Observational Study

Medicine

OPEN

Study on the mechanism of Qiju Dihuang pill in the treatment of ophthalmic diseases based on systems pharmacology

Fei Liu, MSc[a,*], Mi Tian, MA[b]

Abstract

Qiju Dihuang pill is one of the common Traditional Chinese Medicine to treat ophthalmic diseases. In vivo studies have suggested that Qiju Dihuang pill can be used for treating glaucoma, and it can also be used clinically to treat cataract patients. However, the bioactive ingredients and the therapeutic mechanism of Qiju Dihuang pill on treating these ophthalmic diseases remained unclear. Presently, a systems pharmacology approach which combines pharmacokinetic screening, targeted fishing, biological function enrichment, network pharmacology, and molecular docking analysis, was employed. A total of 134 active ingredients with 72 corresponding targets are identified from Qiju Dihuang pill. Additionally, 3 core targets including CHRM1, ESR1, and AR are obtained from the ingredients and drug targets network analysis. Besides, gen ontology and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis reveal 3 important biological pathways, that is, calcium signaling pathway, insulin signaling pathway and Vascular endothelial growth factor signaling pathway. In final, a molecular docking model was constructed to study the interaction mechanism between active components and drug targets at the molecular level. All the findings show that Qiju Dihuang pill achieves therapeutic effects on treating ophthalmic diseases by regulating the crucial targets of the compounds in it. This work not only provides insight into the therapeutic mechanism of herbal medicine in the treatment of ophthalmic diseases from a multiscale perspective, but also offers an effective approach for drug discovery and development of Traditional Chinese Medicine.

Abbreviations: ADRA1A = alpha-1A adrenergic receptor, AR = androgen receptor, BP = biological process, CC = cellular component, CHRM1 = muscarinic acetylcholine receptor M1, DL = drug-like, ESR1 = estrogen receptor, GO = gen ontology, HTR2C = 5-hydroxytryptamine 2C receptor, KEGG = Kyoto Encyclopedia of Genes and Genomes, MF = molecular function, NR3C1 = glucocorticoid receptor, OB = oral bioavailability, OPRD1 = delta-type opioid receptor, PIK3 = phosphoinositide-3-kinase, PPI = protein-protein interaction, TCM = Traditional Chinese herbal medicine, TCMSP = Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform, VEGF = vascular endothelial growth factor.

Keywords: mechanism of action, molecular docking, ophthalmic diseases, Qiju Dihuang pill, systematic pharmacology.

1. Introduction

Generally, ophthalmic diseases include vitreous and retinal diseases, ophthalmology, glaucoma, and optic neuropathy and cataract, among which glaucoma and cataract are 2 major blinding diseases.[1,2] To date, treatment for people with ophthalmic diseases contains medication, laser therapy, and incisional surgery.[1] However, it should not be ignored that drugs have certain adverse effects and surgical therapy has incision infection and induced complications.[1] Additionally, the high cost of surgery limits its application in many underdeveloped countries. Consequently, it is of great significance to develop drugs for the prevention and treatment of ophthalmic diseases.

It is worth mentioning that Traditional Chinese Medicine (TCM), as an alternative therapy for various diseases, has attracted more and more people's great interest.[3–5] Qiju Dihuang pill, as one of the common TCM to treat ophthalmic diseases, is written by Dong Xiyuan in Qing Dynasty. This formula is consisted of 8 herbs, that is, *Lyii Fructus*, *Chrysanthemi Flos*, *Corni Fructus*, *Moutan Cortex*, *Dioscoreae Rhizoma*, *Poria*, *Alismatis Rhizoma*, and *Rehmanniae Radix Praeparata*. Numerous studies have revealed that Qiju Dihuang pill exhibited significant effects on the treatment of diabetic retinopathy, diabetes mellitus with hypertension and dry eye after cataract surgery.[6–9] Additionally, considerable clinical evidence also suggests that Qiju Dihuang pill can be used in the treatment of ocular related diseases.[6–9]

Although the curative effect of Dihuang pill on ophthalmic diseases is certain, the active components and molecular mechanism in it for treating ophthalmic diseases are still unclear.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files]

[a] Faculty of Medical Technology, Ophthalmology Laboratory of Anhui Medical College, Hefei, China, and [b] Department of Ophthalmology, Second Affiliated Hospital of Anhui Medical University, Hefei, China.

** Correspondence: Fei Liu, MSc, Faculty of Medical Technology, Ophthalmology Laboratory of Anhui Medical College, Furong Road 632 #, Hefei 230601, Anhui, China (e-mail: liufei@ahyz.edu.cn).*

How to cite this article: Liu F, Tian M. Study on the mechanism of Qiju Dihuang pill in the treatment of ophthalmic diseases based on systems pharmacology. Medicine 2022;101:31(e30033).

Received: 18 February 2022 / Received in final form: 9 June 2022 / Accepted: 27 June 2022

http://dx.doi.org/10.1097/MD.0000000000030033

In addition, the multicomponent, multitarget, and multipathway features of Dihuang pill also brings more difficulties and challenges to our research. Consequently, it is still necessary to apply the new method to screen out the key ingredients in Dihuang pill as well as to explore its mechanism of action in treating ophthalmic diseases. System pharmacology is a method developed based on system biology and multidirectional pharmacology, which provides a powerful tool for revealing the mechanism of drugs at the molecular level by combining ADME (Absorption, Distribution, Metabolism, and Excretion) screening, target fishing, network construction, and analysis.[10,11]

Presently, using systems pharmacology method, the mechanism of action of Qiju Dihuang pill in the treatment of ophthalmic diseases is explored. First, using computational ADME system, the potential active components of Qiju Dihuang pill were screened. Second, employing a systems drug targeting approach, the corresponding targets of these active ingredients were identified. Subsequently, the interactions between the active compounds and targets were visualized as biological networks. Besides, molecular docking was performed to further verify the reliability of the drug-target interaction. In final, GO and KEGG enrichment analysis were carried out to elucidate the biological function of the obtained targets related to ophthalmic diseases. This work not only provides insight into the therapeutic mechanism of herbal medicine in the treatment of ophthalmic diseases at a systematic perspective, but also offers an effective approach for drug discovery and development of TCM, which is of great significance for wide clinical application of Qiju Dihuang pill.

2. Methods

No ethical permits were required for this work, which involved no experimentation on animals or human samples.

2.1. Screening of drug compositions

The ingredients of herbs in Qiju Dihuang pill were obtained from TCM Systems Pharmacology Database (TCMSP) and 2 pharmacokinetic parameters including oral bioavailability (OB) and drug-like drug (DL) were used further screening the potential compounds of this formula. Presently, a powerful in-house tool, the OBioavail1.1 model,[12] was implemented to calculate the OB values of candidate compounds. In addition, a predictive drug similarity model was developed to distinguish drug-like and nondrug-like for each compound by using the Tanimoto coefficient.[13]

The thresholds values of OB and DL were set at 30% and 0.15, respectively. Compounds that meet OB ≥ 30% and DL ≥ 0.15 were retained as candidate active ingredients.

2.2. Target prediction

TCMSP database was used to predict the targets of the effective active components in Qiju Dihuang pill. All the obtained predicted target protein were converted into the corresponding human gene by using the human tissue specimen in UniProt ("organization" option and selecting "Homo sapiens human").[14]

2.3. Network construction

Presently, 3 networks, that is, compound-target (C-T), target-function (T-F), and protein-protein interactions (PPI) networks were constructed and analyzed by using Cytoscape3.8.0.[15] In these nets, nodes represent the compounds, targets or protein function, while edges represent the relationships of compounds-targets, targets-functions, and protein-protein. Using the Network Analyzer and CentiScaPe 1.2 plugged-in the Cytoscape 3.8.0,[15] 2 important topological parameters "degree" and "betweenness" in the networks are calculated.

2.4. Biological function enrichment analysis

To accurately explore the biological functions of the obtained targets related with ophthalmic diseases, the Gen Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis were performed employing the online tools Genemania (http://genemania.org/), Metascape (https://metascape.org/gp/index), and WeShengXin (http://www.bioinformatics.com.cn/).[16] The species of the targets were set as human, and GO-molecular function (GO-MF), GO-biological process (GO-BP), GO-cellular component (GO-CC), KEGG, protein-protein interaction (PPI) network were selected for further study.

2.5. Molecular docking

Further, to reveal the potential molecular mechanism of Qiju Dihuang pill in the treatment of ophthalmic diseases, 4 C-T interactions from the hub compounds and targets were selected for molecular docking validations by using the Autodock (version 4.2).[17] During the docking process, the original ligand was removed from the Well coordination set and the ordered water molecules in the binding pocket were considered. The crystal structures of all the target proteins were download from PDB Database. The radius around the ligand is set to 10 Å as the binding pocket. In addition, to evaluate all the conformations of the compound, the score fitness function is used, which takes into account the contribution of hydrogen bond energy and van der Waals interaction between the target and the compounds.

3. Results

3.1. Screening bioactive components of Qiju Dihuang pill

Currently, a total of 134 candidate active ingredients in herbs of Qiju Dihuang pill met the screening criteria and the top 20 bioactive compounds with their corresponding OB and DL values are depicted in Table 1. Obviously, in medicinal herb *Lyii Fructus*, there are 50 active ingredients meeting the screening criteria of OB ≥ 30% and DL ≥ 0.15, showing their good pharmacokinetic properties. Among them, physalin A with the highest OB, also shows a good DL value. In addition, there are 20 active ingredients filtered from *Chrysanthemi Flos*, while *Corni Fructus* contains 17 active ingredients. For *Moutan Cortex*, it contains 8 active ingredients and *Dioscoreae Rhizoma* contains 13 active ingredients. With respect to *Poria*, it screened out 13 active ingredients. Besides, *Alismatis Rhizoma* contains 13 active ingredients. All these bioactive ingredients in herbs are added into active ingredients database for further target fishing.

3.2. Target prediction

In order to investigate the molecular mechanism of herbal medicine of Qiju Dihuang pill in the treatment of ophthalmic diseases, the target proteins of these active components were identified by the comprehensive method in TCMSP. The result shows that a total of 72 candidate targets are identified for 129 compounds, while other 5 ingredients have no related targets. The top 23 targets corresponding to the effective components of Qiju Dihuang pill with their details are illustrated in Table 2.

3.3. The pharmacology synergy from network level

3.3.1. Component-target network. After removing 5 compounds with no targets, the resulting 129 candidate compounds with their corresponding 72 potential targets

Table 1

The top 20 bioactive compounds with their OB and DL values.

ID	Compound name	OB	DL	Herbs
GQZ44	Physalin A	91.71	0.27	*Lyii Fructus*
SY10	Diosgenin	80.88	0.81	*Dioscoreae Rhizoma*
SZY07	3-dibenzo furan sulfonic acid	74.42	0.16	*Corni Fructus*
GQZ43	Maaliol	71.19	0.15	*Lyii Fructus*
SZY13	Telocinobufagin	69.99	0.79	*Corni Fructus*
SZY16	Gemin D	68.83	0.56	*Corni Fructus*
MDP01	Paeoniflorin_qt	68.18	0.40	*Moutan Cortex*
MDP05	4-*O*-methylpaeoniflorin_qt	67.24	0.43	*Moutan Cortex*
MDP08	Paeonidanin_qt	65.31	0.35	*Moutan Cortex*
SY05	Hancinol	64.01	0.37	*Dioscoreae Rhizoma*
SY03	Denudatin B	61.47	0.38	*Dioscoreae Rhizoma*
SY02	(–)-Taxifolin	60.51	0.27	*Dioscoreae Rhizoma*
JH17	Naringenin	59.29	0.21	*Chrysanthemi Flos*
SY06	Hancinone C	59.05	0.39	*Dioscoreae Rhizoma*
SZY04	Malkangunin	57.71	0.63	*Corni Fructus*
MDP02	MAIRIN	55.38	0.78	*Moutan Cortex*
MDP03	(+)-catechin	54.83	0.24	*Moutan Cortex*
SY04	Kadsurenone	54.72	0.38	*Dioscoreae Rhizoma*
GQZ15	Glycitein	50.48	0.24	*Lyii Fructus*
JH06	Isorhamnetin	49.60	0.31	*Chrysanthemi Flos*

DL = drug-like, OB = oral bioavailability.

Table 2

The top 23 targets corresponding to the effective components of Qiju Dihuang pill.

Gene	Protein name	UniProt ID
ACHE	Acetylcholinesterase	P22303
ADRA1A	Alpha-1A adrenergic receptor	P35348
ADRA1B	Alpha-1B adrenergic receptor	P35368
ADRA1D	Alpha-1D adrenergic receptor	P25100
ADRA2A	Alpha-2A adrenergic receptor	P08913
ADRA2B	Alpha-2B adrenergic receptor	P18089
ADRA2C	Alpha-2C adrenergic receptor	P18825
ADRB1	Beta-1 adrenergic receptor	P08588
ADRB2	Beta-2 adrenergic receptor	P07550
AR	Androgen receptor	P10275
BACE1	Beta-secretase 1	P56817
CA2	Carbonic anhydrase 2	P00918
CALM1	Calmodulin	P62158
CCNA2	Cyclin-A2	P20248
CDK2	Cell division protein kinase 2	P24941
CHEK1	Serine/threonine-protein kinase Chk1	O14757
CHRM1	Muscarinic acetylcholine receptor M1	P11229
CHRM2	Muscarinic acetylcholine receptor M2	P08172
CHRM3	Muscarinic acetylcholine receptor M3	P20309
CHRM4	Muscarinic acetylcholine receptor M4	P08173
CHRM5	Muscarinic acetylcholine receptor M5	P08912
CHRNA2	Neuronal acetylcholine receptor subunit alpha-2	Q15822
CHRNA7	Neuronal acetylcholine receptor subunit alpha-7	P36544

were applied to generate the C-T network. Figure 1 shows a global view of this network, in which circle nodes represent the herbal ingredients and the octagon nodes represent their corresponding target proteins. Obviously, it is observed that a single active ingredient can act on multiple targets, and a single target can be acted on multiple active ingredients, indicating the polypharmacology effects of Qiju Dihuang pill.

3.3.2. Target-function network. As shown in Figure 2, T-F network was established by using the target proteins. Clearly, the targets of Qiju Dihuang pill are mainly associated with immune regulation and inflammatory response, revealing that this formula mainly regulates these 3 aspects to treat ophthalmic diseases.

3.4. PPI network analysis

To further explore the interaction between proteins, a PPI network was constructed, which was shown in Figure 3. The targets in Figure 3 were seem as core targets, and a total of 39 core targets were obtained. Among these targets, estrogen receptor (ESR1), glucocorticoid receptor (NR3C1), and androgen receptor (AR) were found, which play crucial roles in the treatment of ophthalmic diseases.[18]

3.5. Analysis of biological function enrichment

In order to research the main functions of relevant targets, we used the online tool GeneMANI for enrichment analysis, which was shown in Figure 4. The results show that the targets of Qiju Dihuang pill-related ophthalmic diseases mainly participated in Monoamine G protein-coupled receptors (GPCRs), blood circulation, calcium signaling pathway, monoamine transport, and regulation of ion transport, behavior, rhythmic process, suggesting that Qiju Dihuang pill achieved the therapeutic effect for treating ophthalmic diseases through the above process.

3.6. Gene ontology enrichment analysis

To explore whether the selected targets are related to immune and inflammatory responses, the functional bioinformatics analysis of the obtained targets are performed. All the targets are introduced into Metascape to perform GO enrichment analysis from 3 aspects including MF, CC, and BP enrichment analysis, respectively. As depicted in Figure 5, the target proteins of Qiju Dihuang pill are involved in many processes, and these processes could be used for the regulation of ophthalmic diseases. For example, target proteins Alpha-1A adrenergic receptor (ADRA1A), Muscarinic acetylcholine receptor M1 (CHRM1), 5-hydroxytryptamine 2C receptor (HTR2C), and Delta-type opioid receptor (OPRD1) can be coupled to cyclic nucleotide second messenger, and in turn regulate the intraocular pressure.[19] At the same time, the targets can also affect the growth and reproduction of corneal epithelial cells.[20] Besides, target proteins like ADRA1A, CHRM1, and HTR2C are mainly affected G protein-coupled amine receptor activity, affecting immune regulation.[20]

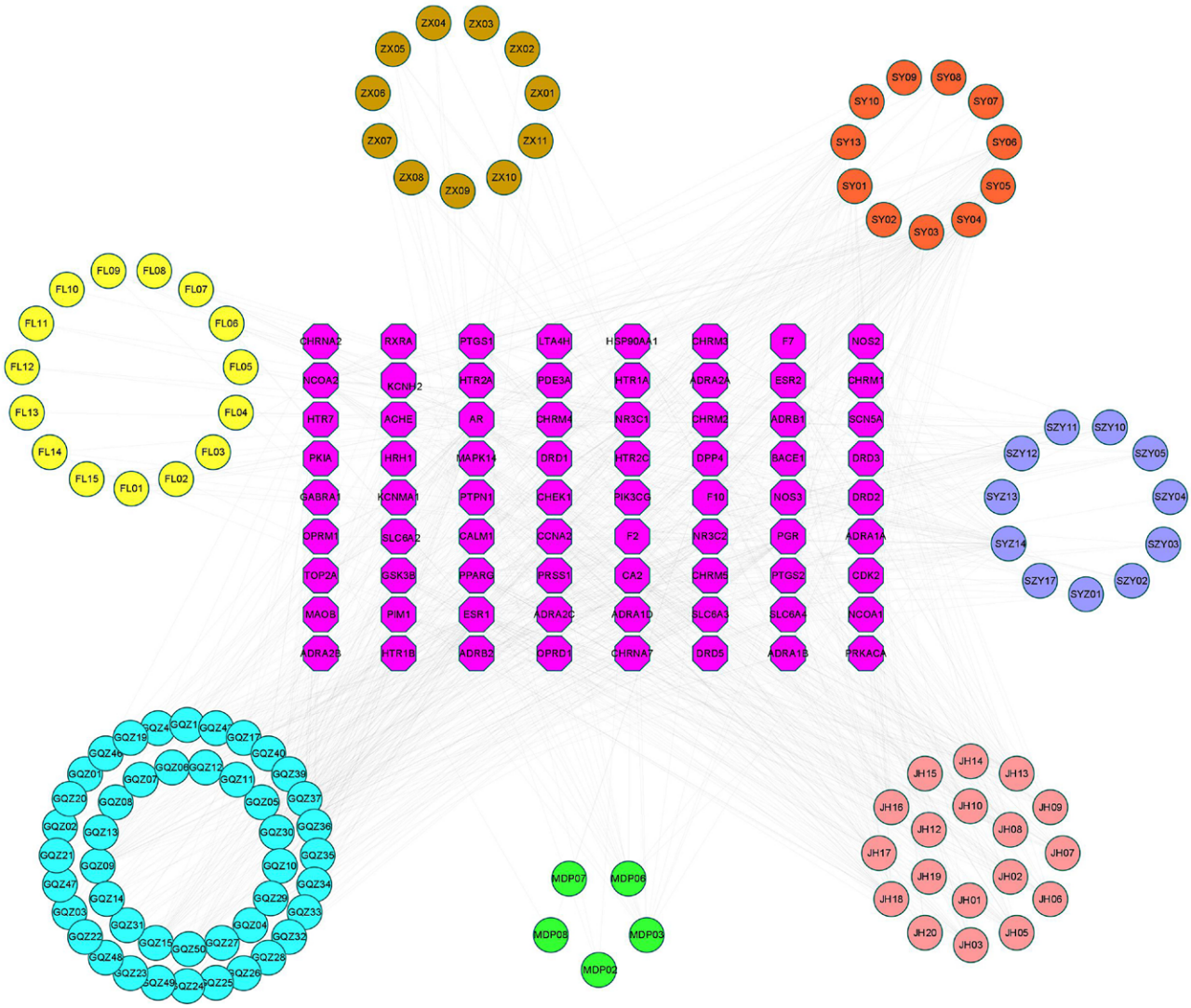

Figure 1. The component—target network, the active compounds and targets are denoted by the circles and octagons, respectively.

3.7. Target-pathway analysis

In addition to the multicomponents and multitargets features, herbal medicines also have the characteristic of multiple biological pathways when they present the favorable therapeutic effects in the treatment of diseases. Consequently, the pathway enrichment analysis was also carried out and the result was shown in Figure 6. It was observed that calcium signaling pathway, insulin signaling pathway and vascular endothelial growth factor (VEGF) signaling pathway were ranked from large to small in terms of the number of related genes, demonstrating that Qiju Dihuang pill mainly acted through these pathways to present the therapeutic effect on ophthalmic diseases.

3.8. Molecular docking

In order to explore the main drug-target binding modes and to increase the reliability of target fishing, the predicted compound-target interactions are validated using molecular docking. As demonstrated in Figures 7 and 8, Hydrogen bond interactions play a key role in influencing the binding affinity between active ingredients and target proteins. In addition, according to the network analysis, 4 crucial active ingredients with their key corresponding target proteins were selected to perform detailed docking analysis.

As shown in Figures 7A and 8A, Alisol B is anchored into a hydrophobic pocket in AR, which is formed by residues Phe891, Leu704, Thr877, LEU707, Met780, Met895, Asn705, and Gly708. Through observation of Figures 7B and 8B, it is found that glycitein is anchored into a hydrophobic pocket in CDK2, which consists of residues Phe891, Leu704, Thr877, LEU707, Met780, Met895, Asn705, Gly70, Lys33, Asp145, Glu12, Gly13, Gln131, Leu134, Leu83, Phc82, Glu81, and Ala31. With respect to the compound hutenlin, it is anchored into a hydrophobic pocket in MAPK14, which is composed of residues Val83, Leu74, Ser56, His64, Arg57, His148, Ile141, Asp168, Leu167, Gly170, Thr68, and Arg70 (Figs. 7C and 8C). Additionally, Figures 7D and 8D demonstrate that Telocinobufagin is anchored into a hydrophobic pocket in NR3C1, which is formed by residues Thr739, Asn564, Met560, Met639, Leu563, Arg611, Met604, Leu732, Leu608, Phe623, Met601, Tyr735, and Cys736. Interestingly, we found that Thr739, Asn564, Met560, H-binding patterns are observed in all these docking simulations, indicating that the drug-amino acid complex can obtain stable structure after combining.[21,22]

4. Discussion

Currently, we aims to discover the bioactive components and targets of Qiju Dihuang pill in the treatment of ophthalmic

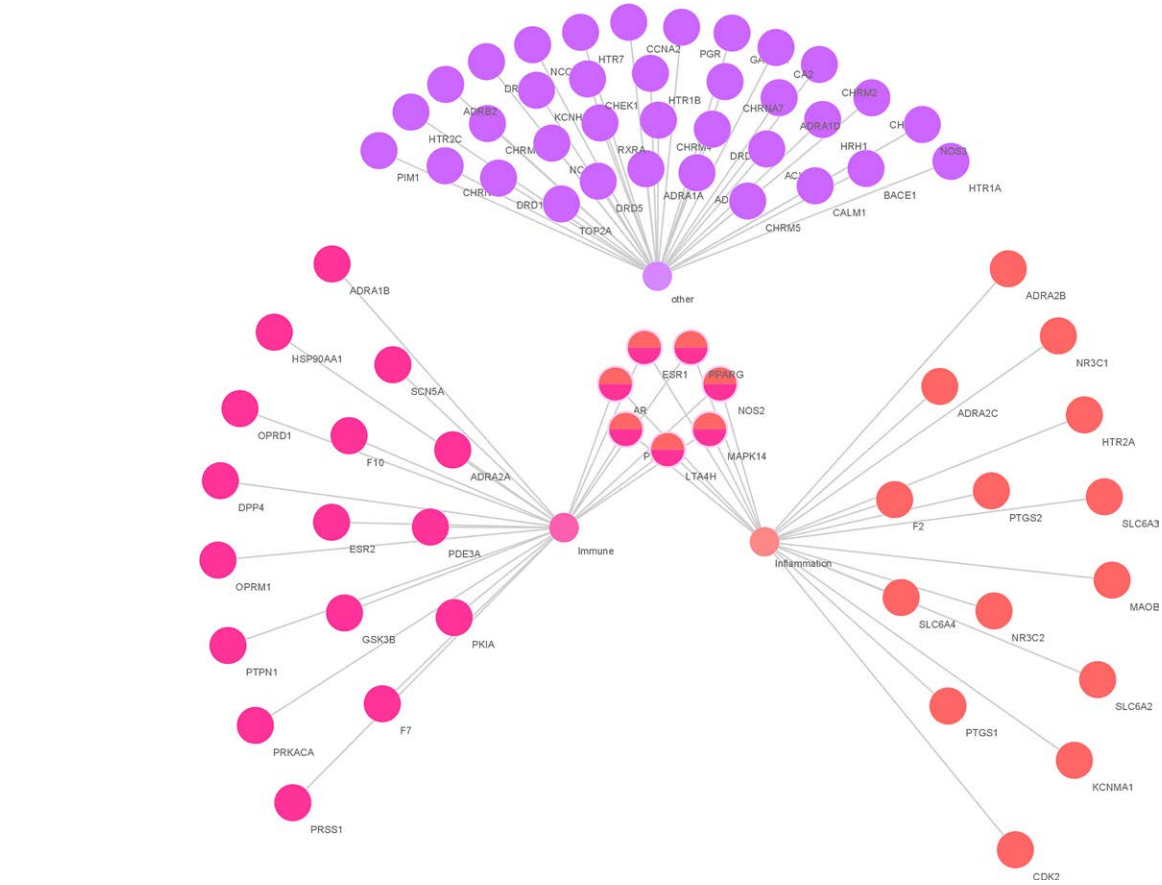

Figure 2. The target-function network.

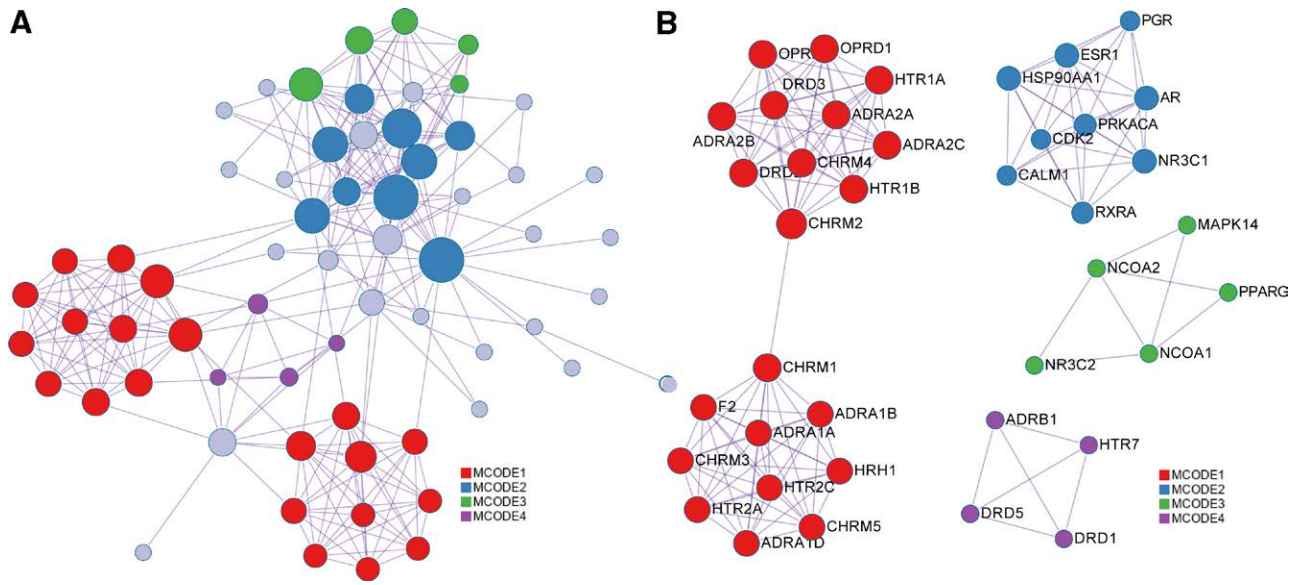

Figure 3. (A) PPI networks analysis. (B) The core targets extracting from all targets. PPI = protein-protein interactions.

diseases employing system pharmacology method. The most inspiring aspect of this paper is the discovery of 3 core targets including CHRM1, ESR1, and AR and 3 important biological pathways, that is, calcium signaling pathway, insulin signaling pathway and VEGF signaling pathway. All these results demonstrate that the mechanism of Qiju Dihuang pill in treating ophthalmic diseases is through its critical target proteins by regulating the key signal pathways.

In detail, we have previously present that the main active components of *Lycium barbarum* in Qiju Dihuang pill are polysaccharides and polyphenols (Table 1). Actually, modern pharmacological researches have suggested that these 2 compounds

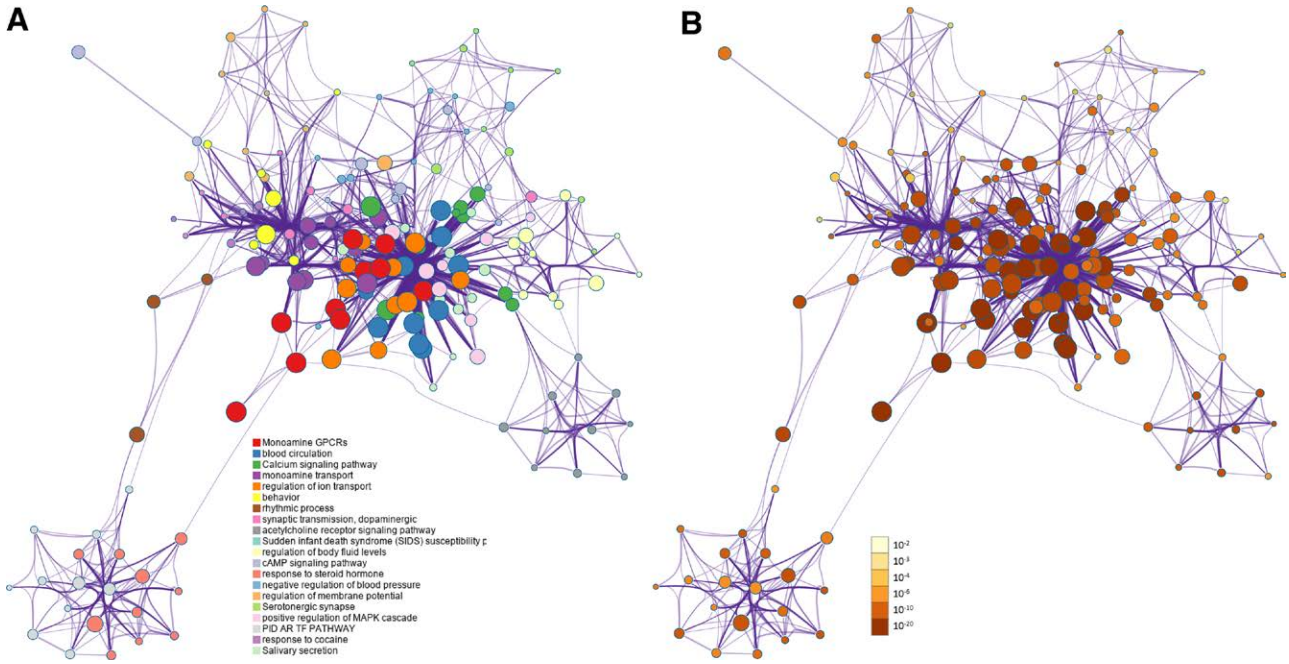

Figure 4. Biological processes enrichment analysis from the potential targets.

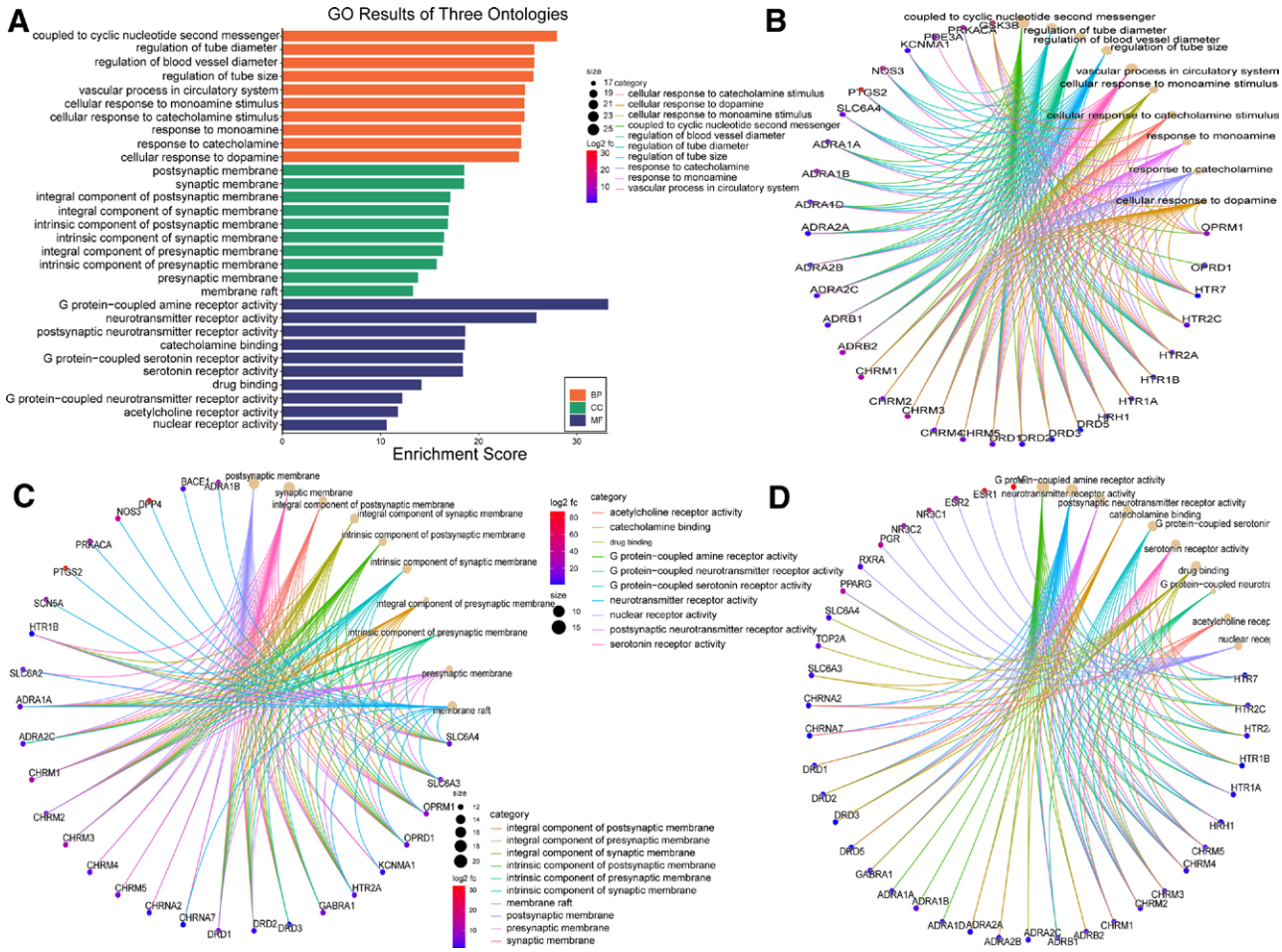

Figure 5. (A) GO analysis of the targets. (B–D) Network to donate the relationship between GO terms and potential targets, which are related to molecular function, cell components, biological process, respectively. GO = gene ontology.

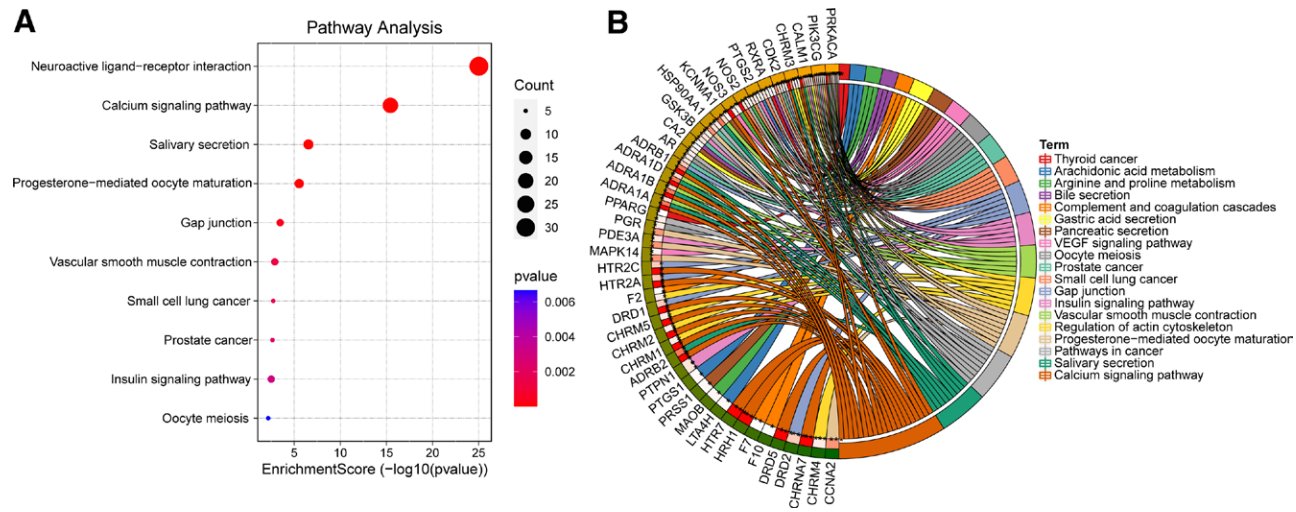

Figure 6. KEGG enrichment analysis from the potential targets. KEGG = Kyoto Encyclopedia of Genes and Genomes.

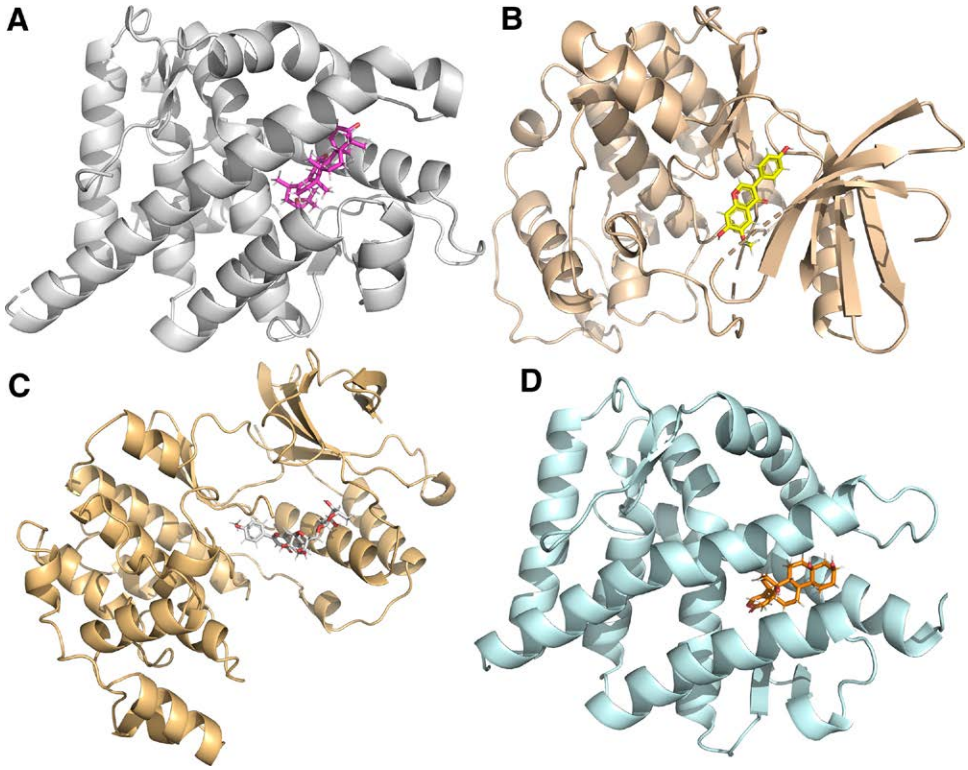

Figure 7. Stereo view of binding mode for compound with its receptors. (A) Alisol B and AR. (B) Glycitein and CDK2. (C) Hutenlin and MAPK14. (D) Telocinobufagin and NR3C1. AR = androgen receptor.

can stimulate human endogenous factors and enhance the activity of antioxidant enzymes, showing the therapeutic effect on ophthalmic diseases.[23,24] In addition, the main ingredients of herbal medicine *Chrysanthemum Flos* in Qiju Dihuang pill is flavonoids and volatile oil. Actually, many studies[25,26] have demonstrated that these compounds can reduce blood glucose, protect vasodilation reactivity and enhance myocardial contractility. Consistent with this study, polysaccharides and 5-hydroxymethylfurfural are found in *Rehmanniae Radix Praeparata* of Qiju Dihuang pill, which have been reported that can promote the proliferation of endothelial cells and enhance immunity.[27,28]

Additionally, a total of 134 active ingredients with 72 corresponding targets are identified from Qiju Dihuang pill (Tables 1 and 2). And 3 core targets including CHRM1, ESR1 and AR are obtained from the ingredients and drug targets network analysis (Figs. 1 and 2). Besides, GO and KEGG pathway enrichment analysis reveal 3 important biological pathways, that is, Calcium signaling pathway, Insulin signaling pathway and VEGF signaling pathway (Figs. 5 and 6). Actually, VEGF is a vascular permeability factor, which can not only promote the proliferation of vascular endothelial cells, but also induce vascular proliferation.[29] At the same time, it can regulate vascular permeability and participate in biological processes such as

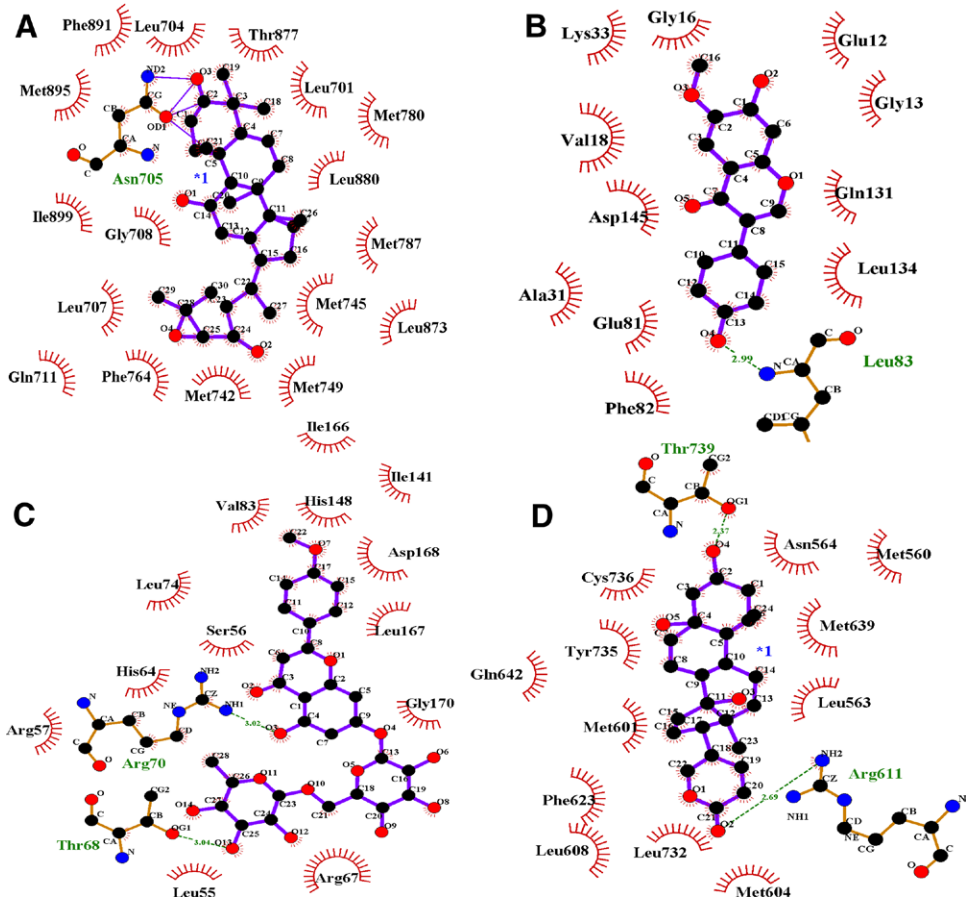

Figure 8. The specific view of the 2D ligand interaction. (A) Alisol B and AR. (B) Glycitein and CDK2. (C) Hutenlin and MAPK14. (D) Telo Cinobufagin and NR3C1. AR = androgen receptor.

vascular endothelial cell migration, body repair and damage. At present, various anti VEGF drugs used in ophthalmology clinic inhibit the growth of choroidal neovascularization and vascular leakage by inhibiting the binding of VEGF to receptors, improving or maintaining the vision of patients. This confirmed the correlation between the occurrence of eye diseases and VEGF signaling pathway. Besides, studies have found that under normal circumstances, the expression level of VEGF in ocular tissues is low. However, under the stress conditions of ischemia, hypoxia and inflammation, the expression level of VEGF will increase significantly and then induce neovascularization, leading to the occurrence of eye diseases.[29] Therefore, it can be inferred that Qiju Dihuang pill play a crucial role in the treatment of eye diseases by reducing the abnormally increased VEGF expression in the body (Figs. 3 and 4).

In addition, insulin signaling pathway mainly activates 2 signaling pathways in cells: mitogen activated protein kinases and phosphoinositide-3-kinase (PI3K) pathways, which control cell growth, metabolism and survival. In fact, PI3K can be activated by G protein-coupled receptor or receptor tyrosine kinase. The activated PI3K phosphorylates PIP2 and produce PIP3. PIP3 activates PDK1 and PDK2 as the second signal in the cell, and then recruits Akt to the cell membrane to phosphorylate Akt and activate its protein kinase activity. Akt phosphorylates many downstream signaling molecules, including phosphorylated glycogen synthase kinase—3β, and lead to the transfer of glucose transporter-2 (GLUT-2) and GLUT-4 from cytosol to plasma membrane, promote cell glucose uptake and inhibit glycogen synthesis, so as to reduce blood glucose.[30] Some results showed that hypoxia ischemia caused by high glucose could activate the expression of Akt in PI3K/Akt signaling pathway in endothelial cells, increase its phosphorylation, and then reduce blood glucose. The mechanism of enhanced signal transduction in PI3K/AKT signaling pathway is believed to be useful in guiding the treatment of diabetic retinopathy.[31] Therefore, we can infer that Qiju Dihuang pill may maintain the blood glucose balance through the insulin signaling pathway, and then prevent and cure the occurrence and development of diabetic ophthalmopathy.

For the calcium signaling pathway, the voltage control channels of excitable cells are controlled by the change of membrane voltage. When there is an electrochemical gradient, Ca^{2+} enters into the cell from outside of the cell. When the concentration of Ca^{2+} in cytoplasm or specific organelles changes, a large number of Ca^{2+} interacting proteins are activated or inhibited. As an important second messenger, Ca^{2+} is involved in regulating physiological activities such as cell growth, differentiation, proliferation and apoptosis. Studies have shown that both extracellular Ca^{2+} influx and endoplasmic reticulum Ca^{2+} release can activate PI3K—Akt—mTOR signaling pathway.[32] Therefore, it is speculated that Qiju Dihuang pill can regulate the occurrence of eye diseases through calcium signaling pathway.

5. Conclusion

Presently, system pharmacology method was employed to clarify the mechanism of action of Qiju Dihuang pill in treating ophthalmic diseases, the findings are as follows:

(1) Eight Chinese herbal medicines in Qiju Dihuang Pill screened out 134 compounds that satisfied the pharmacokinetic characteristics and 72 drug targets were obtained;

(2) Through the analysis of PPI network, 3 core targets including CHRM1, ESR1, and AR were obtained. And the GO and target-pathway analysis demonstrates that the effective components of Qiju Dihuang pill can be used to treat diabetic ophthalmopathy with calcium signaling pathway, insulin signaling pathway and VEGA signaling pathway.
(3) Molecular docking results suggest that the targets and active ingredients screened could interact with each other, further revealing the reliability of the system pharmacology method.

Overall, Qiju Dihuang pill may regulate CHRM1, ESR1, AR targets through calcium signaling pathway, Insulin signaling pathway and VEGF signaling pathway to treat ophthalmic diseases.

Acknowledgments

We would like to acknowledge the senior administrators and microbiology staff at Anhui Medical College and The Second Affiliated Hospital of Anhui Medical University for facilitating the study. In addition, this project was supported by the outstanding young backbone talents of colleges and universities have visited and studied at home and abroad (Fund number: gxgnfx2021182).

Author contributions

Conceptualization: Fei Liu, Mi Tian.
Data curation: Fei Liu, Mi Tian.
Formal analysis: Fei Liu, Mi Tian.
Methodology: Fei Liu, Mi Tian.
Resources: Fei Liu, Mi Tian.
Writing—original draft: Fei Liu, Mi Tian.
Writing—review and editing: Fei Liu, Mi Tian.

References

[1] Jonas JB, Aung T, Bourne RR, et al. Glaucoma. Lancet. 2017;390:2183–93.
[2] Lee CM, Afshari NA. The global state of cataract blindness. Curr Opin Ophthalmol. 2017;28:98–103.
[3] Ige M, Liu J. Herbal Medicines in glaucoma treatment. Yale J Biol Med. 2020;93:347–353. Published 2020 Jun 29.
[4] Pang B, Li QW, Qin YL, et al. Traditional Chinese medicine for diabetic retinopathy: a systematic review and meta-analysis. Medicine (Baltim). 2020;99:e19102.
[5] Chen X, Li L, Xu X, et al. Tianma gouteng decoction combined with Qiju Dihuang pill for the treatment of essential hypertension: a protocol for systematic review and meta-analysis. Medicine (Baltim). 2020;99:e21157.
[6] Wang J, Xiong X, Yang G, et al. Chinese herbal medicine Qi Ju Di Huang Wan for the treatment of essential hypertension: a systematic review of randomized controlled trials. Evid Based Complement Alternat Med. 2013;2013:262685.
[7] Yue ZJ, Zou ZD, Li DH, et al. Effect of reinforcing kidney on blood pressure and kidney blood stream in SHR. Zhong Guo Shi Yan Fang Ji Xue Za Zhi. 2009;15:42–4.
[8] Duo FF, Zou ZD, Wang WJ, et al. Effect of Qi Ju Di Huang Wan on injured vascular endothelial cell ultrastructure induced by Ang II. Zhong Guo Yi Yao Dao Kan. 2010;12:1751–2.
[9] Yue ZJ, Zou ZD, Li DH, et al. Effect of reinforcing kidney on blood pressure and kidney function in SHR. Zhong Guo Shi Yan Fang Ji Xue Za Zhi. 2009;15:63–5.
[10] Wang JH, Li Y, Yang YF, et al. Systems pharmacology dissection of multi-scale mechanisms of action for herbal medicines in treating rheumatoid arthritis. Mol Pharmaceutics. 2017;14:3201–17.
[11] Wang JH, Yang YF, Li Y, et al. Computational study exploring the interaction mechanism of benzimidazole derivatives as potent cattle bovine viral diarrhea. J Agric Food Chem. 2016;64:5941–50.
[12] Xu X, Zhang W, Huang C, et al. A novel chemometric method for the prediction of human oral bioavailability. Int J Mol Sci. 2012;13:6964–82.
[13] Willett P, Barnard JM, Downs GM, et al. Chemical similarity searching. J Chem Inf Comput Sci. 1998;38:983–96.
[14] Zheng L, Wen XL, Dai YC. Mechanism of Jianpi Qingchang Huashi recipe in treating ulcerative colitis: a study based on network pharmacology and molecular docking. World J Clin Cases. 2021;9:7653–70.
[15] Wei J, Ma L, Liu W, et al. Identification of the molecular targets and mechanisms of compound mylabris capsules for hepatocellular carcinoma treatment through network pharmacology and bioinformatics analysis. J Ethnopharmacol. 2021;276:114174.
[16] Chen Y, Chu F, Lin J, et al. The mechanisms of action of WeiChang'An Pill (WCAP) treat diarrhoea-predominant irritable bowel syndrome (IBS-D) using network pharmacology approach and in vivo studies. J Ethnopharmacol. 2021;275:114119.
[17] Yuan C, Wang MH, Wang F, et al. Network pharmacology and molecular docking reveal the mechanism of Scopoletin against non-small cell lung cancer. Life Sci. 2021;270:119105.
[18] Wen S, Zhong Z, He L, et al. Network pharmacology dissection of multiscale mechanisms for jiaoqi powder in treating ulcerative colitis. J Ethnopharmacol. 2021;275:114109.
[19] Høyland-Kroghsbo NM. Cyclic nucleotide signaling: a second messenger of death. Cell Host Microbe. 2019;26:567–8.
[20] Feng P, Li G, Huang Y, Pei J. Systematic investigation of the effect of powerful Tianma Eucommia capsule on ischemic stroke using network pharmacology. Evid Based Complement Alternat Med. 2021;2021:8897313. Published 2021 Jun 4.
[21] Tao Z, Zhang L, Friedemann T, et al. Systematic analyses on the potential immune and anti-inflammatory mechanisms of Shufeng Jiedu capsule against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)-caused pneumonia. J Funct Foods. 2020;75:104243.
[22] Wang E, Wang L, Ding R, et al. Astragaloside IV acts through multiscale mechanisms to effectively reduce diabetic nephropathy. Pharmacol Res. 2020;157:104831.
[23] Gao Y, Wei Y, Wang Y, et al. Lycium barbarum: a traditional Chinese herb and a promising anti-aging agent. Aging Dis. 2017;8:778–791. Published 2017 Dec 1.
[24] Tian X, Liang T, Liu Y, et al. Extraction, structural characterization, and biological functions of polysaccharides: a review. Biomolecules. 2019;9:389. Published 2019 Aug 21.
[25] Shao Y, Sun Y, Li D, et al. Chrysanthemum indicum L.: A comprehensive review of its botany, phytochemistry and pharmacology. Am J Chin Med. 2020;48:871–97.
[26] Li Y, Yang P, Luo Y, et al. Chemical compositions of chrysanthemum teas and their anti-inflammatory and antioxidant properties. Food Chem. 2019;286:8–16.
[27] Li HY, Fang JJ, Shen HD, et al. "Quantity-effect" research strategy for comparison of antioxidant activity and quality of rehmanniae radix and rehmannia radix praeparata by on-line HPLC-UV-ABTS assay. BMC Complement Med Ther. 2020;20:16. Published 2020 Jan 17.
[28] Li M, Jiang H, Hao Y, et al. A systematic review on botany, processing, application, phytochemistry and pharmacological action of radix rehmnniae [published online ahead of print, 2021 Nov 10]. J Ethnopharmacol. 2022;285:114820.
[29] Ling CS, Feng ZK, et al. Curcumin through Akt/ HIF-1 α/ Mechanism of VEGF signaling pathway inhibiting choroidal neovascularization in vitro. Int J Ophthalmol. 2022;22:541–8.
[30] Mei ZS, Juan YQ. Insulin signaling pathway and insulin resistance. Abstr world's latest Med Info. 2019;19:62–3.
[31] Na LY, Yun XF. Mechanism of PTEN/PI3K/AKT pathway alleviating diabetic retinopathy. Chin J Gerontol. 2020;40:3767–70.
[32] Hong HC, Long XW, Dong W, et al. Network pharmacological study on the mechanism of anti pulmonary fibrosis of maimendong decoction. J Shandong Univ Tradit Chin Med. 2022;46:201–9.