. The PI3K/Akt signaling pathway is the classical pathway regulating insulin transduction signals, and a variety of its downstream target proteins are involved in the regulation of apoptosis of peripheral cells of the retina, and the regulation of expression of target genes of the pathway has been shown to prevent DR progression to a certain extent prevent the progression of DR to a certain extent [49]. The PI3K/Akt signaling pathway is activated in retinal microvascular pericytes to drive cytokine signaling of VEGF, which mediates the process of endothelial cell proliferation, migration, and neoangiogenesis, leading to the progression of DR [50]. There is some evidence that CUR may play a role in treating diabetic retinopathy by modulating the AGE-RAGE and the PI3K/Akt signaling pathway to regulate the corresponding target proteins.

Conclusion

In summary, through network pharmacology, molecular docking, and MD simulations, the present study investigated the potential mechanisms of CUR in the treatment of DR. Following its introduction into the body, CUR has multiple targets and pathways for treating DR. Several targets were shown to be used by CUR to exert anti-DR effects, including AKT1, IL-1β, IL-6, ALB, and TNF-α, and regulating several signaling pathways such as PI3K-Akt signaling pathway, lipid and atherosclerosis signaling pathway, and AGE-RAGE signaling pathway in diabetic complications. Biological experiments and extensive medical validation are required at a later stage to ensure the validity of the findings due to the poor accuracy and completeness of the database during the network pharmacology study.

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