

**Original Article**



# Investigating the Mechanism of Action of Qiju Dihuang Pill in Cataract Treatment by Network Pharmacology and Molecular Docking

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## Abstract:

**Objective:** To investigate the pharmacological mechanism of action of Qiju DiHuang Pill in treating cataracts using network pharmacology and molecular docking techniques. **Methods:** TCMSP and Swiss Target Prediction databases were used to screen active components and targets, and the Genecards database was used to collect cataract disease targets, the network diagram of “Compound-traditional Chinese medicine-active ingredients-potential targets” was constructed by Venny, STRING, Cytoscape and other tools, and GO enrichment and KEGG pathway enrichment analysis were carried out. Molecular docking experiments verified the binding ability of some core targets with active components. **Results:** 60 active components, 731 action targets, and 2057 disease targets from Qiju Dihuang Pill. Using Venny analysis to obtain 135 common targets, and constructing a protein interactions network (PPI), 30 core targets were screened out, including BCL2, AKT1, HIF1A, and so on. GO and KEGG enrichment analyses showed that the key pathways involved PI3K-Akt, apoptosis, and inflammation signaling pathways. A molecular docking assay confirmed that the binding energies of active ingredients such as kaempferol and quercetin to the core targets were lower than  $-6.0 \text{ kcal/mol}^{-1}$ , indicating their significant binding activities. **Conclusion:** Qiju DiHuang Pill may play a role in the prevention and treatment of cataracts by inhibiting the abnormal proliferation and oxidative stress of lens epithelial cells through regulating PI3K-Akt-mTOR signaling pathways.

**Keywords:** Qiju Dihuang Pill; cataract; network pharmacology; molecular docking; traditional Chinese medicine; mechanism of action

## 1. Introduction

The elevated prevalence of cataracts, the foremost cause of blindness globally, is intricately linked to demographic aging and environmental influences [1]. According to statistics, cataract blindness affects 51% of the world's blind population, with over 20 million new cases reported annually [2]. Because of environmental pollution, accelerated aging, and a lack of medical resources, 90% of cases occur in developing nations [3]. The oxidative degradation of lens protein is central to the pathogenesis of cataracts, involving the aberrant activation of many signaling cascades, including MAPK and Wnt, resulting in light scattering and diminished visual function [4]. IOL implantation and ultrasonic emulsification are the

mainstays of current treatment. Even though technological advancements like femtosecond laser-assisted capsule tearing and functional IOLs (such as multifocal and astigmatism-correcting lenses) have raised the surgical success rate to over 95%, complications like posterior capsule membrane clouding and refractive error still occur at rates of up to 15% to 30% [5]. High-end IOLs have limitations concerning dynamic adjustment and biocompatibility. Due to the limitations of the blood-aqueous fluid barrier and the avascular nature of the lens, the local drug penetration rate is less than 0.3%, and the efficacy has not yet reached the standard of clinical transformation, even though N-acetyl carnosine eye drops can inhibit

metalloproteinase activity by chelating copper ions and lanosterol nanoemulsion can dissolve  $\beta$ -amyloid deposition. Remarkably, innovative research, including tailored systems for delivering nano drugs, gene editing technology, and biomimetic adaptable crystals, offers fresh perspectives on overcoming the current therapeutic obstacles <sup>[6]</sup>. But these innovative cataract treatments are still in the testing phase and haven't helped anyone yet.

Qiju Dihuang Pill (QJDHW) originates from the "Medical Grade Bao Jian" and is formulated from the six components of Di Huang Wan, supplemented with Wolfberry and Chrysanthemum. This amalgamation of eight Chinese medicinal herbs aims to nourish yin and tonify the kidneys while simultaneously clearing the liver and enhancing vision, embodying the core principle of Chinese medicine regarding the regulation of the liver and kidneys. Traditional Chinese medicine utilizes this prescription to address visual impairment, ocular astringency, light sensitivity, and weakness in the waist and knees resulting from liver and kidney yin deficiency, highlighting the physiological connection between "liver opening in the eyes" and "kidney essence transforming blood <sup>[7]</sup>." Modern research has demonstrated that QJDHW's pharmacological actions are synergistic, including multiple components, targets, and pathways <sup>[8]</sup>. As an illustration, the lens epithelium can be protected by *Lycium barbarum* polysaccharides and *chrysanthemum* flavonoids, which have an antioxidant effect by scavenging free radicals <sup>[9, 10]</sup>. *Salvinorin*, on the other hand, inhibits the NF- $\kappa$ B pathway and lowers the levels of inflammatory factors like IL-6 and TNF- $\alpha$  <sup>[11]</sup>. *Poria cocos* triterpenoids enhance atrial water circulation, and *Radix Rehmanniae* polysaccharides improve retinal microcirculation <sup>[12]</sup>. In terms of clinical use, the prescription is common in ocular illnesses, where it can enhance tear production, extend the time it takes for the tear film to break, postpone the onset of cataracts in patients with dry eye, and help treat diabetic retinopathy microvascular leaks <sup>[13]</sup>.

However, most of the existing studies are limited to basic experiments or clinical observation and lack systematic analysis of molecular mechanisms. Network pharmacology technology can overcome the shortcomings of conventional

research by methodically integrating the possible targets and interactions of active ingredients, elucidating the fundamental action connections, and building a multi-dimensional network of "component-target-pathway-disease." By forecasting the capacity of QJDHW's active components to interact with cataract-associated targets and identifying principal targets and critical signaling pathways, the study will establish a theoretical foundation for refining traditional Chinese medicine formulations, creating novel preparations, and advancing the modernization and precision transformation of this traditional prescription, thereby offering new therapeutic alternatives for ophthalmic conditions, including cataracts.

## 1. Materials and methods

### 1.1 Software and databases are required

TCMSP (<http://tcmspw.com/tcmsp.php>),

Swiss Target Prediction (<http://swisstargetprediction.ch/>),

PubChem (<https://pubchem.ncbi.nlm.nih.gov/>),

Genecards (<https://www.genecards.org/>),

OMIM (<https://www.omim.org/>),

TTD (<https://db.idrblab.net/ttd/>),

STRING (<https://string-db.org/>),

UniProt (<https://www.uniprot.org/>),

Cytoscape 3.10.3 Software,

Venny 2.1.0 (<https://bioinfo.gp.cnb.csic.es/tools/venny>)

DIVID (<https://david.ncifcrf.gov/>),

Metascape (<https://metascape.org/gp/index.html>),

WeChat visual platform (<https://www.bioinformatics.com.cn>),

PDB (<http://www.rcsb.org>),

CB-Dock2 (<https://cadd.labshare.cn/cb-dock2/php/index.php>).

### 1.2 Active Ingredients and QJDHP-Related Target Screening

The keywords of eight Chinese medicines in QJDHW were entered into the TCMSP platform to identify relevant compounds and action targets. The criteria for screening included an oral bioavailability (OB) of at least 30% and drug-like

properties (DL) of at least 0.18. The SMILES representations of the compounds were obtained, and the action targets of each compound were predicted using the PubChem and Swiss Target Prediction databases, with the species specified as human.

### 1.3 Collection of Cataract Targets

A dataset targeting cataract disease was created by applying a score  $\geq 2.0$  for cardinality, removing duplicates, and screening pertinent gene targets for cataracts using the Genecards, OMIM, and TTD databases.

### 1.4 Screening of common targets for medicines and diseases

The active ingredients in eight Chinese herbal medicines were all put into the online analysis program Venny 2.1.0, along with their action and illness targets. This produced common targets that were shown as Venn diagrams.

### 1.5. Construction of the protein-protein interaction (PPI) network and prediction of core targets

The common targets of medications and disorders are entered into the STRING database, the species is set to human, and the PPI protein interaction network is shown. The data that was gathered was put into the software Cytoscape 3.10.3, and the Centiscape 2.2 plug-in was used to look at the PPI network's topology. Degree, Closeness, and Betweenness were used as filtering criteria for the main targets.

### 1.6 Construction of the herbal medicines-active components-potential targets network

For visual analysis and network mapping, QJDHW, active components, and possible targets were loaded into the Cytoscape 3.10.3 program.

### 1.7. Analysis of GO and KEGG Pathway

With the use of the microbiological platform, enrichment bubble maps were created after the acquired core targets were entered into the Metascape and DAVID databases, respectively, for gene ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment pathway analysis.

### 1.8 Molecular docking

Select the top 6 targets in the "compound-herbal medicine-active ingredient-potential target" network in terms of degree value, download the 3D structure of the core protein from the PDB database, and save it (PDB format). The active ingredients with the top 6 degrees values in the network diagram were selected and the structure files of the active ingredients (SDF format) were downloaded using the PubChem database. Molecular docking assays were performed and binding energies were calculated using the CB-Dock2 online site.

## 2. The results and analysis

### 2.1 Screening results: active components and targets of QJDHW

A total of 60 active ingredients were obtained from TCMSP, Swiss Target Prediction and Pubchem databases according to the screening conditions, including 0 active ingredients of Radix Rehmanniae Praeparata, 9 active ingredients of Corni Fructus, 10 active ingredients of Yam, 8 active ingredients of Alisma, 8 active ingredients of Moutan Cortex, 3 active ingredients of Poria cocos, 9 active ingredients of Wolfberry, and 13 active ingredients of Chrysanthemum. The total number of drug targets was 731 by eliminating duplicates (See Table 1).

**Table 1 Basic information on Chinese medicine-active ingredients-targets of action**

TCM	Number of active ingredients	Number of targets
Radix Rehmanniae Praeparata	0	0
Corni Fructus	9	347
Yam	10	289
Alisma	8	253
Moutan Cortex	8	143
Poria cocos	3	172
Wolfberry	9	299
Chrysanthemum	13	279

### 2.2 Results from the target collection for cataract disease

Cataract target genes were obtained using Genecards, OMIM, and TTD databases, and 2057 target genes were obtained by screening with Score  $\geq 2$  and removing duplicates.

### 2.3 Results of screening for common targets of medicines and disease

The screened 731 drug targets and 2057 disease targets were imported into the Venny 2.1.0 online analysis software to obtain the Venn diagram, and 135 common targets were obtained (See Figure 1).

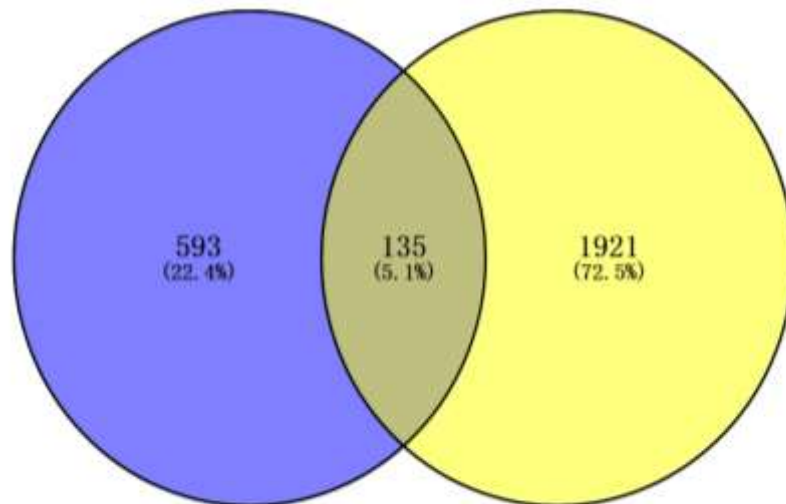


Fig.1 The Venn diagram of QJDHW drug targets and cataract disease targets

### 2.4. Construction of the PPI network and screening of core targets

The 135 common targets obtained were imported into the STRING database to obtain the PPI

interaction network diagram, and the obtained target information was imported into Cytoscape 3.10.3 software for analysis, and a total of 30 core targets were obtained (See Figure 2).

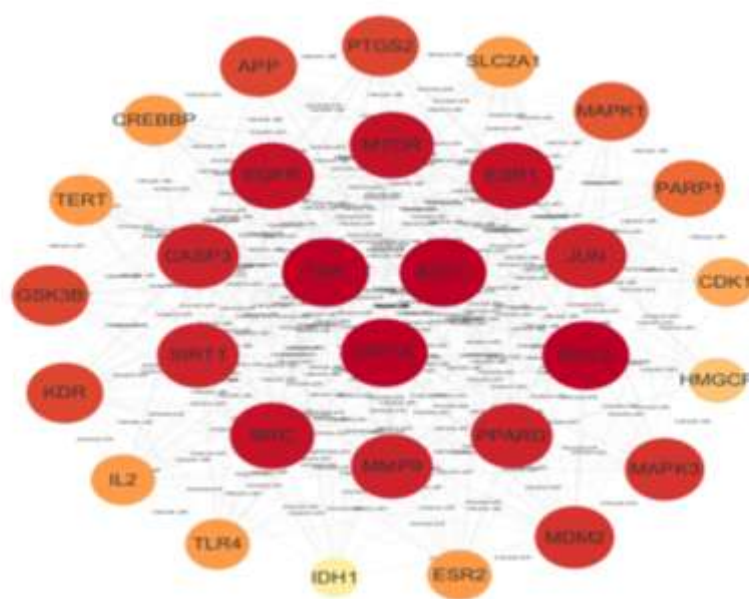
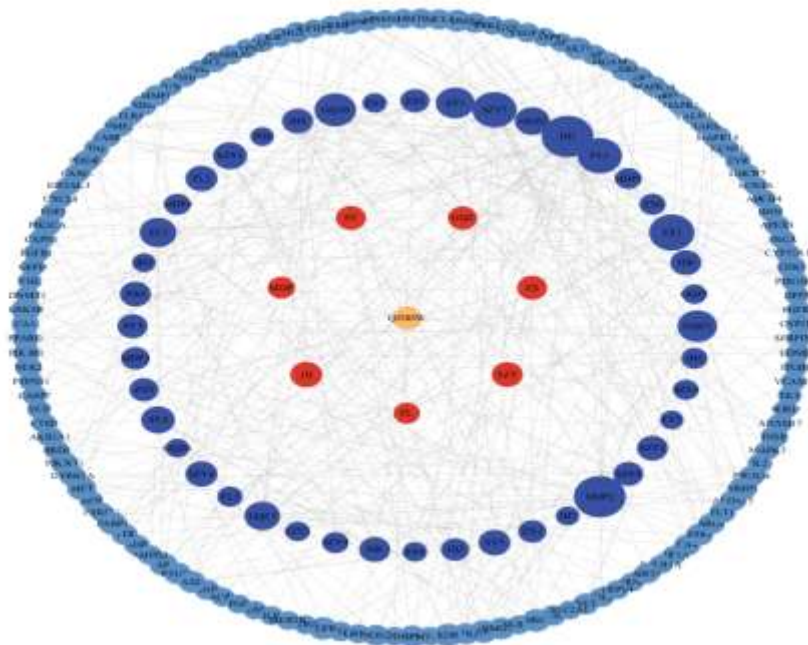


Fig. 2 Diagram of the core targets screened

### 2.5 Construction of a compound-herbal medicine-active ingredient-potential target network diagram

The 60 active ingredients and 135 potential targets

in QJDHW were imported into Cytoscape 3.10.3 software to construct a visualization network diagram of “Compound formula - Traditional Chinese medicine - Active ingredient - Potential target”. Network diagram (See Figure 3).

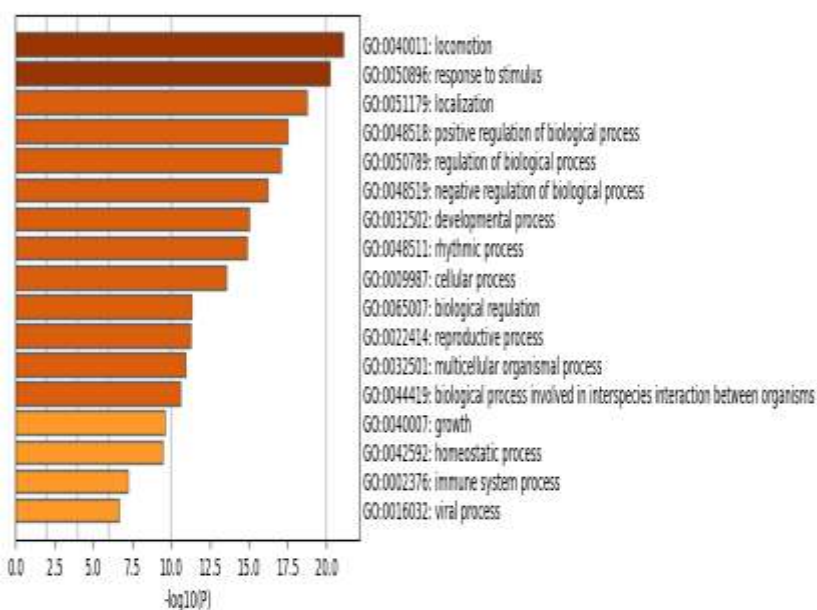


**Fig. 3 Visualization network diagram of “compound-herbal medicine-active ingredient-potential target”**

### 2.6 Results of GO accumulation and KEGG pathway enrichment analysis

The 30 core targets were entered into Metascape

and DAVID databases for GO enrichment analysis, respectively, and the top 10 of each of the enriched BP, CC, and MF were visualized (See Figure 4).



**Fig. 4 Analytic diagram of GO function enrichment**

The KEGG pathway enrichment analysis showed that there were mainly 20 key pathways for

QJDHW treatment of cataracts (See Figure 5).

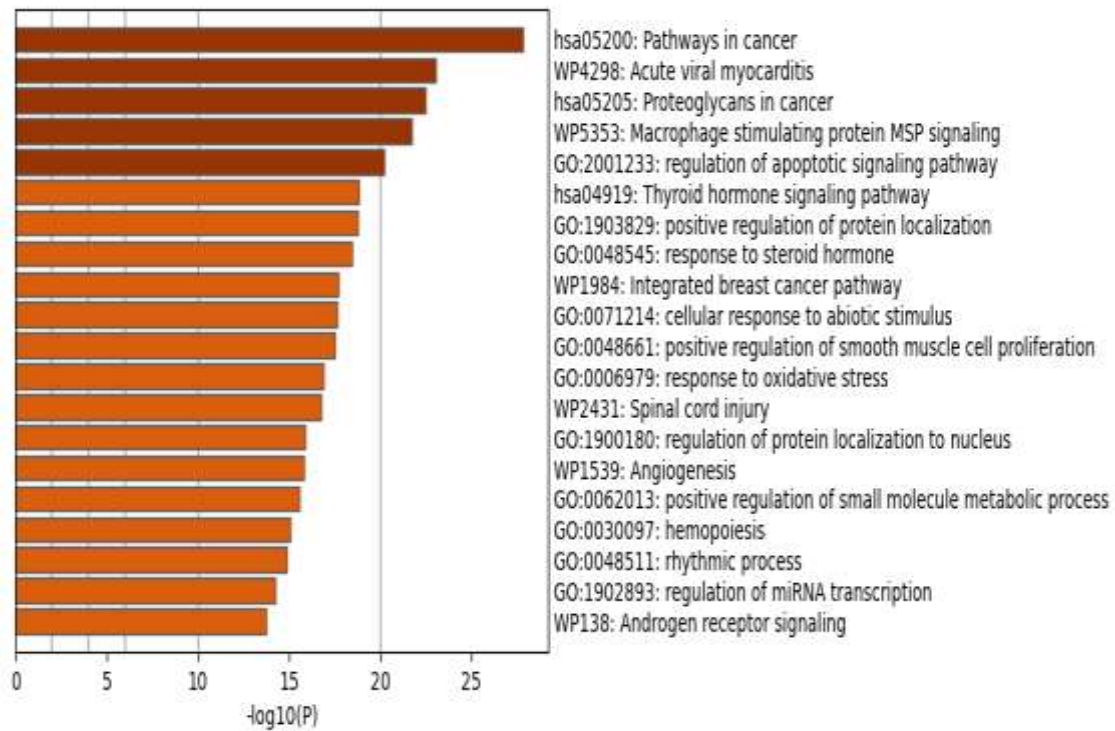


Fig. 5 Enrichment analysis diagram of the KEGG pathway

Bubble plots of the results of GO enrichment analysis and KEGG pathway enrichment analysis

were plotted using the microbotics platform (See Figure 6 and Figure 7).

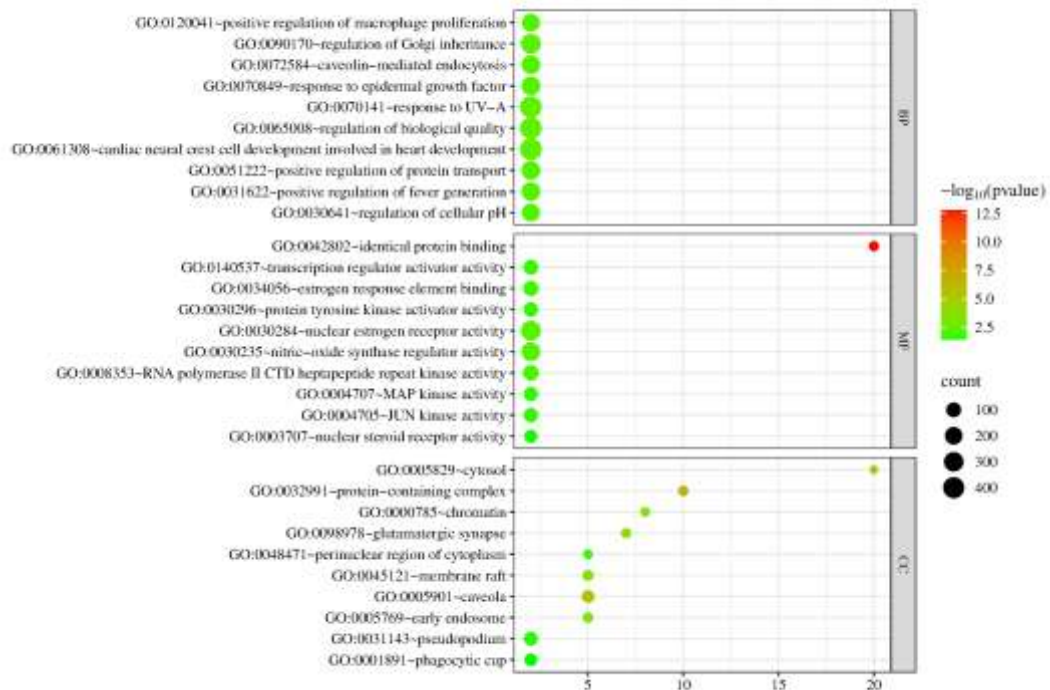


Fig. 6 The bubble diagram of GO enrichment analysis

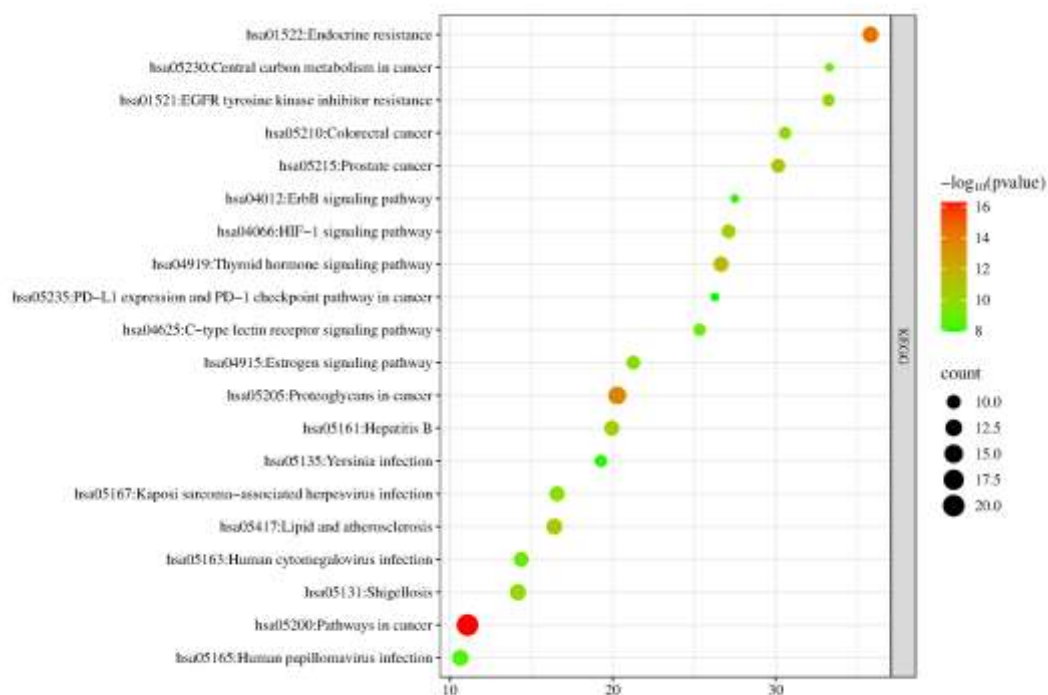
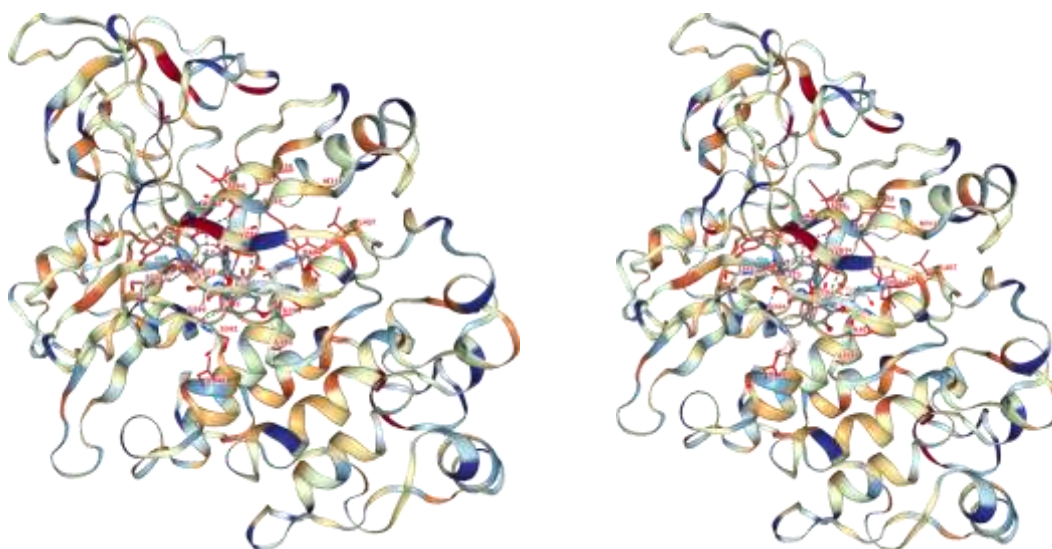


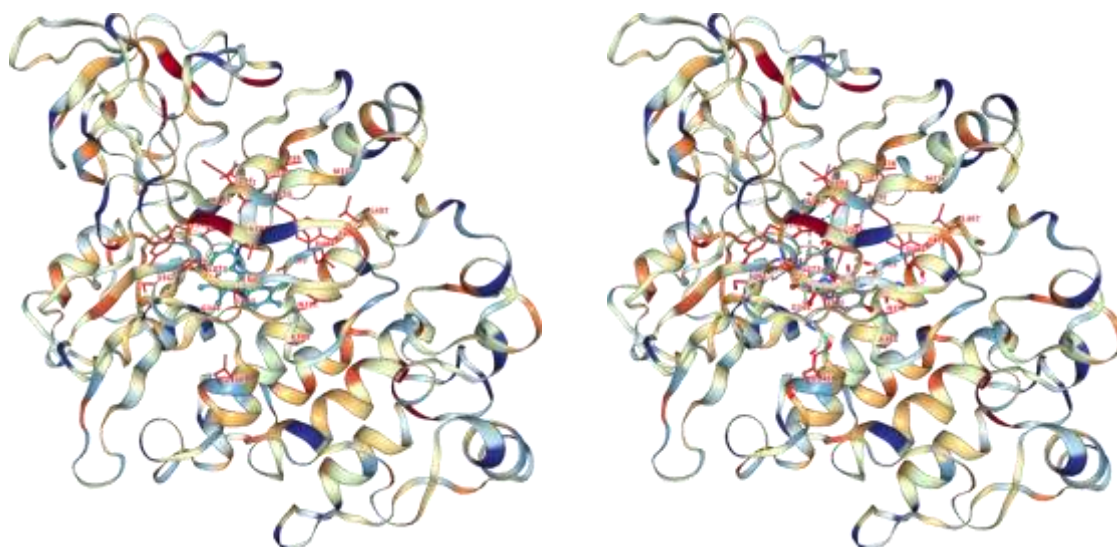
Fig. 7 The bubble diagram of KEGG enrichment analysis

## 2.7 Results of Molecular Docking Experiments

In molecular docking assays, the lower the total energy, the more tightly the target is bound to the active ingredient. The molecular docking

predictions are shown in Table 2, and the binding energies were all  $\leq -6.0$  kcal/mol<sup>-1</sup>, indicating a strong binding activity, of which the top-ranked binding activities are shown in Figure 8.





**Fig. 8 Docking diagram of the top-ranked molecules in terms of binding activity**

**Table 2 Docking of core components to target molecules**

Target proteins	Chemical compounds	Total energy/kcal.mol <sup>-1</sup>
SRC	Alisol B	-10.3
SRC	Cerevisterol	-9.8
SRC	quercetin	-8.2
SRC	acacetin	-8.1
MTOR	Cerevisterol	-8.1
BCL2	Cerevisterol	-8.0
SRC	Hydroxygenkwanin	-8.0
TNF	quercetin	-7.9
MTOR	Alisol B	-7.9
MTOR	quercetin	-7.9
MTOR	kaempferol	-7.8
HIF1A	Hydroxygenkwanin	-7.7
HIF1A	Cerevisterol	-7.7
TNF	kaempferol	-7.6
MTOR	Hydroxygenkwanin	-7.6
HIF1A	kaempferol	-7.5
HIF1A	acacetin	-7.5
HIF1A	Alisol B	-7.5
AKT1	Cerevisterol	-7.5
TNF	Alisol B	-7.5
HIF1A	quercetin	-7.4
TNF	acacetin	-7.3
TNF	Hydroxygenkwanin	-7.3
MTOR	acacetin	-7.3
BCL2	Alisol B	-7.1
TNF	Cerevisterol	-6.9
SRC	kaempferol	-6.9
AKT1	Alisol B	-6.8
BCL2	Hydroxygenkwanin	-6.7
BCL2	quercetin	-6.7
BCL2	kaempferol	-6.6
BCL2	acacetin	-6.5

AKT1	acacetin	-6.3
AKT1	Hydroxygenkwanin	-6.1
AKT1	kaempferol	-6.0
AKT1	quercetin	-6.0

### 3. Discussion and Prospect

In Chinese medicine, cataract belongs to the category of “round cataract”. According to Chinese medicine, cataracts are caused by deficiencies of the liver and kidney, insufficient essence and blood, and loss of nourishment for the eyes. Qiju Dihuang Pill is a commonly used formula for treating cataracts, which is based on the Liuwei Dihuang Pill, with the addition of wolfberry and chrysanthemum, which can nourish the liver and kidneys, nourish the essence and brighten the eyes. It can target patients with liver and kidney yin deficiency type cataracts to improve symptoms such as blurred vision <sup>[14]</sup>. Modern pharmacological studies have also shown that the ingredients in this formula can inhibit oxidative damage and mitigate copper-induced death to protect lens epithelial cells, thus effectively preventing and treating cataracts <sup>[15]</sup>.

According to Cytoscape 3.10.3 software, the network diagram of “Traditional Chinese Medicine - Active Ingredients - Targets of Action” was analyzed, and the components with the highest degree values of the targets included kaempferol, acetin, Alisol B, Hydroxygenkwanin, Cerevisterol, quercetin and so on. Kaempferol (KAE) is a class of compounds with significant antioxidant, anti-inflammatory, anti-tumor bioactivities and neuroprotective effects. The research on kaempferol in the treatment of cataracts has focused on its antioxidant and aldose reductase inhibiting effects. The study suggests that KAE may ameliorate selenite-induced lens tissue damage in cataract-prone rats by activating the PI3K/Akt signaling pathway <sup>[16]</sup>. In addition, kaempferol has an antioxidant function, which can enhance cell viability, reduce reactive oxygen species levels, and elevate superoxide dismutase activity, thus protecting the lens epithelial cells <sup>[17]</sup>. Quercetin has a powerful antioxidant capacity, which can effectively scavenge free radicals and reduce the damage of oxidative stress on lens epithelial cells. It was found that quercetin could inhibit apoptosis of lens epithelial cells in diabetic rats, protect the lens structure, and thus slow down the progression of cataracts <sup>[18]</sup>. In the “Traditional

Chinese Medicine-Active Ingredients-Targets of Action” network diagram, the targets with the highest degree ranking, such as BCL2, HIF1a, Akt1, TNF, SRC, mTOR, ESRL, EGFR, and so on also play an important role. Akt1 is a key protein in the PI3k/Akt signaling pathway, which plays an important role in the proliferation, migration, and apoptosis of lens epithelial cells <sup>[19]</sup>. The study found that the activation of the PI3k/Akt signaling pathway can also inhibit the migration and mesenchymal transdifferentiation of lens epithelial cells, thereby delaying the progression of cataracts <sup>[20]</sup>. In the process of lens development, hypoxia can up-regulate HIF1A expression, and then regulate the degradation of non-nuclear organelles in lens fiber cells by affecting the transcription of BNIP3L <sup>[21]</sup>. In addition, HIF1A may also affect the pathophysiological processes of the lens through other mechanisms, but its specific application in cataract treatment still needs further research. GO enrichment analysis involves locomotion, response to stimulus localization, and positive regulation of the biological and cellular processes. KEGG metabolic pathway enrichment analysis was mainly related to angiogenic apoptosis (such as apoptosis signaling pathway), cellular response to abiotic stimuli, inflammatory response, and so on.

In summary, the QiJu DiHuang Pill may act on the PI3K-Akt-mTOR signaling pathway through key targets such as BCL2, HIF1A, AKT1, TNF, MTOR, and so on, and then inhibit the abnormal growth and differentiation of lens epithelial cells to play the role of preventing and treating cataract. However, the prediction of network pharmacology has certain limitations, which need to be further verified by in vitro and in vivo experiments, so as to provide new ideas and new directions for the further study and development of the effective material basis of QiJu DiHuang Pill. Future studies will continue to explore its specific mechanism of action to provide more effective solutions for the treatment of cataracts.

#### Declarations

**Ethical Approval:** Not applicable.

**Availability of Data and Materials:** Not applicable.

**Acknowledgments:** Not applicable.

**Conflict of Interest:** The author declares no competing interests.

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