Integrated data mining and network pharmacology to discover a novel traditional Chinese medicine prescription against diabetic retinopathy and reveal its mechanism

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Author contributions

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
DR, Diabetic retinopathy; TCM, traditional Chinese medicine; MD, molecular dynamics; PPI, Protein-protein interaction; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; RMSD, root mean square deviation; Rg, radius of gyration; RMSF, root mean square fluctuation; RPE, retinal pigment epithelium.

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Abstract
Background: Diabetic retinopathy (DR) is currently the leading cause of blindness in elderly individuals with diabetes. Traditional Chinese medicine (TCM) prescriptions have shown remarkable effectiveness for treating DR. This study aimed to screen a novel TCM prescription against DR from patents and elucidate its mechanism using data mining, network pharmacology, molecular docking, and molecular dynamics (MD) simulation. Method: TCM prescriptions for treating DR were collected from patents and a novel TCM prescription was identified using data mining. Subsequently, the mechanism of the novel TCM prescription against DR was explored by constructing a network of core TCMs-core active ingredients-targets-core pathways. Finally, molecular docking and MD simulation were employed to validate the findings from network pharmacology. Result: The TCMs of the collected prescriptions primarily possessed bitter and cold properties with heat-clearing and supplementing effects. Twenty core active ingredients and ten core targets of the novel TCM prescription for treating DR were screened. Moreover, the novel TCM prescription played a crucial role in treating DR by inhibiting inflammatory response, oxidative stress, and retinal pigment epithelium apoptosis. Conclusions: This study identified a novel TCM prescription and unveiled its multi-component, multi-target and multi-pathway characteristics for treating DR. These findings provide a scientific basis and novel insights into the development of drugs for DR prevention and treatment.

Keywords: TCM prescriptions; diabetic retinopathy; medication rule; molecular mechanism; data mining; network pharmacology; molecular docking
**Introduction**

Diabetic retinopathy (DR) is not only a severe microvascular complication of diabetes but also one of the leading primary causes of blindness and visual impairment [1]. Globally, the prevalence of DR is projected to increase from 103 million individuals in 2020 to 161 million by 2045 [2]. Despite the growing body of research dedicated to the treatment of DR, effective management of this disease remains challenging in clinical practice. Currently, the primary treatment modalities for DR include drugs and surgical interventions. Clinical drugs for treating DR mainly include hypoglycemic agents and anti-vascular endothelial growth factor agents such as metformin and aflibercept [3, 4]. Patients with advanced DR are treated with surgical therapy including intravitreal injections of corticosteroids, pan-retinal laser photocoagulation and micro-vitreoretinal surgery [5, 6]. However, these therapies may lead to undesirable side effects such as hypoglycemia, gastrointestinal discomfort, reduced renal function and peripheral visual field loss [7, 8]. Therefore, there is a pressing need for the development of effective therapeutic strategies with multi-targets, multi-pathways and fewer side effects for the treatment of DR.

Traditional Chinese medicine (TCM), steeped in a history spanning thousands of years and underpinned by its unique philosophical framework, has been the main approach to disease prevention and treatment in China and certain other countries. TCM is recognized for its ability to enhance the internal environment of the body, causing minimal toxic side effects while exerting multi-component, multi-target therapeutic effects in various diseases [9]. In recent years, several TCM prescriptions, such as Danhong Huayu oral liquid, Tangning Tongluo prescription and Bushen Huoxue prescription, have demonstrated remarkable clinical efficacy in delaying the progression of DR, reducing the incidence of blindness and improving the quality of life of patients with DR [10–13]. Consequently, TCM prescriptions hold promising prospects and potential for development in the treatment of DR.

TCM patents represent the latest advancements and technological achievements in the field of TCM, often harboring valuable prescription rules applicable in clinical practice. Data mining, a widely used information processing technology, enables researchers to extract novel insights and gain unprecedented cognition from medical datasets [14]. In data mining, modern computer technology facilitates the analysis of pertinent information and medication rule within TCM patents, offering valuable data for the development of new drugs. Network pharmacology, a pioneering technique, investigates the mechanism of drug action in the context of intricate biological networks, shifting from the conventional research paradigm of “one target, one drug” to the “network target, multi-ingredients” model [15, 16]. Molecular docking, a theoretical simulation method, is used to predict binding interactions between proteins and molecular ligands and is extensively employed to validate results derived from network pharmacology. Molecular dynamics (MD) simulation is a technology of simulating the movement of small molecules in the body environment by computer. In recent years, the fusion of network pharmacology with molecular docking and MD simulation technology has been employed to investigate the underlying mechanism of TCM [17, 18]. For instance, Zhang et al. explored the potential mechanism of *Sauarea involucrata* against COVID-19 through network pharmacology, molecular docking and MD simulation [17]. Shi’s term elucidated the mechanism of bufalin in treating lung adenocarcinoma using network pharmacology, molecular docking and MD simulation methods [18]. However, to the best of our knowledge, no study has used data mining approach to screen patents and identify a TCM prescription for treating DR as well as the medication rule and molecular mechanism of the TCM prescription for the treatment of DR by applying the application of network pharmacology, molecular docking and MD simulation techniques.

In light of the above, an integrated strategy of data mining, network pharmacology, molecular docking and MD simulation was developed to screen patent databases to identify a novel TCM prescription for treating DR and elucidate its medication rule and molecular mechanism. First, comprehensive information on TCM prescriptions for treating DR was collected from patents, and the overall patent landscape was revealed through statistical analysis. Subsequently, a novel TCM prescription for treating DR was identified using data mining. Next, a network of core TCMs-core active ingredients-core targets-core pathways was constructed to elucidate molecular mechanism of the novel TCM prescription for treating DR through network pharmacology. Finally, molecular docking and MD simulation were employed to validate the findings from network pharmacology. In summary, this study provides a reliable reference and valuable insights for future pharmacological research on TCM for treating DR and guides the development of new drugs for DR. A flowchart of the analytical approaches used in this study is presented in Figure 1.

**Materials and methods**

**Data sources**

The National Intellectual Property Administration of the People’s Republic of China (https://psa-system.cponline.cnipa.gov.cn/), the Patents Global Patent Database (https://www.patsnap.com/) and the Qizhidao Global Patent Database (https://patents.qizhidao.com/) served as the primary data sources. A comprehensive searching of global patents was performed for the period January 1, 1985, to July 20, 2023. The search included both computer-based retrieval and manual reading checks, employing the following search criteria for patent titles, abstracts and claims: “diabetes,” “diabetes mellitus,” “retina,” “diabetes retina,” “diabetic retinopathy” and “Chinese Materia medica,” “Chinese medicine,” “Chinese patent medicine” and “prescription.” The retrieved results were checked thoroughly and manually screened to identify all relevant patents in the database. Subsequently, the prescriptions in the patents were analyzed based on specific inclusion and exclusion criteria.

**Inclusion and exclusion criteria**

The inclusion criteria were TCM prescriptions specifically used for treating DR with clearly stated provenance, composition and dosage. Patents were excluded if they fell under the following categories: (1) prescriptions for DR comprising only a single TCM; (2) prescriptions for DR involving Western medicine; (3) patents on food, beverage and health care products related to DR; (4) patents related to testing equipment, devices and instruments; (5) patent of biological agents.

**Prescription input and TCM name specification**

Office Excel 2019 was used to input data extracted from patents and establish the patent database. This study primarily referenced the People’s Republic of China Pharmacopoeia and the 10th edition of Chinese Materia Medica, supplemented by the Encyclopedia of Traditional Chinese Medicinal Substances. The names of TCMs described in the patents were uniformly modified into standardized names. For instance, unifying “Qízi” and “Gōngjú” as “*Lycii Fructus*” and “*Chrysanthemi Flos*,” respectively. Additionally, the same TCMs whose medicinal properties significantly alter owing to diverse processing methods were treated as distinct entities. For instance, “*Rehmannia Radix*” and “*Rehmanniae Radix Parasperana*” To ensure the accuracy of the data mining process, the patent data were inputted by two researchers and reviewed twice.

**Data analysis**

**Analysis of the overall landscape of TCM prescription patents against DR.** The original data extracted from patent databases included temporal and spatial distribution, types of applicants and distribution of dosage forms for TCM prescription patents, and the overall landscape of patent was unveiled by statistical analysis.

**Analysis of the medication rule of TCM prescriptions against DR by data mining approach.** Statistical analysis, conducted using Microsoft Office Excel 2019, focused on the frequency, classification
of TCM efficacy, four natures, five flavors and meridian tropisms of the TCMs used for treating DR. The apriori algorithm in IBM SPSS Modeler 18.0 software was applied to identify association rule for high-frequency TCMs. The parameters were set as follows: minimum support ≥ 10%, minimum confidence ≥ 60%, and the maximum preceding item set to two. Additionally, IBM SPSS Modeler was used for modeling analysis of all TCMs, with strong links set to twenty, moderate links set to ten, and others as weak links. Topological analysis was performed on all TCMs with strong links and moderate links, and Cytoscape 3.7.1 software was utilized to construct the complex network of TCMs. Network topological parameters of TCMs were analyzed to screen four core TCMs with a higher degree as a novel TCM prescription for the treatment of DR.

![Figure 1 Schematic diagram of the analytical process followed in this study](image-url)
Analysis of the molecular mechanism of the novel TCM prescription against DR based on network pharmacology. The potential active ingredients of the novel TCM prescription were obtained from the TCMSp database (https://tcmsp-e.com/tcmsp.php). The parameters for retrieving pharmacokinetic data were set as follows: oral bioavailability ≥ 30% and drug-likeness ≥ 0.18. Concurrently, relevant potential active ingredients documented in the literature were consulted and collected to preliminarily establish a database for the potential active ingredients in the novel TCM prescription. Subsequently, based on the potential active ingredients of the novel TCM prescription, we predicted the corresponding targets using the SwissTargetPrediction database (http://www.swistargetprediction.ch/), SEA database (https://sea.bkslab.org/) and PharmMapper database (http://www.lilab-ecust.cn/pharmmapper/). “Homo sapiens” was selected as the target organism and excluded duplicate targets.

Data on the DR-associated protein targets were obtained from the TTD database (http://db.idrblab.net/tdt), DrugBank database (https://go.drugbank.com/), OMIM database (http://omim.org/) and DisGeNet database (http://www.disgenet.org/) by searching for the keyword “diabetic retinopathy.” We also used UniProt database (https://www.uniprot.org/) to standardize the target names, limiting the species to “Homo sapiens.” Targets of potential active ingredients and DR-related targets were verified through Uniprot database, and the target names were normalized using UniProtKB IDs. The overlapping targets between active ingredients and DR-associated targets were considered potential targets for treating DR. Venn diagrams for potential targets and their distribution in the novel TCM prescription were created using the Bioinformatics platform (http://www.bioinformatics.com.cn/).

Next, a protein-protein interaction (PPI) network of potential targets was constructed using the STRING database (https://string-db.org/) with a confidence score greater than 0.9 and species limited to “Homo sapiens” as the species. Subsequently, PPI data were imported into Cytoscape (version 3.7.1) for visualization and topological analysis. To analyze the target interactions, the network parameters of PPI were calculated using NetworkAnalyzer. Targets with degree values greater than twice the median were selected as key targets for treating DR. The DAVID database (https://david.abcc.ncifcrf.gov/) was used to analyze the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of key targets for treating DR. Gene symbols of key targets were uploaded into the DAVID database, with “Homo sapiens” as the organism and “OFFICIAL_GENE_SYMBOL” as the identifier, and an adjusted P-value of 0.05. Subsequently, the top twenty GO and KEGG terms were uploaded to Bioinformatics platform to create a bubble diagram. The top twenty pathways with the highest P-values were selected as key pathways against DR. Furthermore, the top ten pathways with the highest P-values were considered core pathways of the novel TCM prescription for treating DR. Based on the above analysis, a network of potential active ingredients-key targets was constructed by Cytoscape, and topological analysis was further performed. Potential active ingredients with degree values greater than the median were considered key active ingredients of the novel TCM prescription for treating DR.

The TCMSs of the novel TCM prescription, key active ingredients, key targets and key pathways were inputted into Cytoscape to establish a network of TCMSs-active ingredients-key targets-key pathways, elucidating the potential interactions between disease target genes and the active ingredients of the novel TCM prescription. Next, a network topological analysis was performed using NetworkAnalyzer to further identify core active ingredients and core targets. The top twenty key active ingredients with the highest degree were further considered core active ingredients. Similarly, the top ten key targets with the highest degree were selected as core targets. Finally, to elucidate the molecular mechanism of the novel TCM prescription for treating DR and extract biologically valuable information, a network of core TCMSs-active ingredients-core targets-core pathways was constructed using Cytoscape.

Molecular docking of core targets and core active ingredients of the novel TCM prescription against DR. To validate the findings of network pharmacology, the binding affinity and binding sites between core active ingredients and core targets were analyzed using molecular docking technology. First, the PDB files of the core targets were obtained from the PDB database (https://www.rcsb.org/). Then, we obtained the SDF files of the core active ingredients from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and converted them to PDB format using Open Babel (version 3.1.1). Next, AutoDock MGL Tools (version 1.5.7) was used to preprocess the core targets and core active ingredients to confirm the active sites, and the output was saved as PDBQT files. Finally, molecular docking was performed using AutoDock Vina to determine their free binding energies, and the results with superior scores and stable conformations were analyzed and visualized using PyMol (version 2.5.4) software.

Molecular dynamics simulation. The core active ingredients-core targets complexes with the lowest binding energy in molecular docking were selected for MD simulation using the AMBER18 software. The Amber99sb-ldn force field and the general Amber force field were used to analyze proteins and active ingredients, respectively. The TIP3P water model was employed to simulate the human environment and the periodic boundary conditions were set. Then, a water box was established, followed by adding Na+ and Cl− to balance the system. A 50000-step steepest descent method was further adopted to get the minimization of energy in complex system. Next, the system was slowly heated from 0 K to 300 K at a fixed volume and a constant heating rate. Subsequently, a 100 ps NVT (isothermal and isovolume) simulation was employed to equilibrate the system at a maintenance temperature of 300 K. Finally, a 100 ns NPT (isothermal and isobaric) simulation was performed on the complex system, with the temperature, pressure and time step controlled at 300K, 1 bar and 2 fs, respectively. AMBER18 and Origin 2022 software were adopted to analyze and visualize the MD simulation results, such as root mean square deviation (RMSD), radius of gyration (Rg) and root mean square fluctuation (RMSF). The above evaluation indicators of MD simulation lay the foundation for evaluating the stability of complex systems of ingredients and proteins.

Results

Patient analysis

Temporal and spatial distribution of TCM prescription patents against DR. As of July 2023, a total of 138 TCM prescription patents for treating DR were retrieved. When analyzing the statistics of the number of patents related to the treatment of DR based on the application and publication time (Supplementary Figure S1), the absence of related patents indicated the lack of advances in innovative research and development of TCM prescriptions for the treatment of DR globally before 2002. From 2002 to 2009, a gradual increase in the number of applications for TCM was observed, with the number of applications fluctuating to approximately ten each year. Only in 2008 did the number of patents disclosed exceed ten. Since 2010, a gradual increase in patent applications for TCM was observed, with the number surpassing twenty in 2016, reaching its peak. However, from 2017 to 2023, the number of applications entered a recession period. Overall, the number of applications and publications of TCM prescriptions patents for treating DR has remained relatively low, showing fluctuation without a clear growth or decline trend.

The geographical distribution of TCM prescription patents for DR (Supplementary Figure S2) exhibits significant divergence. While, the number of patent applications in various regions of the country displays an imbalanced trend, but the regions with the highest number of applications are predominantly located in coastal areas. Beijing held the highest number of patents, followed by Shandong province, with Guangdong province ranking third, followed by Sichuan province and Hebei province. Additionally, one patent each in the United States, Japan and South Korea was observed.

Types of applicants for TCM prescription patents against DR. To gain insights into the leading patent applicants for treating DR and
their competitive status, a statistical analysis of the types of applicants for TCM prescription patents related to DR was conducted (Supplementary Figure S3). Enterprises constituted the majority of applicants for TCM prescriptions for the treatment of DR, accounting for 53%, followed by individual applicants (24%). The number of applications of patents filed by hospitals, research institutes and universities in this field was relatively small, accounting for 9%, 8% and 6% respectively.

Distribution of dosage forms for TCM prescription patents against DR. When examining the dosage forms of the 138 TCM prescription patents for treating DR (Supplementary Figure S4), capsules, tablets, granules and pills were the most commonly utilized forms, constituting for 67.34% of the total prescription forms. Among these, capsules were the preferred choice because of their easy carrying, high bioavailability and favorable stability. Capsules also help mask the unpleasant odor of raw TCM extracts, making them more palatable to patients. Additionally, tablets, granules and pills offer various advantages, making them extensively adopted in TCM prescriptions for treating DR.

Analysis of the medication rule of TCM prescriptions collected from patent databases
Analysis of frequency and efficacy categories of TCMs in 138 TCM prescriptions collected from patent databases. Following data collection and processing, a total of 274 TCMs were identified from the 138 patents. These 274 TCMs were used a total of 1321 times, with 23 of them being used more than 15 times each. Notably, the top 23 high-frequency TCMs included Astragali Radix (62 times), Notoginseng Radix et Rhizoma (48 times), Rehmanniae Radix (44 times), Lycii Fructus (41 times), Salviae Miltorrhizae Radix et Rhizoma (40 times), Angelicae Sinensis Radix (38 times) and Chrysanthemii Flos (32 times), indicating the significant roles of these TCMs for treating DR (Supplementary Table S1).

In TCM theories, TCMs can be categorized into 21 groups based on their diverse medicinal efficacies. As depicted in Figure 2, the 274 TCMs examined in this study were classified into twenty categories, with heat-clearing medicinal (57 times) being the most frequently used. Moreover, supplementing medicinals (53 times) accounted for the second-highest proportion. Additionally, blood-invigorating and stasis-dissolving medicinals (33 times) ranked third, while exterior-releasing medicinals (24 times) ranked the fourth. Thus, the basic principles for the treatment of DR were to reduce inflammation, promote blood circulation, decrease swelling and relieve fever.

Analysis on four natures, five flavors and meridian tropisms of TCMs in 138 TCM prescriptions collected from patent databases. TCM theories encompass a comprehensive understanding of the nature and fundamental attributes of TCM, which include four natures, five flavors and meridian tropisms. In this study, statistical analysis was conducted on these aspects for the 274 TCMs (Figure 3).

As shown in Figure 3A, cold TCMs were the most commonly used (105 times, 42.78%), followed by warm TCMs (78 times, 29.35%), with heat TCMs being the least commonly used (5 times, 1.33%). As shown in Figure 3B, the primary flavors of TCMs were bitter (141 times, 40.26%), sweet (135 times, 29.63%) and acid (94 times, 16.39%). As shown in Figure 3C, most of the 274 TCMs were attributed to the liver, lung, kidney and spleen.

Figure 2 Efficacy categories of 274 TCMs in 138 TCM prescriptions collected from patent databases
Figure 3 Frequency distribution of four natures. (A) Five flavors. (B) Meridian tropisms. (C) TCMs in 138 TCM prescriptions collected from patent databases.
Analysis of association rules of TCM prescriptions collected from patent databases. High-frequency TCM combinations for treating DR were analyzed by IBM SPSS Modeler 18.0 software, resulting in 51 distinct combinations. Among these, 25 were one-to-one TCM association rules (Supplementary Table S2) and 26 were multiple-to-one TCM association rules (Supplementary Table S3). Chrysanthemi Flos-Lycii Fructus exhibited the highest support (23.02%), with confidence and lift values of 71.88% and 2.44%, respectively. As shown in Supplementary Table S3, Angelicae Sinensis Radix-Rehmanniae Radix-Notoginseng Radix et Rhi zona showed the highest support, with support, confidence and lift values of 15.83%, 63.64% and 1.84%, respectively.

Screening of a novel TCM prescription for treating DR. Modeling analysis was performed on all TCMs using SPSS Modeler 18.0 software, followed by topological analysis using Cytoscape on strongly and moderately linked TCMs. In the resulting graph, node size and color represented degree values, with larger and redder nodes indicating greater TCM importance. Based on degree, closeness centrality and betweenness centrality analysis, the four TCMs with the most distinct color and size were Astragali Radix, Lycii Fructus, Chrysanthemi Flos and Angelicae Sinensis Radix (Figure 4). Intriguingly, these four core TCMs constituted a novel TCM prescription for treating DR. Their topological information is provided in Table 1.

Analysis of the molecular mechanism of the novel TCM prescription against DR. Prediction of targets and potential active ingredients of the novel TCM prescription against DR. To identify potential active ingredients in the novel TCM prescription against DR, data were retrieved from the TCMSp database and literature, resulting in a total of 285 potential active ingredients. Among these, 40 were sourced from Astragali Radix, 125 from Lycii Fructus, 78 from Chrysanthemi Flos and 42 from Angelicae Sinensis Radix, as detailed in Supplementary Table S4-S7. Subsequently, 2319 targets were predicted through SwissTargetPrediction,SEA and PharmMapper databases after combining and removing duplicates.

Figure 4 Screening of a novel TCM prescription for treating DR based on association rule analysis. Each node represents a TCM in the network. A larger node indicates TCM of higher importance.

<table>
<thead>
<tr>
<th>TCM name and latin abbreviation</th>
<th>Degree value</th>
<th>Closeness centrality</th>
<th>Betweenness centrality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astragali Radix (ASR)</td>
<td>64</td>
<td>0.796296</td>
<td>0.196201</td>
</tr>
<tr>
<td>Lycii Fructus (LYF)</td>
<td>58</td>
<td>0.754386</td>
<td>0.105579</td>
</tr>
<tr>
<td>Chrysanthemi Flos (CHF)</td>
<td>57</td>
<td>0.747826</td>
<td>0.114497</td>
</tr>
<tr>
<td>Angelicae Sinensis Radix (ANSR)</td>
<td>50</td>
<td>0.704918</td>
<td>0.093656</td>
</tr>
</tbody>
</table>
Prediction of DR targets and acquisition of overlapping targets of the novel TCM prescription and DR. Data on DR-related targets were gathered from TTD, Drug Bank, OMIM and DisGeNET databases, yielding 585 targets. The potential active ingredient targets were matched with DR-related targets, resulting in 229 overlapping targets, which were considered the potential therapeutic targets of the novel TCM prescription against DR (Figure 5A). Furthermore, the distribution of these 229 intersection targets among each TCM of the novel TCM prescription is depicted in Figure 5B.

Construction of PPI network and screening of key targets of the novel TCM prescription against DR. To investigate the potential pharmacological mechanism of the novel TCM prescription for treating DR, 229 potential targets were imported to the STRING database to constructed a PPI network. The network was pruned by removing disconnected nodes, resulting in 191 nodes and 803 edges. Subsequently, the original network data was reconstructed using Cytoscape for better visualization and comprehension. By analyzing the degree value, 54 targets with a degree value greater than ten (twice the median) were identified as key targets (Figure 6). The reconstructed PPI network consisted of 54 nodes and 386 edges, representing 386 interactions among these 54 key targets.

GO function and KEGG pathway analysis of the key targets of the novel TCM prescription against DR. For functional analysis, GO analysis was performed on these 54 key targets using the DAVID database. The results encompassed 541 biological processes, 61 cellular components and 96 molecular functions (P < 0.05). The top twenty results for both GO and KEGG enrichment analyses were displayed on a bioinformatics website (Figure 7). Notably, the key targets in the biological processes were mainly involved in response to regulation of apoptotic process, response to regulation of gene expression and response to regulation of ERK1 and ERK2 cascade (Figure 7A). The cellular components of these key targets were predominantly localized in the nucleus, cytoplasm and glutamatergic synapse (Figure 7B). Regarding molecular functions, the key targets were mainly involved in enzyme binding, identical protein binding and insulin receptor substrate binding (Figure 7C). Additionally, the key targets were performed on KEGG enrichment analysis, which yielded 166 pathways with a significance threshold of P < 0.05. The top twenty pathways were considered key pathways and are presented in Figure 7D. The KEGG pathways were associated with the AGE-RAGE signaling pathway in diabetic complications, pathways in cancer, proteoglycans in cancer and the MAPK signaling pathway, among others. Furthermore, the top ten pathways were designated as core pathways, including the AGE-RAGE signaling pathway in diabetic complications and the MAPK signaling pathway.

Screening of key active ingredients and network construction of the TCMs-key active ingredients-key targets-key pathways of the novel TCM prescription against DR. All potential active ingredients and the 54 key targets were inputted into Cytoscape to construct a network of potential active ingredients-key targets (Figure 8). This network comprised 335 nodes and 1947 edges. The degree value was selected as the measuring unit, and 112 ingredients with a degree greater than six (the median) were identified as the key active ingredients of the novel TCM prescription for treating DR. Detailed information on these key active ingredients is provided in Supplementary Table S8. To characterize the multi-compound, multi-target and multi-pathway therapeutic characteristics of the novel TCM prescription against DR, Cytoscape was employed to construct a network of TCMs-key active ingredients-key targets-key pathways (Figure 9). This comprehensive network encompassed 112 ingredient nodes, 54 target nodes, 20 pathway nodes and 1563 edges.

![Figure 5 Venn diagram of the novel TCM prescription-DR common targets.](image1)

![Figure 6 Key targets obtained from PPI network analysis.](image2)
Figure 7 GO and KEGG pathway analyses of the key targets of the novel TCM prescription for treating DR. (A) Biological processes. (B) Cellular components. (C) Molecular functions. (D) KEGG pathway analysis.

Figure 8 Construction of a network of potential active ingredients-key targets of the novel TCM prescription against DR. Blue diamonds represent key targets, green hexagons represent core TCMs and orange circles represent potential active ingredients.

Figure 9 Construction of a network of TCMs-key active ingredients-key targets-key pathways of the novel TCM prescription against DR. Blue diamonds represent the key targets, yellow hexagons represent the core TCMs, purple circles represent the unique key active ingredients of different TCMs, red circles represent the common key active ingredients of different TCMs and orange V shapes represent the key pathways.
Network analysis of core TCMs-core active ingredients-core targets-core pathways of the novel TCM prescription against DR.

As shown in Figure 9, the top twenty active ingredients with a higher degree were identified, including butyl octyl phthalate, ferulic acid, eupatilin,isorhamnetin, ethyl ferulate, chrysoeriol, hesperetin-7-O-glucose, acetyl-L-tryptophan, caffeic acid, methyl palmitoleate, kaempferide, dihydroferulic acid, 4'-O-methyllynasol, sedanolide, 9,12-octadecadienoic acid, linoleic acid, kaempferol, methyl linoleate, diosmetin-7-O-β-D-glucopyranoside and quercetin. These were further identified as core active ingredients in the novel TCM prescription for the treatment of DR, encompassing eight flavonoids, four phenolic acids, four esters, two fatty acids, one amino acid and one lignan. Detailed topological information and 2D chemical structural formulas for all core active ingredients are provided in Table 2 and Figure 10, respectively. Moreover, the top ten targets with the highest degree were selected as the core targets: MMP2, EGFR, IGF1R, MMP9, KDR, NFKB1, PTPN1, VEGFA, AKT1 and PPARG. Table 3 presents detailed topological information for all core targets. To further elucidate the relationship between the novel TCM prescription and the treatment of DR, a network of core TCMs-core active ingredients-core targets-core pathway was further constructed (Figure 11). This network included a total of twenty core active ingredients, ten core targets and ten core pathways.

### Table 2 Basic information of the core active ingredients in the novel TCM prescription for treating DR

<table>
<thead>
<tr>
<th>NO.</th>
<th>Core active ingredients</th>
<th>Pubchem ID</th>
<th>Degree</th>
<th>Closeness centrality</th>
<th>Betweenness centrality</th>
</tr>
</thead>
<tbody>
<tr>
<td>JH21</td>
<td>Butyl octyl phthalate</td>
<td>66540</td>
<td>19</td>
<td>0.474747</td>
<td>0.009541</td>
</tr>
<tr>
<td>A11</td>
<td>Ferulic acid</td>
<td>445858</td>
<td>18</td>
<td>0.472362</td>
<td>0.00741</td>
</tr>
<tr>
<td>JH38</td>
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<td>17</td>
<td>0.460784</td>
<td>0.007309</td>
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<tr>
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<td>17</td>
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<td>0.005578</td>
</tr>
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![Figure 10](https://www.tmrjournals.com/mhm)
Table 3 Topological information of the core targets in the novel TCM prescription for the treatment of DR

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<th>Closeness centrality</th>
<th>Betweenness centrality</th>
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Figure 11 Construction of a network of core TCMs-core active ingredients-core targets-core pathways of the novel TCM prescription against DR. Yellow hexagons represent TCMs of novel TCM prescription, purple parallelograms represent the unique core active ingredients of different TCMs, red parallelograms represent the common core active ingredients of different TCMs, blue diamonds represent the core targets and orange V shapes represent the core pathways.

Molecular docking results of core active ingredients and core targets of the novel TCM prescription against DR

Molecular docking was performed with all core active ingredients and core targets. Generally, a binding energy of less than 0 indicated that the core active ingredient can effectively bind to the core target. When the binding energy was ≤ −5.0 kcal/mol, a decent binding between the ligand and the receptor was observed. When the binding energy was ≤ −9.0 kcal/mol, a strong binding was observed between the ligand and the receptor [19]. The docking results for binding energy are displayed in the form of a heat map (Figure 12A). Almost all core active ingredients exhibited strong binding activities to core targets, validating the findings from network pharmacology. Representative molecular docking results for four groups were selected for visualization (Figure 12B), further supporting the potential of the novel TCM prescription for treating DR through these core active ingredients and core targets.

Molecular dynamics simulation

MD simulation provide an important basis for predicting the stability of ligand-protein complexes. In this study, the best docked conformations of the core active ingredients in four core TCMs and the core targets were selected to perform MD simulation analysis. RMSD is generally used to measure the conformational stability of the ligand-protein complex and the RMSD curves of docked complexes are illustrated in Figure 13A, Supplementary Figures S5–S8. Rg is an indicator for evaluating the compactness of protein structure and the Rg curves of the MD simulation analysis of docked complexes are shown in Figure 13B. The RMSF curves in Figure 14 reflects the degree of freedom of movement of each residue in the molecule.

As shown in Figure 13A, the RMSD of all docked complexes fluctuated in the early stage and stabilized after 25 ns, and the fluctuation was relatively slight. This indicated that the conformation of the four docked complexes were stable and did not change significantly. As illustrated in Figure 13B, the Rg curves of all docked complexes performed well, which demonstrated that they could exist steadily without affecting the structure itself. Notably, the Rg result of hesperetin-7-O-glucoside-MMP2 complex (green broken lines shown in Figure 13B) were observably lower than other systems and did not fluctuate drastically, which indicated that the hesperetin-7-O-glucoside-MMP2 complex possessed the tightest structure. The RMSF curves of four docked complexes are shown in Figure 14, in which the average RMSF of caffeic acid-MMP9 complex,

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kaempferol-MMP9 complex, quercetin-MMP9 complex and hesperetin-7-O-glucoside-MMP2 complex were 0.167, 0.239, 0.178, 0.084 nm, respectively. In terms of RMSD, Rg and RMSF, the hesperetin-7-O-glucoside-MMP2 complex (green broken line shown in Figures 13 and 14) had the lowest RMSD and Rg, the most stable RMSF and showed the best state in all aspects. Therefore, MMP2 was possible a novel target for treating DR. Our study confirms that the core active ingredients could combine well with the core targets, which illustrated that the novel TCM prescription could promote the improvement or treatment of DR to a certain extent by acting on the core targets.

![Molecular docking results of core active ingredients and core targets of the novel TCM prescription for treating DR. (A) Heatmap of the docking scores of core active ingredients and core targets of the novel TCM prescription. (B) Representative 3D molecular docking structures of core active ingredients and core targets of the novel TCM prescription. Yellow lines represent hydrogen bond interaction force.](image)

![MD simulation profiles of four core active ingredients and core targets of the novel TCM prescription for treating DR. (A) The RMSD change of docked complexes. (B) The Rg change of docked complexes. RMSD, root mean square deviation; Rg, radius of gyration.](image)
DR is the most prevalent microvascular complication of diabetes, with an estimated increase in affected individuals to 161 million by 2045 [2]. Hence, there is an urgent need to explore more effective methods for the prevention and treatment of DR. According to ancient TCM theory, the deficiency of liver and kidney “yin” (“yin” represents the fluids and water in the human body and reflects the functions of organs) and loss of body fluids are the fundamental causes of DR [20]. The declined functions of the five zang-organs stimulate the increase of liver “fire” (“fire” represents the body’s fever and inflammatory response) in DR patients, which further causes eye redness, swelling, bleeding, and even vision loss [20]. TCM prescriptions with the functions of removing heat and “fire” from the body, activating blood circulation and clearing blood stasis, and invigorating “qi” (“qi” and blood are the material basis for the physiological activities of viscera, meridian and other organs in human body. The formation and operation of “qi” and blood depends on the normal physiological function of viscera) are usually used to improve the symptoms of DR, which is consistent with the results of this study [20, 21]. In this context, a novel TCM prescription comprising Lycii Fructus, Chrysanthemi Flos, Astragali Radix and Angelicae Sinensis Radix has shown potential therapeutic effects on DR. Among the novel TCM prescription screened in this study, Astragali Radix is the monarch drug, Angelicae Sinensis Radix is the minister drug, and Lycii Fructus and Chrysanthemi Flos are the assistant drugs. Thereinto, Astragali Radix has the effects of reinforcing “qi”, elevating “yang” (“yang” is an important driving force for metabolism and physiological functions of human body) and solidifying the surface (enhance the body’s immunity) [22, 23]. Angelicae Sinensis Radix has the effects of nourishing blood and invigorating blood circulation [24, 25]. The combination of Astragali Radix and Angelicae Sinensis Radix can be used to replenish “qi” and blood [26, 27]. Lycii Fructus has the effects of tonifying kidney and essence (enhance the function of kidney), nourishing liver (improve the function of liver) and improving eyesight [28]. Chrysanthemi Flos has the effects of calming liver, brightening eyes (treat impaired vision), cleaning heat and toxins (relieve fever and reduce inflammation) [29, 30]. Therefore, the composition of the novel TCM prescription is streamlined, well-combined, and consistent with the compatibility theory of TCM, indicating that it has great potential in the treatment of DR. Modern pharmacological research has indicated that Lycii Fructus enhances the viability of retinal ganglion cells and alleviates retinal oxidative stress damage in DR rats [31]. Chrysanthemi Flos has demonstrated its ability to ameliorate retinal damage caused by diabetes. The combination of Lycii Fructus and Chrysanthemi Flos effectively prevents retinal damage and exhibits a favorable therapeutic effect on diabetic rats with retinopathy, aligning with the results of the highest support value for association rule in this study [32]. Astragali Radix, known for reducing the incidence of retinopathy in diabetic rats, plays a therapeutic role in the treatment of DR by inhibiting inflammation and retinal pericyte apoptosis [33]. Angelicae Sinensis Radix was known as the assistant drug for the improvement of eyesight and plays a significant role in protecting retinal function in patients with DR [34]. These findings are consistent with our discovery that these four TCMs are essential for treating DR and merit further investigation.

In this study, network pharmacology was utilized to analyze the active ingredients, potential targets and molecular mechanism of the novel TCM prescription for treating DR. Our investigation identified twenty core active ingredients in the novel TCM prescription, including eight flavonoids, four phenolic acids, four esters, two fatty acids, and other key components such as Caffeic acid and Kaempferol.

**Figure 14** The RMSF profiles. (A) Caffeic acid-MMP9 complex. (B) Kaempferol-MMP9 complex. (C) Quercetin-MMP9 complex. (D) Hesperetin-7-O-glucoside-MMP2 complex. RMSF, root mean square fluctuation.

**Discussion**

In this study, network pharmacology was utilized to analyze the active ingredients, potential targets and molecular mechanism of the novel TCM prescription for treating DR. Our investigation identified twenty core active ingredients in the novel TCM prescription, including eight flavonoids, four phenolic acids, four esters, two fatty acids, and other key components such as Caffeic acid and Kaempferol.
acids, one amino acid and one lignan, which intervene in DR through direct and indirect regulation of ten core targets and ten core pathways. Oxidative stress and inflammation play crucial roles in the pathogenesis of DR, and the novel TCM prescription mitigated inflammatory response and oxidative stress, thereby preventing the onset and progression of DR. Ferulic acid, a major active ingredient in *Angelicae Sinensis Radix*, *Chrysanthemi Flos* and *Lycii Fructus*, can reduce neuroinflammation mediated by microglial cells in retinal degeneration [35]. The AGE-RAGE signaling pathway in diabetic complications plays important roles in the progression of DR, as advanced glycation end-products can induce inflammation and oxidative stress in diabetes complications including DR [36, 37]. Kaempferol, a flavonoid present in *Chrysanthemi Flos*, *Astragali Radix* and *Lycii Fructus*, possesses antioxidant activity and protects human retinal pigment epithelium (RPE) cells from damage caused by oxidative stress by suppressing the AGE-RAGE signaling pathway through the regulation of EGFR and KDR expression [38]. Isohamnetin, another flavonoid present in *Chrysanthemi Flos*, *Lycii Fructus* and *Astragal Radix*, acts on EGFR targets, thereby inhibiting the production of inflammatory factors in retinal pericytes and mitigating oxidative stress [39]. The activation of MAPK signaling pathway contributes to inflammation in RPE cells, and quercetin, the primary ingredient in *Chrysanthemi Flos* and *Lycii Fructus*, inhibits the MAPK signaling pathway, alleviating inflammation and exhibiting therapeutic effects on DR [40, 41]. MMP9 may be a crucial target for preventing oxidative injury in retinal endothelial cells [42]. Molecular docking results demonstrated that nearly all core active ingredients in the novel prescription effectively bind to the EGFR, KDR and MMP9 targets, suggesting that these targets may be crucial for efficacy of the novel TCM prescription against DR.

Furthermore, the novel TCM prescription may effectively treat DR by suppressing the development of retinal neovascularization. As is widely known, DR is a vascular disease induced by diabetes, characterized by vasculopathy in the retina, including alterations in blood flow and vascular leakage [43]. Notably, pathological angiogenesis is the primary cause of vision loss in DR [44]. VEGFA is not only the predominant factor responsible for vascular leakage but also plays a significant role in the angiogenesis associated with DR [45, 46]. Caffeic acid, a phenolic acid active component commonly found in *Chrysanthemi Flos*, *Lycii Fructus* and *Angelicae Sinensis Radix*, inhibits VEGFA expression in retinal endothelial cells, thereby effectively preventing retinal neovascularization in DR [47]. In diabetic patients, the overexpression of MMP2 promotes angiogenesis, contributing to the pathogenesis of DR [48]. Additionally, the AGE-RAGE signaling pathway plays a critical role in retinal neovascularization of DR, and its activation leads to endothelial barrier dysfunction and increased vascular permeability, worsening the symptoms of DR [36]. Isohamnetin has been demonstrated to inhibit the AGE-RAGE signaling pathway, significantly reducing the expression of related genes such as NF-kB and MMP2, and have a beneficial effect on the vascular pathological symptoms of DR [49]. In conclusion, the novel TCM prescription shows promise in treating DR by inhibiting retinal neovascularization through the regulation of VEGFA, MMP2 and NF-κB expression.

The apoptosis of PRE cells and retinal ganglion cells, which are pivotal pathological processes in DR, accelerates the progression of the disease. The increased apoptosis observed in diabetic retinas is believed to be mediated by the overexpression of NF-κB. Quercetin has been shown to inhibit NF-κB expression and reduce the apoptosis of retinal ganglion cells, offering a potential treatment for DR [50]. Additionally, recent studies have reported that kaempferol reduces apoptosis in retinal ganglion cells, offering another avenue for treating DR [51]. Ferulic acid has demonstrated the ability to reverse the expression of apoptosis-related proteins in RPE cells and alleviate high glucose-induced RPE cell apoptosis, making it a potential treatment for DR [52]. Moreover, isorhamnetin has been shown to protect RPE cells from apoptosis induced by oxidative stress by inhibiting the production of reactive oxygen species and the activation of caspase-3 [35]. In summary, the novel TCM prescription for treating DR, identified in this study, exhibits characteristics of multi-component and multi-target therapeutic potential.

Next, we will further systematically optimize the ratio between different TCMS of the novel TCM prescription to achieve the best efficacy in treating DR. The optimal dose of the novel TCM prescription to exert DR therapeutic effects will also be explored based on cell and animal levels. Based on the above study, a series of clinical experiments will be carried out to confirm the clinical efficacy of the novel TCM prescription against DR and provide data support for its clinical application.

**Conclusions**

In the present study, an integrated strategy combining data mining, network pharmacology, molecular docking and MD simulation was developed to identify a novel TCM prescription against DR from patent databases, and elucidate its medication rule and molecular mechanism. Initially, a total of 138 TCM prescriptions against DR were collected, with most of them featuring cold and bitter TCMS involving heat-clearing and supplementing efficacies. By integrating big data information, a novel TCM prescription composed of four core TCMS was identified, which has potential clinical value in the treatment of DR. Subsequently, network pharmacology was employed to uncover the molecular mechanism of this novel TCM prescription for DR. The twenty compounds and ten targets were identified as core active ingredients and core targets of the novel TCM prescription for treating DR. The novel TCM prescription exerted its anti-DR effect by modulating ten pathways, including the AGE-RAGE signaling pathway in diabetic complications and the MAPK signaling pathway, while reducing inflammatory response, oxidative stress, apoptosis of RPE cells and retinal neovascularization. Additionally, molecular docking and MD simulation results revealed strong binding potency between core active ingredients and core targets. In summary, this study screens out a novel TCM prescription for treating DR and elucidates its molecular mechanism, characterized by its multi-component, multi-target and multi-pathway nature. This research provides a reliable reference and scientific framework for future development of new drugs against DR.

**References**

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