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ORIGINAL RESEARCH

Medication Rules and Mechanism of Topical Traditional Chinese Medicine for Meibomian Gland Dysfunction-Related Dry Eye Disease

Huan Zhou, MM; Qiping Wei, MM; Lin Yang, MM; Ying Gao, MM

ABSTRACT

Objective • To summarize the use of traditional Chinese medicine in the treatment of meibomian gland dysfunction-related dry eye disease through data mining. Additionally, it aims to explore the signaling pathways and mechanisms of critical drugs used in the treatment of this condition through network pharmacology analysis.

Methods • Clinical trial literature on the topical application of traditional Chinese medicine for meibomian gland dysfunction-related dry eye disease in the past 20 years was collected from Chinese academic databases (Zhiwang, Wanfang Data, and Weipu). Association rule analysis and clustering analysis were performed using IBM SPSS. Active ingredients and target sites of critical drugs were obtained from the TCSMP and BATMAN-TCM databases. Disease target sites were sourced from databases such as DrugBank and OMIM. The drug-disease intersecting target genes were used to construct a protein-protein interaction (PPI) network in the String database. Common target genes were subjected to GO function and KEGG signaling pathway enrichment analyses using the DAVID platform. The molecular docking of active ingredients and key targets was validated using AutoDock Vina (1.1.2).

Results • A total of 93 Chinese herbal medicines in 56 prescriptions were collected. The critical drugs identified were *flos chrysanthemi, flos lonicerae japonicae, fructus forsythiae, radix scrophulariae, radix rehmanniae recens,* and *radix ophiopogonis*. There were 63 active ingredients and 905 potential targets. Key targets identified through PPI analysis included AKT1, TP53, TNF, EGFR, IL6, VEGFA, IL1B, INS, EGF, and CXCL8. GO function analysis revealed processes such as positive regulation of expression, positive regulation of cell proliferation, negative regulation of apoptosis, and inflammatory reactions. The main signaling pathways identified were the MAPK signaling pathway, PI3K-Akt signaling pathway, HIF-1 signaling pathway, calcium signaling pathway, and cytokine-cytokine receptor interactions. Molecular docking indicated relatively strong binding activity between the small molecules of the active ingredients and the target proteins.

Conclusions • The critical drugs analyzed in this study potentially exert therapeutic effects on meibomian gland dysfunction-related dry eye disease by regulating related biological processes such as anti-inflammation and repairing the corneal epithelial barrier. These findings provide a theoretical basis for future research and development of new drugs and subsequent experimental investigations. (*Altern Ther Health Med.* 2023;29(7):126-132).

Huan Zhou, MM; Qiping Wei, MM; Lin Yang, MM; Ying Gao, MM; Department of Ophthalmology, Dongfang Hospital Beijing University of Chinese Medicine, Beijing, China.

Corresponding author: Ying Gao, MM
E-mail: gying0429@163.com

INTRODUCTION

Dry eye disease and meibomian gland dysfunction (MGD) are prevalent ophthalmic conditions.[1,2] Among the different subtypes of dry eye disease, MGD-related dry eye disease is the most common, with approximately 86% of dry eye disease patients exhibiting signs of MGD.[3] In recent years, the incidence of MGD-related dry eye disease has been increasing, and there is a growing trend of the condition affecting individuals at a younger age.[2-3] Despite treatment with Western medicine, complete recovery from the disease is often not achieved, resulting in unmet medical needs for patients.[4]

There is limited documentation regarding the name, diagnosis, and treatment of MGD-related dry eye disease in traditional Chinese medicine. Individualised, precise treatment is typically administered based on the patient's specific condition using a holistic approach and the treatment principle of syndrome differentiation. Traditional Chinese

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medicine has shown effectiveness in treating MGD-related dry eye disease; however, there is a lack of comprehensive data compilation and a clear understanding of its mechanism of action. Therefore, this study aims to utilize data mining and network pharmacology to summarize the use of topical traditional Chinese medicine in the treatment of MGD-related dry eye disease. Furthermore, it aims to explore the targets of active ingredients, signaling pathways, and mechanisms of action, thus providing valuable insights into the holistic approach and syndrome differentiation in traditional Chinese medicine.

MATERIALS AND METHODS

Study Design and Data Collection

Relevant literature spanning from January 2000 to February 2023 was systematically gathered from Chinese academic databases, including Zhiwang, Wanfang Data, and Weipu. The selection of these literature sources followed the latest expert consensuses on the dry eye[1] and MGD.[5] with the *Chinese Pharmacopoeia* (2020 Edition) serving as a supplementary reference. The prescriptions from the collected literature were analyzed for association rules and subjected to systematic clustering using IBM SPSS Modeler 18.1 and IBM SPSS Statistical 25.0 to identify critical drugs.

Network Pharmacology Analysis for Prediction of Key Targets and Signaling Pathways

Screening of Active Ingredients. The active ingredients of the critical drugs were screened using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP). The screening criteria included WM (molecular weight) ≤ 500, DL (drug-likeness) ≥ 0.18, and AlogP (partition coefficient) values between 1 and 3. In cases where no search results were found in TCMSP, the BATMAN-TCM database was used as a supplementary resource. For supplementation, the screening conditions in BATMAN-TCM included WM ≤ 500 and a SwissADME drug-likeness score of two or more "yes" indications. The target proteins were calibrated by specifying the species as human in the UniProt database. Subsequently, the target proteins were de-duplicated and expressed in standard gene names.

Target Identification and Analysis. The targets associated with MGD-related dry eye disease were investigated by querying the GeneCard, OMIM, TTD, and Drugbank databases for relevant entries. A Venn diagram analysis was performed to identify the intersection of drug-disease targets.

Network Construction and Analysis. The intersecting target genes were utilized to construct a "drug-ingredient-target" network using Cytoscape 3.7.2.

Protein-Protein Interaction Network Construction and Analysis. The protein-protein interaction (PPI) network for the intersecting genes was constructed using the String database (https://string-db.org/). The network was built by selecting Homo sapiens as the species, setting the lowest interaction score to 0.7, and keeping the remaining parameters at their default values. Visual analysis of the network was performed using Cytoscape 3.7.2.

Gene Function and Signaling Pathway Analysis using DAVID Database. The target proteins associated with the critical drugs were analyzed using the DAVID database (https://david.ncifcrf.gov/summary.jsp) to perform GO function gene and KEGG pathway analysis. This analysis aimed to explore the roles of these proteins in gene function and signaling pathways relevant to the treatment of MGD-related dry eye disease. Significant findings from the analysis were selected to generate bubble charts.

Molecular Docking Analysis. To verify the interaction activity between the five most important pharmaceutical active ingredients and the key targets, molecular docking was conducted using AutoDock Vina (1.1.2). This analysis examined the binding and affinity between the active ingredients and the target proteins.

RESULTS

Drug Association Rule Analysis and Systematic Clustering Analysis

The association rules reveal significant combinations of traditional Chinese medicine ingredients in the topical prescriptions for MGD-related dry eye disease. See Table 1. The high confidence percentages indicate a strong correlation between the prescribed items, suggesting their potential effectiveness in the treatment of the condition.

Table 1. Association Rule Analysis of Topical Traditional Chinese Medicine Prescriptions

No	Item A	Item B	Frequency	Support (%)	Confidence (%)	Lift
1	*Flos chrysanthemi*	*Radix rehmanniae recens and radix ophiopogonis*	12	21.43	83.33	1.67
2	*Fructus forsythiae*	*Radix scrophulariae and radix rehmanniae recens*	11	19.64	81.82	2.70
3	*Radix ophiopogonis*	*Radix scrophulariae and radix rehmanniae recens*	11	19.64	81.82	1.99
4	*Flos chrysanthemi*	*Radix scrophulariae and radix rehmanniae recens*	11	19.64	81.82	1.64
5	*Radix scrophulariae*	*Fructus forsythiae and flos lonicerae japonicae*	11	19.64	81.82	2.86

Note: The support represents the percentage of prescriptions containing the association rule. Confidence indicates the likelihood of item B being prescribed when item A is included. Lift indicates the degree of association between item A and item B.

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Figure 1. Clustering spectrum of high-frequency topical traditional Chinese medicine for treating MGD-related dry eye disease.

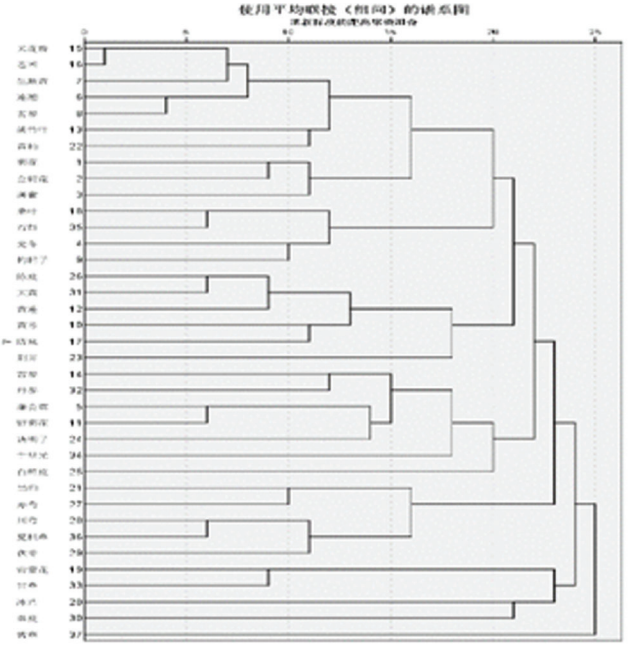


Figure 2. Intersecting target genes of MGD-related dry eye disease and critical drugs

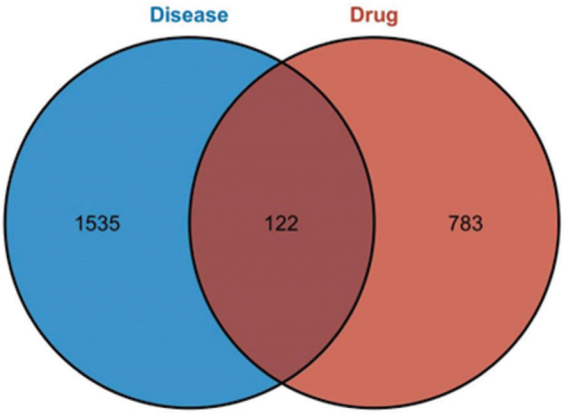


Figure 3. Drug-ingredient-target network of the critical drugs

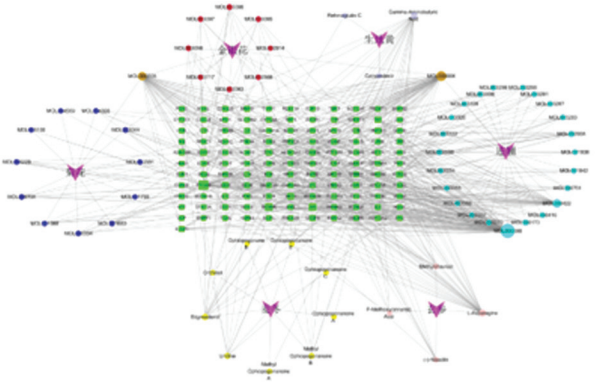
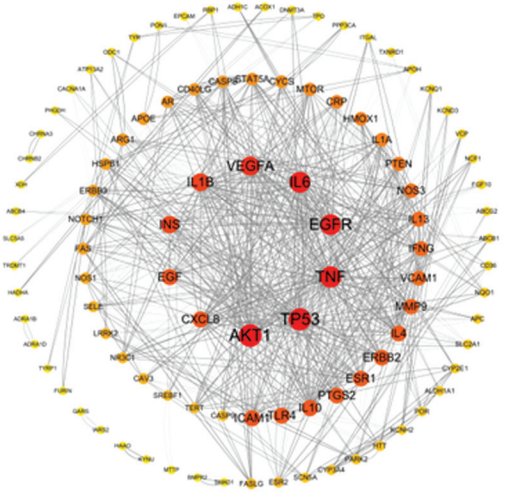


Figure 4. Interaction network of common target proteins of critical drugs and MGD-related dry eye disease



Screening of Active Ingredients and Identification of Potential Targets

15 active ingredients were screened from *flos chrysanthemi*, 13 from *flos lonicerae japonicae*, 27 from *fructus forsythiae*, and 1 from *radix scrophulariae* using TCMSP. Additionally, 4, 4, and 10 active ingredients were supplemented from *radix scrophulariae, radix rehmanniae recens*, and *radix ophiopogonis*, respectively, using BATMAN-TCM. In total, 63 active ingredients from 6 Chinese herbal medicines and 905 potential targets were obtained.

Disease-Related Targets and Screening of Intersection Targets

A total of 1,678 targets related to MGD-related dry eye disease and 122 drug-disease intersection genes were obtained. To visualize the overlapping genes, a Venn diagram was created using the aforementioned information, see Figure 2.

Drug-Ingredient-Target Prediction Results

The drug-ingredient-target prediction resulted in a network with a total of 188 nodes and 582 edges. Among the critical drugs, the top 5 compounds with the highest Degree values were identified as quercetin, luteolin, apigenin, kaempferol, and L-asparagine. Refer to Figure 3 for a detailed visualization of the network.

Construction and Analysis of Target Protein Interaction Network

The target protein interaction network was constructed, resulting in a total of 101 nodes and 838 edges. Among these, AKT1, TP53, TNF, EGFR, IL6, VEGFA, IL1B, INS, EGF, and CXCL8 were identified as the key targets. Please refer to Figure 4 for a detailed visualization of the network.

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Figure 5. Bubble chart of top 10 targets of critical drugs in treating MGD-related dry eye disease by GO function enrichment analysis.

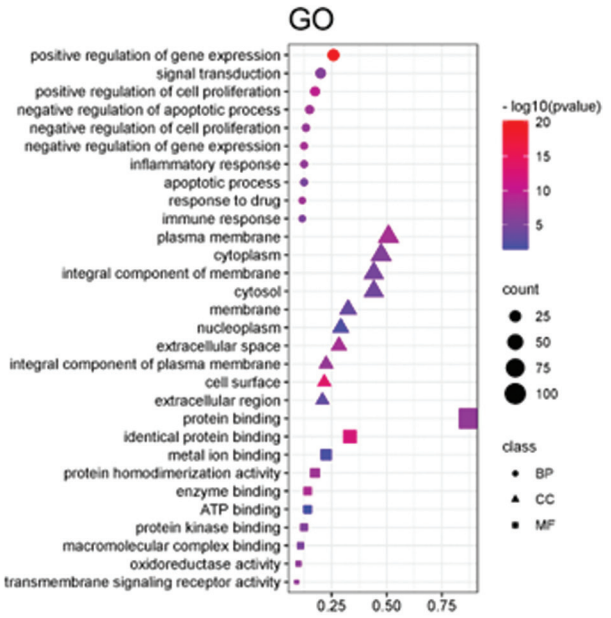

Figure 6. Bubble chart of top 20 targets of critical drugs in treating MGD-related dry eye disease by KEGG pathways enrichment analysis.

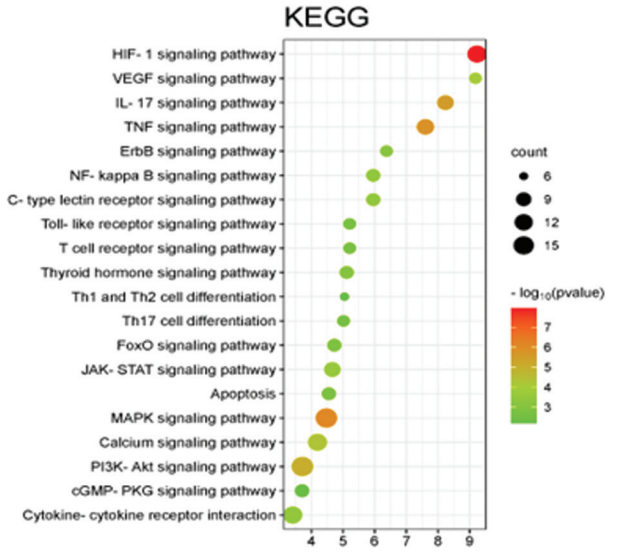

Table 2. Docking Results of Key Small Molecules and Key Target Proteins

Target	PDB ID	Compound	Binding Energy (Kcal/Mol)	Target	PDB ID	Compound	Binding Energy (Kcal/Mol)
Il6	1alu	Mol000098	-4.6	Tnf	2e7a	Mol000098	-4.9
		MOL000006	-7			MOL000006	-8.9
		MOL000008	-6.8			MOL000008	-8.5
		MOL000422	-6.9			MOL000422	-9.1
		MOL000429	-6.8			MOL000429	-9
Akt1	1unq	Mol000098	-4.9	Tp53	1uol	Mol000098	-4.1
		MOL000006	-6.4			MOL000006	-7.1
		MOL000008	-6.2			MOL000008	-6.8
		MOL000422	-6			MOL000422	-6.5
		MOL000429	-5.9			MOL000429	-6.2
Egfr	2gs2	Mol000098	-4.5				
		MOL000006	-7.6				
		MOL000008	-7.5				
		MOL000422	-7.7				
		MOL000429	-7.5				

Note: PDB ID represents the Protein Data Bank identification number. Binding energy values indicate the strength of interaction between the small molecules and the target proteins. Lower values indicate stronger binding affinity.

Abbreviations: IL6, Interleukin-6; TNF, Tumor Necrosis Factor; AKT1: Protein Kinase B; TP53: Tumor Protein p53; EGFR: Epidermal Growth Factor Receptor.

Results of GO Enrichment Analysis and KEGG Pathway Analysis

A comprehensive analysis of 530 biological functions (BP), molecular function (MF), and cell component (CC) entries was conducted, revealing a total of 107 enriched pathways. Utilizing a significance threshold of $P < .05$, the top 10 entries for BP, MF, and CC, as well as the top 20 KEGG metabolic pathways, were presented in bubble charts. Please refer to Figures 5-6 for a visual representation of the results.

Results of Molecular Docking Analysis

The small molecules successfully entered the active center of the target proteins, and the docking results are presented in Table 2. Among them, the small molecules that exhibited the most favorable docking with the top three proteins were selected. The binding energy values represent the strength of interaction between the small molecules and the target proteins. Lower binding energy values indicate stronger binding affinity. The results demonstrate the potential interactions between the small molecules and the

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key target proteins, indicating their potential as therapeutic agents for MGD-related dry eye disease. Schematic representations of the molecular docking interactions are depicted in Figures 7-9.

DISCUSSION

Based on the analysis conducted, the critical drug for treating MGD-related dry eye disease consists of several traditional Chinese medicine components, including *flos chrysanthemi, radix rehmanniae recens, radix ophiopogonis, fructus forsythiae, radix scrophulariae*, and *flos lonicerae japonicae*. These herbal medicines work synergistically to address the underlying imbalances associated with the condition. *Radix rehmanniae recens, radix scrophulariae*, and *radix ophiopogonis* help tonify "Yin," reduce heat, promote fluid production, and alleviate dryness. On the other hand, *flos chrysanthemi, flos lonicerae japonicae*, and *fructus forsythiae* are responsible for dispersing wind heat, clearing heat, and resolving toxins. Combining these herbs helps nourish Yin, clear heat, disperse pathogenic wind, and address the disease's symptoms and root causes.

The drug association rules and clustering analysis employed in this study primarily reflect the treatment principles of nourishing Yin, clearing heat, dispersing wind-heat, eliminating dampness, activating Qi, and improving blood circulation to dredge collaterals. Professor Wei Qiping, a fourth-generation heir of Yanjing Wei's academic school of ophthalmology, has emphasized the reciprocal relationship between MGD and dry eye disease, with both conditions acting as causes and effects of each other.[6] Professor Wei underscores the importance of selecting specific prescriptions and medicines based on individual diseases and symptoms. For ocular surface disorders like dry eye disease and MGD, he highlights the significance of topical treatments that directly target the eyes.[7-11]

An example of an effective clinical prescription is the Qiju Ganlu Powder, which consists of *lycii fructus, flos chrysanthemi, dendrobii caulis, radix glehniae, radix ophiopogonis, polygonati odorati rhizoma, mori folium*, and *menthae haplocalycis herba*.[12-15] This formula aligns with the aforementioned conclusions as *dendrobii caulis, radix glehniae*, *radix ophiopogonis*, and *polygonati odorati rhizoma* tonify Yin, clear heat, generate body fluids, and moisturize dryness. *Flos chrysanthemi, mori folium*, and *menthae haplocalycis herba* disperse wind-heat and enhance the upward movement of the herbal properties toward the eyes. Additionally, *lycii fructus* tonifies the kidney, nourishes the liver, and improves eyesight. The clinical efficacy of Qiju Ganlu Powder provides supporting evidence for the findings discussed in this study.[11,15]

Network pharmacology analysis revealed that quercetin, luteolin, apigenin, kaempferol, and L-asparagine are the main active ingredients involved in the treatment of MGD-related dry eye disease. The gene ontology (GO) analysis indicated that these active ingredients are primarily associated with positive regulation of gene expression, signal transduction, cell proliferation (both positive and negative regulation), apoptosis (negative regulation), negative regulation of gene expression, and inflammatory reactions. Furthermore, the key signaling pathways influenced by these active ingredients include the MAPK signaling pathway, PI3K-Akt signaling pathway, HIF-1 signaling pathway, calcium signaling pathway, and cytokine-cytokine receptor interactions.

Quercetin, luteolin, apigenin, and kaempferol are flavonoids with natural antioxidant, anti-inflammatory, and apoptosis-inducing properties. These compounds have the ability to scavenge free radicals, protect cells from reactive oxygen species (ROS)-induced damage, and promote cell survival. Studies conducted on animal models of dry eye disease and pilot studies in healthy subjects[16] have shown that quercetin can inhibit ROS production, prevent lacrimal cell senescence, and selectively eliminate aging cells damaged by oxidative stress. Administration of high doses of quercetin has also been found to prolong the tear film break-up time (BUT). Quercetin has also demonstrated effectiveness as an anti-inflammatory agent for dry eye disease.[17]

Figure 7. Interaction mode analysis between *luteolin* and AKT1 protein

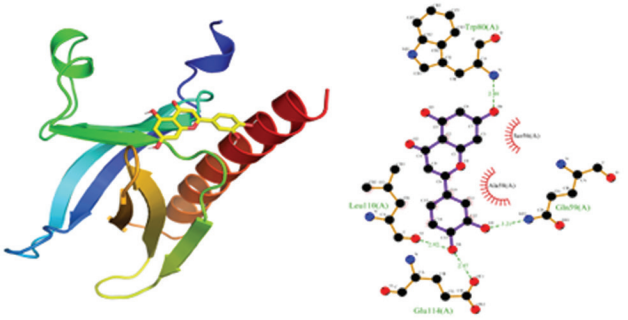


Figure 8. Interaction mode analysis between *quercetin* and EGFR protein

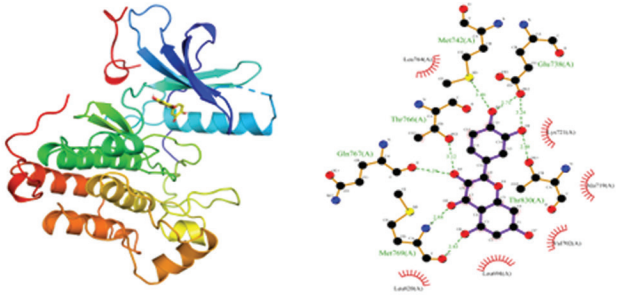
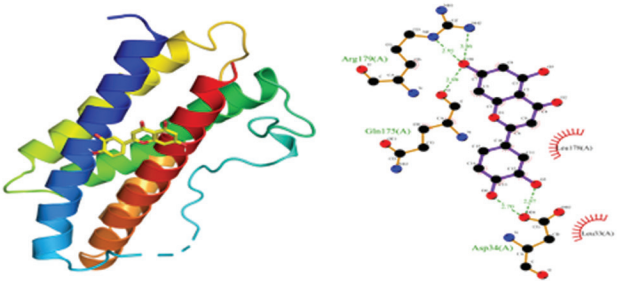


Figure 9. Interaction mode analysis between *luteolin* and IL6 protein



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Apigenin, apart from its potential antioxidant and anti-inflammatory effects, has been found to have a hypoglycemic effect. It can improve corneal epithelial lesions, nerve injuries, tear reduction, and meibomian gland changes induced by oxidative stress and inflammatory mediators in chronic hyperglycemia.[18] In a study by Hung-Chang Chen et al.,[19] eye drops containing ferulic acid and kaempferol extracts resulted in less corneal epithelial damage and increased tear volume in a rabbit model of dry eye disease. These findings suggest that the active ingredients possess antioxidant, anti-inflammatory, and anti-angiogenic activities.

Dry corneas exhibit higher levels of inflammation and neovascularization compared to non-dry corneas. Furthermore, specific endothelial metabolic pathways involving L-asparagine play a critical role in physiological and pathological angiogenic processes.[20] The key targets involved in the mechanism of action include TNF, IL6, IL1B, and CXCL8, which are proinflammatory mediators known to induce dry eye symptoms and impair epithelial barrier function.[21,22] TNF-α, for example, disrupts corneal endothelial barrier integrity through p38 MAP kinase activation.[23] EGF and EGFR, on the other hand, play a role in repairing corneal epithelial barriers, activating the PI3K/AKT signaling pathway, and promoting anti-apoptotic, anti-inflammatory functions, and wound healing in the corneal epithelium.[24-27] The calcium signaling pathway is crucial for cell proliferation, apoptosis, cell division, differentiation, and the reconstruction of the epithelial barrier.[28,29] Additionally, the HIF-1 signaling pathway regulates lymphangiogenesis, facilitates immune cell migration, and aids in the clearance of inflammatory cells, thereby accelerating the regression of inflammation.[30]

Based on the above analysis, it is evident that the active ingredients present in critical topical traditional Chinese medicines primarily exert their therapeutic effects in the treatment of MGD-related dry eye disease by modulating and influencing various biological processes, including anti-inflammation and the repair of the corneal epithelial barrier. These effects are achieved through their interactions with multiple targets

Study Limitations

Despite the valuable insights provided by this study, it is important to acknowledge its limitations. Firstly, the findings are based on in silico network pharmacology analysis and molecular docking simulations, which may not fully reflect the complexity of biological systems. Further experimental validation is necessary to confirm the interactions between the identified active ingredients and their target proteins. Secondly, the study focused on the analysis of known compounds and targets, and additional undiscovered components may exist in the examined traditional Chinese medicines. Furthermore, the study relied on existing databases for target identification and pathway analysis, which may introduce biases and limitations inherent to these resources. Lastly, while the results highlight the potential therapeutic effects of the identified active ingredients, their clinical efficacy and safety need to be evaluated through rigorous clinical trials. Despite these limitations, this study provides a valuable foundation for future research in the field of MGD-related dry eye disease treatment.

CONCLUSION

In conclusion, the medication rules, active ingredients, targets, signaling pathways, and mechanism of topical traditional Chinese medicine in treating MGD-related dry eye disease were investigated and summarized through data mining and network pharmacology. The docking mode between the drugs and the targets was predicted using the molecular docking technology and the intrinsic biomolecular processes in which the main active ingredients of the topical Chinese medicine exert their curative effects in treating MGD-related dry eye disease were discussed. These results can provide a reference for clinical prescriptions, and also lay a theoretical foundation for further experimental verification.

DATA AVAILABILITY

The data used to support this study are available from the corresponding author upon request.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHORS' CONTRIBUTIONS

All authors contributed equally; they read and approved the final manuscript.

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All authors contributed to the study and agreed to be listed as authors.

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