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Integrating Network Pharmacology and Molecular Docking to Identify the Active Substances and Mechanisms of Chrysanthemum against Dry Eye

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Objective: The objective of this study is to explore the bioactive components and potential mechanism of chrysanthemum on dry eye using network pharmacology and molecular docking.

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GJMR-B Classification: *NLMC Code: WW270-290*

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Methods: We used the TCMSP database to search and screen the active ingredients of chrysanthemum and their related targets. Targets associated with dry eye were collected and screened using the Genecards database. The intersection targets of chrysanthemum and dry eye were used to perform protein network analysis, KEGG pathway analysis, and GO enrichment analysis using Metascape. PPI and compound-target networks were constructed using Cytoscape. Finally, molecular docking simulations were performed using Autodock-vina and PyMol.

Results: We collected 20 potential active compounds and 220 component targets of chrysanthemum, as well as 1564 targets of dry eye, of which 118 intersection targets were obtained. PPI network analysis identified 5 key targets: TP53, JUN, MAPK3, MAPK1, and AKT1. These targets were mainly involved in biological processes such as apoptotic signaling pathway, response to oxygen levels, regulation of inflammatory response, regulation of cellular response to stress and aging. Enrichment analysis of KEGG pathways revealed IL-17 signaling pathway, PI3K-Akt signaling pathway, HIF-1 signaling pathway, NF-kappa B signaling pathway, Jak-STAT signaling pathway, Calcium signaling pathway, Leukocyte transendothelial migration pathway, Regulation of lipolysis in adipocytes pathway, Dopaminergic synapse pathway, etc.

Conclusion: Our study provides novel insights into the multiple targets and pathways involved in the effects of chrysanthemum in preventing dry eye. This data may aid in the development of new drugs and hypotheses for the treatment of dry eye.

Keywords: chrysanthemum, dry eye, chinese medicine, network pharmacology, molecular docking.

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I. Introduction

Dry eye is a common condition diagnosed in ophthalmic clinics that can significantly affect a patient's quality of life. The clinical manifestations of patients with dry eye include tear secretion disorder, along with itchiness, photophobia, blurred vision, and foreign body sensation in the eye [1]. The prevalence of dry eye is expected to continue to rise as the elderly population grows [2]. Currently, mainstream treatments for dry eye include tear substitutes, anti-inflammatory drugs, immunosuppressive drugs, and hormones. However, in cases of severe dry eye, tear supplementation may not be enough therapeutically. Additionally, some anti-inflammatory drugs and hormone replacement therapies may cause side effects [3]. Chinese medicine (CM), originating in China, regards the human body as an organic whole, and its therapies involve the interaction of multiple viscera and the adjustment of qi, blood, fluid, and humor [4]. CM is an independent and complete system, which has shown unique therapeutic effects with fewer side effects in the treatment of dry eye [5][6]. The use of CM has broad prospects in the field of dry eye treatment. In CM theory, dry eye is considered a white xerotic syndrome, first proposed in Compendium of Ophthalmology (Shen Shi Yao Han). White xerotic syndrome is believed to be a result of latent heat in the qi aspect, and dampness-heat in the spleen-lung collateral [7]. Chrysanthemum is clinically considered to possess the effects of dispersing wind-heat and pacifying the liver to improve vision. Therefore, chrysanthemum is a common drug for dry eye treatment in CM. The effectiveness of chrysanthemum against dry eye is not only applied in the clinical practice of CM but also in daily life, such as in medicated tea and medicated diets.

As molecular biology, pharmacology, and bioinformatics continue to develop, the modernization of CM is necessary [8][9]. Our group has explored the anti-inflammatory mechanism of total flavonoids of chrysanthemum on dry eye. By inhibiting the expression of IL-1β and TNF-α and promoting the synthesis of TGF-β1 mRNA and TGF-β1, the flavonoid-class active ingredients can reduce inflammation in a castrated male rabbit dry eye model[10]. However, the potential pharmacological mechanism of chrysanthemum and its

interaction with dry eye targets are still unclear and need further study.

Network pharmacology combined with molecular docking is a common method to study the effects of drugs on diseases. Network pharmacology is based on a network composed of chemicals, targets, and pathways, which combines computer science with medical science [11]. Its application in CM provides compelling evidence for the protein targets and potential mechanism of CM in the treatment of diseases. Additionally, molecular docking is a frequently used docking simulation method for predicting the optimal interaction of molecules. Our study aims to clarify the molecular targets and potential mechanism of chrysanthemum against dry eye by utilizing network pharmacology. Furthermore, we use molecular docking to simulate the binding mode of receptor proteins and ligands.

Chrysanthemum belongs to the Asteraceae family. In the Pharmacopeia of the National Health Commission of the People's Republic of China, chrysanthemum is listed as a dietary herbal medicine. Chrysanthemum contains a rich amount of flavonoids, which have superior free radical scavenging and antioxidant functions [12][13]. Additionally, it contains a number of other chemicals, such as phenylpropanoids, triterpenoids, and steroids [14]. What specific components of chrysanthemum act on dry eye and how do they work? We conducted this study to analyze the vital ingredients, important targets, and key pathways of chrysanthemum in dry eye treatment.

II. Materials and Methods

a) *Active components and targets retrieval of Chrysanthemum*

The main active components and corresponding targets of chrysanthemum were collected by using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, http://tcmspw.com/tcmsp.php) with screening conditions "oral bioavailability (OB) ≥ 30%" and "drug-likeness (DL)≥ 0.18". TCMSP is a common ly used, comprehensive botanical platform that can retrieve related compounds, related protein targets, and their pharmacokinetic properties [15]. Next, the UniProt database was utilized to obtain the protein sequence of humans. The protein names and annotations were standardized and matched with chrysanthemum component targets using Excel. After that, the targets of unmatched genes were searched again with TCMSP. All matching genes were considered to be the targets of chrysanthemum.

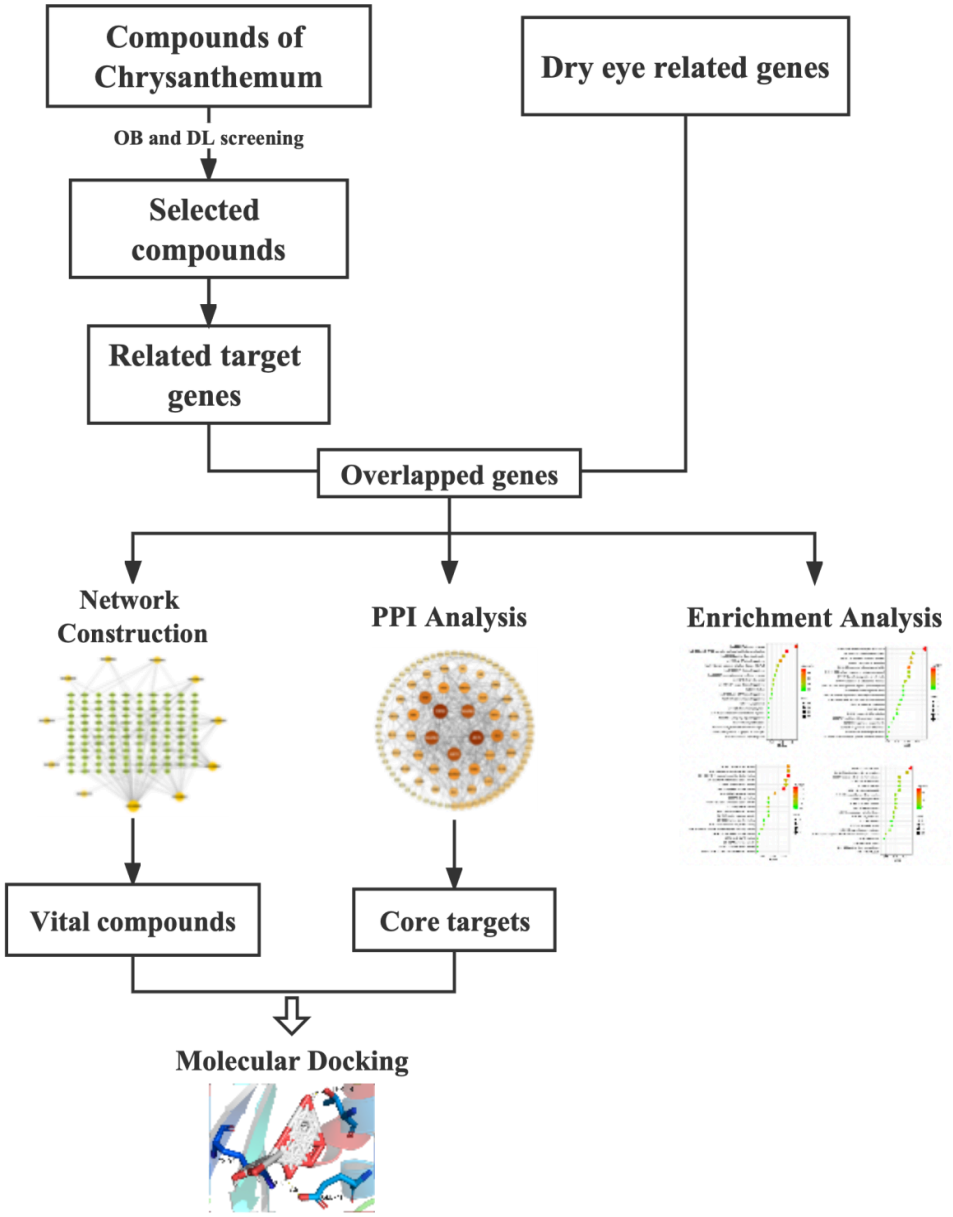

Fig.1: Flow chart of the experimental design

b) *Dry eye related targets retrieval and intersection targets visualization*

The related targets of dry eye were searched for in the GeneCards database using the keywords "dry eye" and "xerophthalmia" [16]. The relevance scores of the search result were ranked and the median was calculated to set the screen-out threshold score at 3 (≥3). The targets of dry eye identified, along with the chrysanthemum component targets, were inputted into VENNY 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/index.html), and the intersection of drug targets and disease targets was collected as the potential targets of chrysanthemum for treating dry eye. The resulting chrysanthemum-dry eye target Venn diagram was drawn. The data for the chrysanthemum vital components and the intersection targets were then imported into Cytoscape 3.8.2 to construct the network of vital compound-disease interaction targets [17].

c) *PPI network constructing of chrysanthemum and dry eye*

118 intersection targets were imported into the STRING platform (https://cn.string-db.org) [18]. The protein organism was configured as "Homo sapiens" and the minimum required interaction score was set to the highest confidence (0.900). The protein-protein interaction (PPI) network was constructed with the disconnected nodes hidden. Import the tsv suffix file into Cytoscape 3.8.2 to draw a clearer PPI network. Additionally, a histogram should be plotted for the top 25 proteins based on their in-degree value.

d) GO and KEGG pathway enrichment analysis

The 118 intersection targets of chrysanthemum and dry eye were uploaded to Metascape database (https://metascape.org). Custom analysis was performed with Gene Ontology (GO) and KEGG pathway enrichment under the condition of $P \leq 0.01$. The enrichment results were imported into an online bioinformatics platform (http://www.bioinformatics.com.cn) to draw the relevant enrichment bubble plots.

e) Molecular docking

We chose the top 5 proteins ranked by degree as protein receptors. The 3D structure of TP53, JUN, MAPK3, MAPK1 and AKT1 were downloaded from PDB database (https://www. rcsb.org). Then, we use PyMOL 2.5.2. software to remove the organics and solvent. 3D structures of the top 4 vital compounds were downloaded from PubChem database (https://pubchem.ncbi.nlm.nih.gov). Additionally, molecular docking was performed using Autodock-Vina. TP53, JUN, MAPK3, MAPK1 and AKT1 were docked with quercetin (MOL000098), kaempferol (MOL000422), luteolin (MOL000006) and acacetin (MOL001689) respectively. The affinity score smaller than 0 indicates that the ligand and receptor can bind spontaneously. It is generally believed that the components with lower scores are the active ones interacting with the protein. Matrix heatmap was plotted by http://www.bioinformatics.com.cn, a free online platform for data analysis and visualization. At last, the docking results were analyzed by using PyMOL 2.5.2.

III. Result

a) Components and the corresponding targets of chrysanthemum

Twenty active components were obtained from chrysanthemum by using screening conditions of OB≥30% and DL≥0.18, including acacetin, linarin, chryseriol, isorhamnetin, kaempferol, and others. The corresponding targets were identified by searching for the chemical names and matching them with the protein sequence of human. After filtering out the remaining unmatched items, we obtained 220 targets of chrysanthemum components.

Table 1: The active compounds of chrysanthemum

MOLID	Molecule Name	OB	DL
MOL001689	acacetin	34.97%	0.24
MOL001790	Linarin	39.84%	0.71
MOL003044	Chryseriol	35.85%	0.27
MOL000354	isorhamnetin	49.60%	0.31
MOL000422	kaempferol	41.88%	0.24
MOL005100	5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)chroman-4-one	47.74%	0.27
MOL000006	luteolin	36.16%	0.25
MOL000098	quercetin	46.43%	0.28
MOL000358	beta-sitosterol	36.91%	0.75
MOL001506	Supraene	33.55%	0.42
MOL001733	EUPATORIN	30.23%	0.37
MOL001755	24-Ethylcholest-4-en-3-one	36.08%	0.76
MOL001771	poriferast-5-en-3beta-ol	36.91%	0.75
MOL002881	Diosmetin	31.14%	0.27
MOL004328	naringenin	59.29%	0.21
MOL005229	Artemetin	49.55%	0.48
MOL007326	Cynarin(e)	31.76%	0.68
MOL011319	TruflexOBP	43.74%	0.24
MOL011802	(24r)-saringosterol	39.36%	0.79
MOL011816	[(1S,5S,7S)-7-acetoxy-5-isopropenyl-2,8-dimethylene-cyclodecyl]acetate	37.02%	0.19

b) Candidate targets associated with Dry eye and chrysanthemum-dry eye intersection targets

After filtering out the targets with a relevance score smaller than the median (≥3), we obtained 1564 dry eye targets. Matching them with the chrysanthemum component targets resulted in a compound-target network of chrysanthemum on dry eye, which revealed 118 matched targets (as shown in Fig. 2) and 11 corresponding compounds. The interaction targets network (as shown in Fig. 3) highlighted the most vital four compounds: quercetin (MOL000098, 44 targets), kaempferol (MOL000422, 21 targets), luteolin (MOL000006, 19 targets), and acacetin (MOL001689, 11 targets).

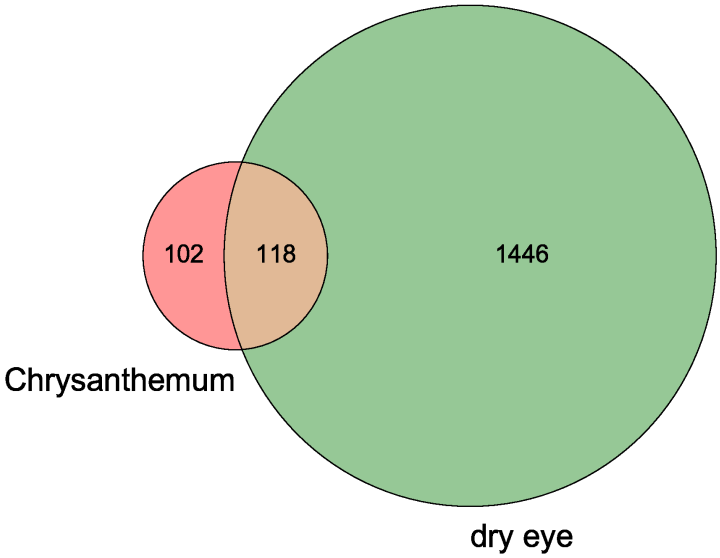

Fig. 2: Venn diagram of active compound targets of Chrysanthemum and related targets of dry eye.

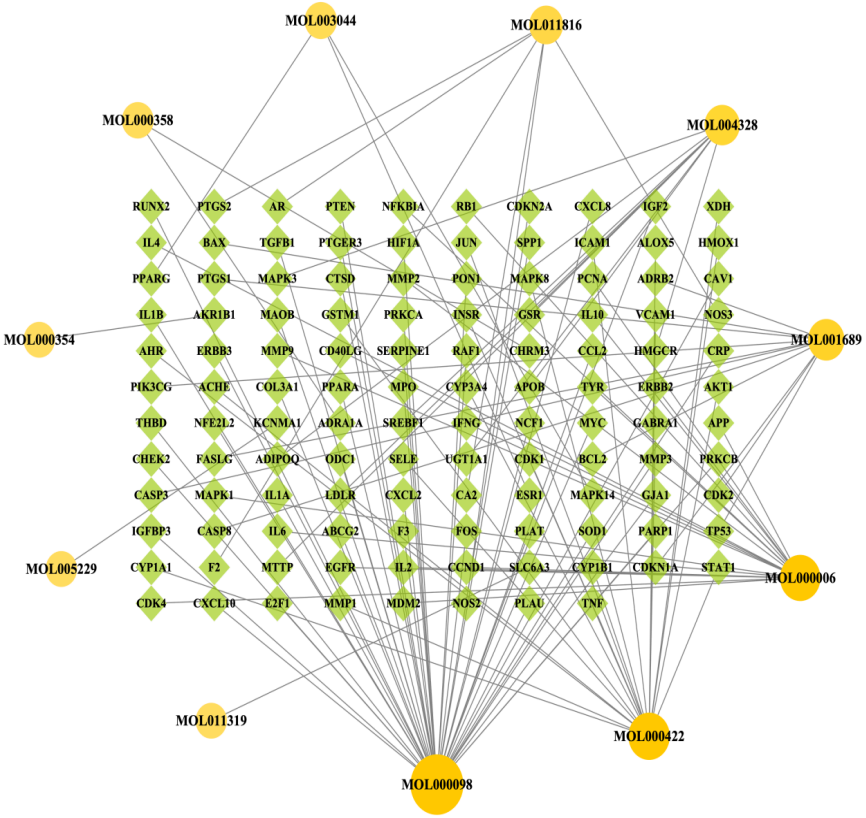

Fig. 3: The compound-target network of Chrysanthemum on dry eye. Yellow solid circles represent compounds and green diamonds represent targets.

c) PPI network analysis

The PPI network (Fig. 4) displays 118 nodes and 467 edges, with an average node degree of 7.92. The PPI enrichment p-value is <1.0e-16. The node degree indicates the number of edges of the target line. The higher the node degree, the more likely it is to be a key target of functional ingredients and play a significant role in the network. The nodes in the figure represent protein targets, and the edges represent protein-protein interactions. The more lines, the closer the relationship between targets. To illustrate this, the top 25 genes with the highest degree value were plotted in a histogram (Fig. 5), showing that TP53, JUN, MAPK3, MAPK1, and AKT1 are the most prominent proteins.

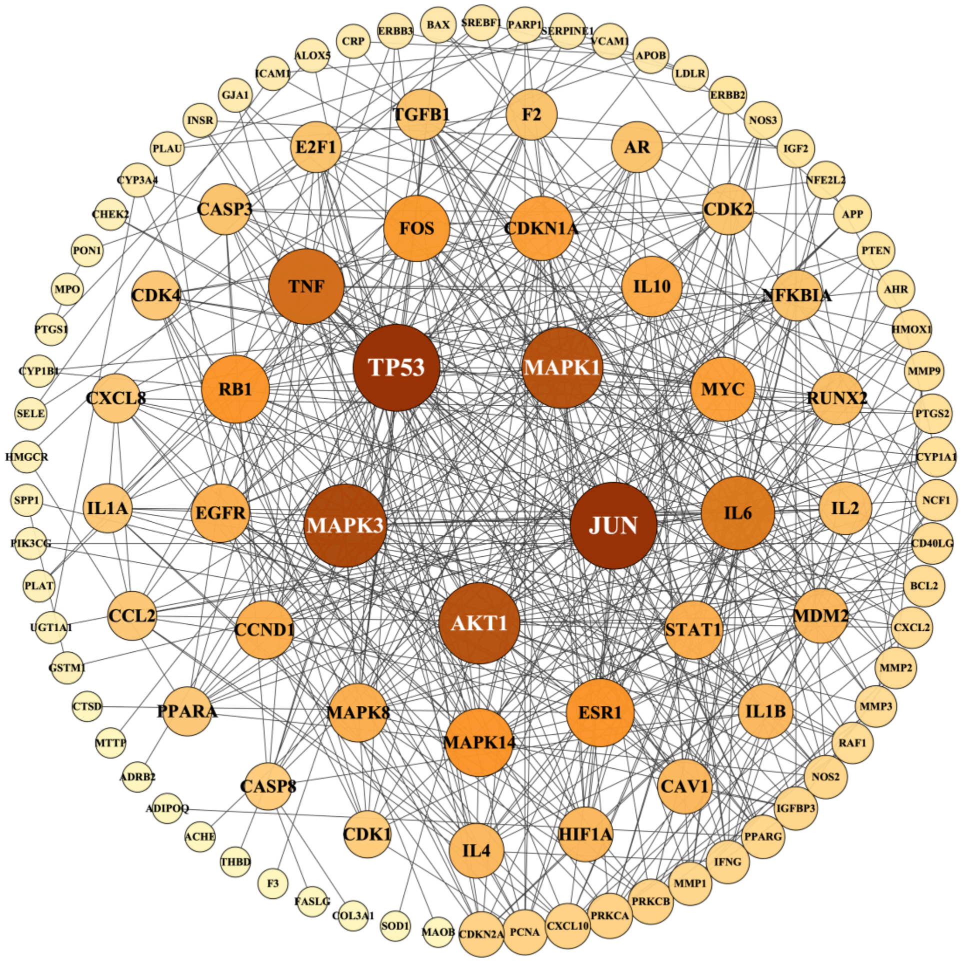

Fig. 4: Network diagram of protein-protein interaction (PPI)

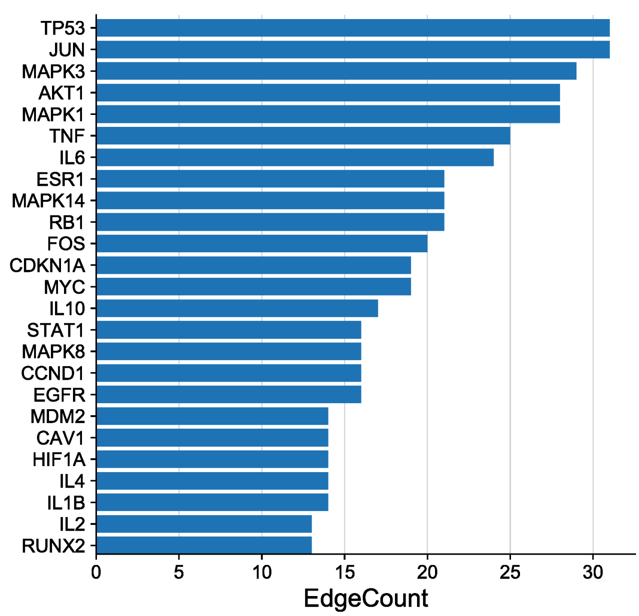

Fig. 5: Top25 targets by degree value

d) GO&KEGG pathway enrichment analysis

Enrichment result shows 431 cellular components (CC), 719 molecular functions (MF), 5365 biological processes (BP) and 455KEGG pathways. The top 20 significantly enriched entries in the results are arranged in an ascending order of p value (Fig. 6). The results showed important MF such as kinase binding, protease binding, cytokine receptor binding, DNA-binding transcription factor binding, kinase activity and cytokine activity; significant BP such as apoptotic signaling pathway, response to oxygen levels, regulation of inflammatory response, regulation of cellular response to stress and aging; important CC contains membrane, cytoplasm, endoplasmic reticulum, etc. The enrichment analysis results of KEGG pathways mainly manifested IL-17 signaling pathway (hsa04657), PI3K-Akt signaling pathway (hsa04151), HIF-1 signaling pathway (hsa04066), NF-kappa B signaling pathway (hsa04064), Jak-STAT signaling pathway (hsa04630), Calcium signaling pathway (hsa04020), Leukocyte transendothelial migration pathway (hsa04670), Regulation of lipolysis in adipocytes pathway (hsa04923) and Dopaminergic synapse pathway (hsa04728).

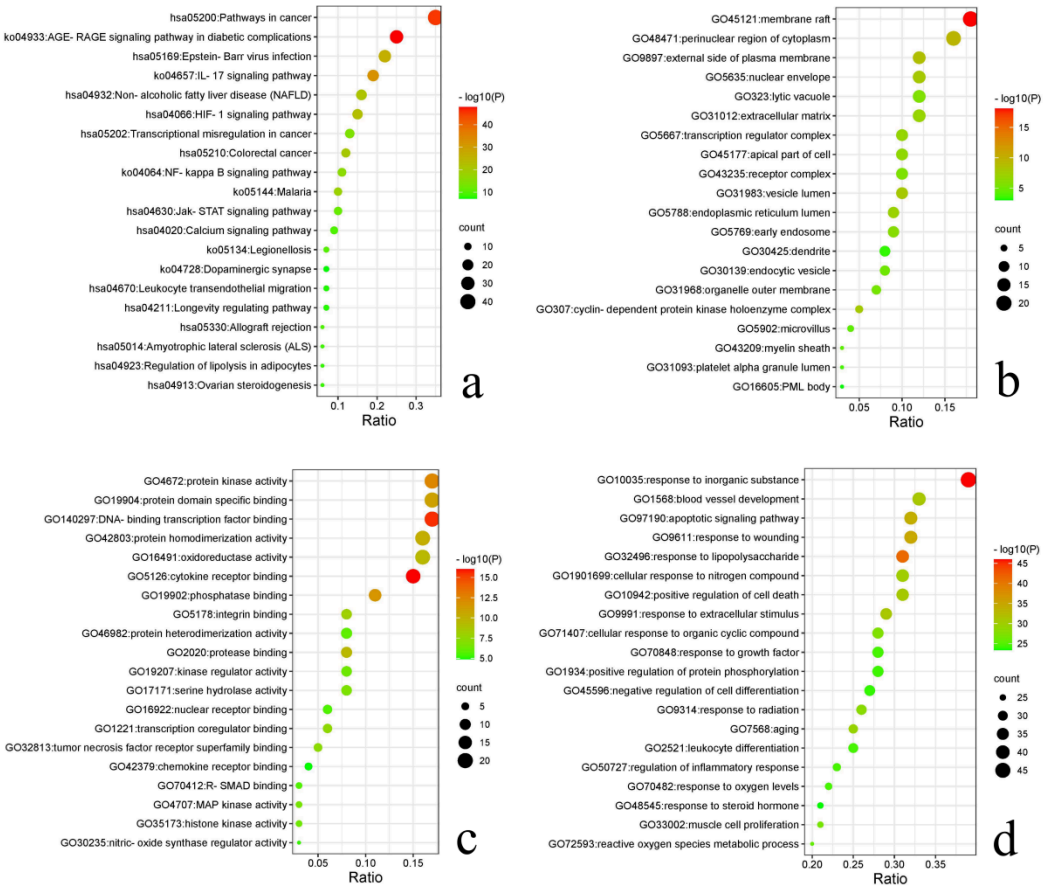

Fig. 6: Enrichment bubble plots of GO&KEGG pathway enrichment analysis
.a Enrichment analysis results of KEGG pathways; b Enrichment analysis results of CC; c Enrichment analysis results of MF; d Enrichment analysis results of BP. Size and color of the dots represent the degree of GO enrichment analysis.

e) Molecular docking results and analysis

The top 5 core targets were respectively docked onto the top 4 vital chemicals. All docking simulations show good combination states. The affiniy scores of TP53, JUN, MAPK3 and MAPK1 are slightly more ideal than AKT1. The representative ones in the docking results are TP53 with luteolin (-9kcal/mol), JUN with quercetin (-9.4kcal/mol), MAPK3 with quercetin (-10kcal/mol) and MAPK1 with quercetin (-9.5kcal/mol). These four receptors and their best docked ligands were picked out to draw the molecular docking diagram subsequently. Notably, MAPK3 also shows remarkable docking state with other 3 ligands. Its docking score with kaempferol, luteolin and acacetin are -9kcal/mol, -9.4kcal/mol, -9.2kcal/mol, respectively. The affinity scores heatmap and docking simulation images are shown in figure 7 and figure 8.

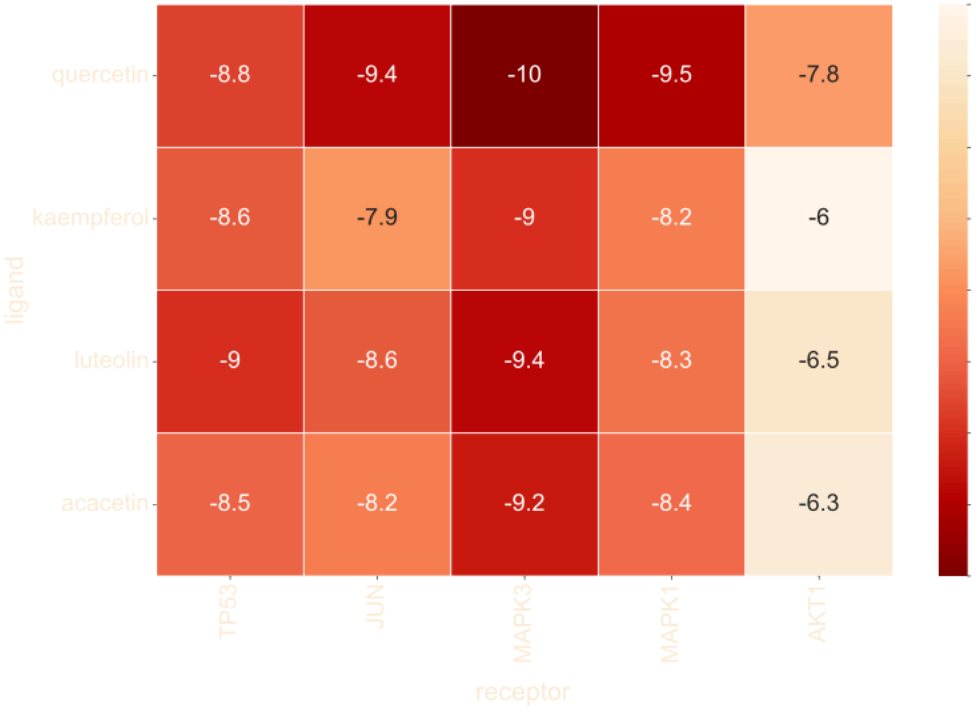

Fig. 7: The heat map of the affinity score

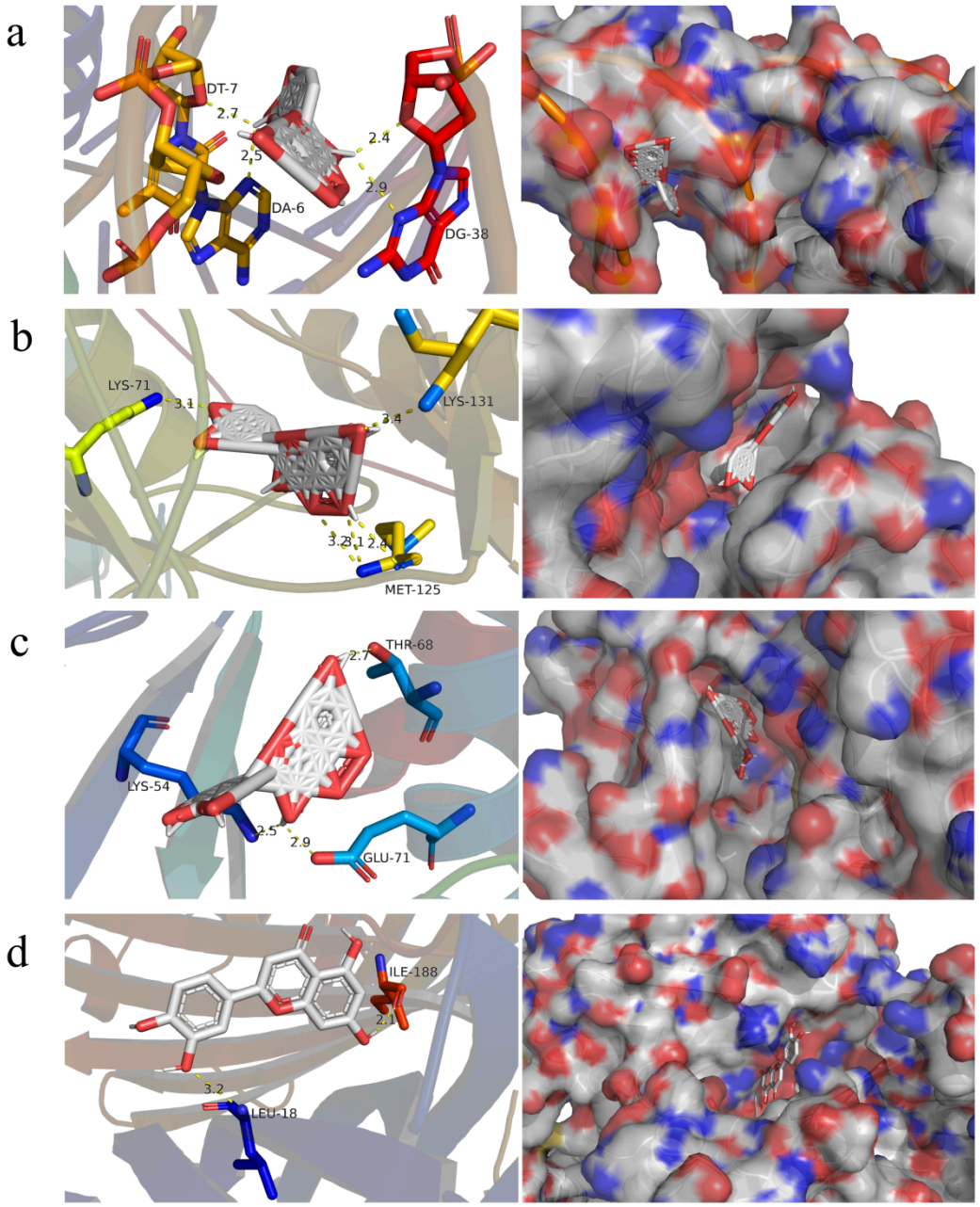

Fig. 8: The notable results of molecular docking analysis. aAction mode of quercetin with target JUN(PDB ID:5T01); bAction mode of quercetin with target MAPK3(PDB ID:4QTB); cAction mode of quercetin and MAPK1(PDB ID:7NR8); dAction mode of luteolin and TP53(PDB ID:7BWN)

IV. Discussion

In CM theory, chrysanthemum is believed to be effective in treating dry eye by dispersing wind-heat and pacifying the liver, which in turn improves vision. However, due to the complex composition of herbal medicine, it is often difficult to understand its underlying mechanisms. To address this issue, we used network pharmacology to establish a drug-target-disease network, which helped us to explore the active ingredients and therapeutic targets of chrysanthemum. Our results suggest that chrysanthemum can treat dry eye through the action of multiple targets and components, which is consistent with the manifold therapeutic effects of CM. Although chrysanthemum and chrysanthemum-containing formulas have been the subject of some clinical experiments[10][19], there is still much to learn about the combination of its components and the enrichment of its targets. Therefore, we believe that exploring the vital components and targets before experimental validation may be more conducive to research in this field.

It is widely recognized that inflammation is a central mechanism of dry eye, as supported by

numerous in vitro, in vivo, and human studies [20]. Inflammatory cytokines are the main culprits of dry eye-associated inflammation [21]. Moreover, research suggests that an abnormal immune response in the ocular system can also contribute to ocular surface injury, further exacerbating dry eye symptoms [22]. Additionally, oxidative stress is also a critical factor in the pathogenesis of dry eye. Oxidative stress mouse models have shown decreased tear secretion, leukocyte infiltration, and fibrosis [23]. Chrysanthemum's bioactive components have the effect of anti-inflammation, antibacterial, antifungal, anti-spirochete, anti-human immunodeficiency virus, and antioxidant [13].This provides theoretical support for the anti-inflammatory effect of chrysanthemum treating dry eye.

According to the degree ranking of targets interaction, the corresponding most important components are quercetin, kaempferol, luteolin and acetin, which all belong to the ranks of natural flavonoids. Previous studies have already shown that flavonoid compound has strong anti-inflammatory and antioxidant effects [19][24], which is consistent with our earlier research[10]. Quercetin's topical application can not only reduce the irregularity of the ocular surface, but also increases the amount of tears and goblet cell density [25]. However, quercetin's oral bioavailability is still controversial, so we need more information about its pharmacokinetics in experiments [26]. Intragastric kaempferol feeding can inhibit nlrp1 / NLRP3 inflammasomes and caspase8 through NF-κB and JNK pathway, so as to reduce the inflammatory damage of retinal ganglion cells in acute glaucoma mice model [27]. Kaempferol-contianing eye drops in rabbit dry eye model have also been proved to reduce corneal epithelial injury and increase tear secretion [28]. In the rat uveitis model, luteolin inhibits the inflammatory markers and activates NF-κB pathway, thereby reducing iris-ciliary body inflammation. The anti-inflammatory effect of 10 mg / kg luteolin being injected intraperitoneally was proved to be as strong as 1 mg / kg prednisolone [29]. Interestingly, Acacetin has shown therapeutic potential in inflammation, infections and other metabolic disorders [30][31][32]. However, there are few studies on its application in the field of Ophthalmology, which deserves our attention.

According to the our PPI network data as well as molecular docking results, we conclude that the core targets chrysanthemum regulating dry eye are TP53, JUN, MAPK3 and MAPK1, which all showed stable structure and high binding activity with the vital ingredients in molecular docking. TP53 cooperating with mitochondrial PPIF is involved in activating oxidative stress-induced necrosis, which damages the ocular surface and plays an important role in the mechanism of dry eye disease [33]. MAPK family is involved in many processes, such as cell proliferation, stress, inflammation, apoptosis and so on. Studies have proved the efficacy of p38 MAPK inhibitor on lacrimal gland secretion and neurotransmitter secretion in dry eye [34]. JUN protein is also related to cell aging induced by oxidative stress, however, its related studies in dry eye remain limited. Considering its good affinity scores with the ligands, it may serve as another latent therapeutic target of dry eye. Docking is broadly applied in the field of drug discovery and design as well as the identification of ligands binding to a target receptor [35]. We expect to see "pocket-like" docking simulation status. As can be seen in the docking image, the docking model reveals a good morphologic complementary between the receptors and ligands contact areas. Quercetin formed 4 hydrogen bonds with residue DT-6/7 and residue DG-38 of the JUN protein that shows a good binding affinity (-9.4kcal/mol).Whilst it could form 5 hydrogen bonds with residue LYS-71/131 and residue MET-125 of MPK3 which both show good binding affinity(-10kcal/mol). It also could form 3 hydrogen bonds with residue LYS-54, residue THR-68 and residue GLU-71 of MPK1 showing a good binding affinity (-9.5kcal/mol). Meanwhile, Luteolin could form 2 hydrogen bonds with residue ILE-188 and residue LEU-18 of TP53, displaying a good binding affinity (-9kcal/mol). These ligand-receptor combinations need to be further studied theoretically and experimentally.

The enrichment results have revealed several important KEGG pathways. The interleukin 17 (IL-17) family has been found to play a crucial role in both acute and chronic inflammatory responses. Topical application of IL-17 therapy has been shown to reduce ocular surface symptoms of tear evaporation and meibomian gland dysfunction [36]. The activation of the PI3K–AKT signaling pathway has also been found to have protective effects on injured RGCs [37]. Additionally, the NF-κB signaling pathway and JAK-STAT signaling pathway have been found to be critically involved in cellular stress and inflammation, and have been the focus of numerous studies in ophthalmology and Sjögren's syndrome[38][39][40]. It is worth noting that inflammation is also the primary mechanism of Sjögren's syndrome, which can trigger dry eye. Studies have shown that Dll4/Notch Signaling and HIF-1α Stimulating lymphangiogenesis may protect lacrimal glands from dry eye-induced inflammation by helping to clear immune cells in the lacrimal glands[41].The deficiency of HIF-1α enhances the recruitment of inflammatory cells to lacrimal glands[42]. Our enrichment analysis has also identified some core functions and processes, including oxidoreductase activity and response to oxygen levels, which have drawn our attention. These results provide guidance for the direction of our subsequent experimental research and may provide new insights for the treatment of dry eye.

V. Conclusion

The results of our enrichment analysis and molecular docking revealed that quercetin and luteolin are the important components of chrysanthemum in the treatment of dry eye, followed by kaempferol and acacetin. These components have shown promising anti-inflammatory and antioxidant properties. Interestingly, the anti-inflammatory mechanism of acacetin in ophthalmology has not been studied extensively, and further research is needed to explore its potential therapeutic effects. Our molecular docking studies showed that TP53, JUN, and MAPK3/1 are the core targets of chrysanthemum in the treatment of dry eye. Quercetin with JUN, quercetin with MAPK3/1, and luteolin with TP53 were identified as the most stable docking combinations, indicating their potential as effective therapeutic combinations for the treatment of dry eye. These findings provide valuable insights for further experimental studies on the potential therapeutic effects of chrysanthemum in the treatment of dry eye.

Declarations

Ethics approval and consent to participate

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article. All data generated or used during the study are available from the corresponding author by request.

Competing interests

The authors declare no conflict of interests.

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Authors' contributions

Yanxue Zhang wrote and revised the manuscript. Xiaolei Yao designed and adjusted structure of the manuscript. Yu Tang, Kai Wu collected and analyzed the data. All authors discussed the results and revised the manuscript.

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Not applicable.

Abbreviations

CM: Chinese Medicine; TCMSP: Traditional Chinese Medicine Systems Pharmacology; OB: Oral Bioavailability; DL: Druglikeness; GO: Gene ontology, KEGG: Kyoto Encyclopedia of Genes and Genomes; PPI: Protein-protein interaction; BP: Biological Processes; CC: Cell Components; MF: Molecular Functions; TP53: Cellular tumor antigen p53; JUN: Transcription factor AP-1; MAPK3:Mitogen-activated protein kinase 3; MAPK1:Mitogen-activated protein kinase 1; IL-17: Interleukin-17; HIF-1 :Hypoxia-inducible factor 1; AKT1: RAC-alpha serine/threonine-protein kinase; PI3K-Akt:The phosphatidylinositol 3'-kinase-serine/threonine-protein kinase; Jak-STAT: Janus kinase/signal transducers and activators of transcription; NF-kappa B:Nuclear factor-kappa B

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