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Mechanisms of Chinese herbal medicine in modulating gut microbiota on primary open-angle glaucoma: a study based on data mining, network pharmacology, and Mendelian randomization

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ABSTRACT

Objective To elucidate the potential mechanisms by which Chinese herbal medicine (CHM) regulates gut microbiota (GM) to influence the development of primary open-angle glaucoma (POAG).

Methods Data mining, network pharmacology, and Mendelian randomization (MR) analyses (two-sample design) were conducted in integration to systematically explore the CHM-GM-POAG axis. Literature-based data mining method was applied to identify frequently used herbs and herb pairs for POAG, and the properties and meridian tropism of the herbs were analyzed as well. Target prediction and pathway enrichment analyses were performed to identify shared molecular pathways among CHM components, GM, and POAG. MR analysis was performed to assess the genetically predicted causal associations between specific microbial taxa and POAG risk.

Results Our data mining work indicated that commonly used CHMs were mainly bitter and sweet in flavors and cold in property, with meridian tropism toward the liver, lung, and kidney. The predominant therapeutic effects of the CHMs included soothing the liver and regulating Qi, promoting blood circulation, and reducing fluid retention. Representative herb pairs were Shudihuang (Rehmanniae Radix Praeparata)-Gouqi (Lycii Fructus) with Zexie (Alismatis Rhizoma), Gouqi (Lycii Fructus)-Fuling (Poria) with Shudihuang (Rehmanniae Radix), and Juhua (Chrysanthemi Flos)-Gouqi (Lycii Fructus) with Zexie (Alismatis Rhizoma). Network pharmacology revealed overlapping targets involving antioxidative, anti-inflammatory, and metabolic regulation pathways. MR analysis demonstrated that higher abundances of *Ruminiclostridium 6* [odds ratio (OR) = 0.73, 95% confidence interval (CI): 0.58 – 0.92, P = 0.007], *Ruminococcaceae UCG-002* (OR = 0.77, 95% CI: 0.63 – 0.96, P = 0.018), *Ruminococcus torques* group (OR = 0.71, 95% CI: 0.57 – 0.90, P = 0.004), and *Victivallis* (OR = 0.82, 95% CI: 0.70 – 0.96, P = 0.016) were causally associated with reduced POAG risk, whereas *Actinomyces* (OR = 1.34, 95% CI: 1.06 – 1.68, P = 0.013) and *Blautia* (OR = 1.39, 95% CI: 1.01 – 1.90, P = 0.042) showed positive associations.

Conclusion This study revealed potential causal links between GM and POAG and provided

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integrative evidence that CHM may modulate the microbiota to exert neuroprotective effects. These findings offer new integrative insights into the gut-eye axis and a theoretical basis for developing microbiota-targeted CHM strategies in glaucoma management.

1 Introduction

Primary open-angle glaucoma (POAG) is a disease characterized by pathological intraocular pressure (IOP) and progressive optic neuropathy. It is one of the leading causes of irreversible blindness [1]. Globally, millions suffer from visual impairment due to glaucoma [2], yet its early symptoms are subtle, and diagnosis often occurs after irreversible visual field damage. Current clinical therapies mainly focus on lowering IOP, and neuroprotective drugs remain scarce [3], with potential local and systemic adverse effects [4, 5]. Moreover, the disease involves complex molecular regulatory networks beyond IOP control [6, 7].

Chinese herbal medicine (CHM), rooted in holistic and multi-target therapeutic principles, has long been used to treat POAG in China. Modern evidence indicates that CHMs can delay disease progression and protect retinal neurons [8, 9], with pharmacological studies confirming its antioxidant, anti-inflammatory, and metabolic regulatory effects [10, 11]. However, the underlying medication patterns and molecular mechanisms remain insufficiently characterized.

In recent years, the gut microbiota (GM), a key modulator of immune and metabolic homeostasis, has emerged as an important factor in ocular diseases, supporting the gut-eye axis hypothesis [12-14]. Dysbiosis of GM and its metabolites may influence aqueous humor outflow, IOP, and retinal ganglion cell (RGC) survival [15-18]. Moreover, GM and its metabolites can translocate through the bloodstream or mesenteric lymphatic system to the retina and optic nerve, inducing neuroinflammation and autoimmune responses [19-21]. These findings suggest a potential connection between gut microecology and POAG pathogenesis, in which intestinal barrier integrity and digestive function—the physiological counterparts of the spleen and stomach in traditional theory—may also play contributory roles.

From a traditional Chinese medicine (TCM) perspective, the liver is believed to “store blood” and “open into the eyes”, making it the primary organ responsible for visual function. The liver governs the regulation of Qi and is functionally connected with the spleen and stomach. When liver Qi flows smoothly, Qi and blood circulate harmoniously; when the spleen and stomach function properly, fluid metabolism remains balanced and clear Yang ascends. The two organs thus regulate reciprocally in the metabolism of Qi, blood, and body fluids. This theoretical foundation provides a traditional medical rationale for the gut-liver-eye axis. Modern biomedical studies have also demonstrated that GM can regulate intestinal barrier function and influence the hepatic portal system and liver metabolic status, thereby triggering systemic immune and inflammatory responses [22, 23]. These effects may extend to ocular tissues, lending biological plausibility to the gut-liver-eye axis concept. This integrative study, combining TCM theories and modern medical evidence, provides a novel foundation for understanding the complex pathophysiology of POAG.

Although some CHMs have been shown to exert therapeutic effects by modulating GM [24], the synergistic mechanisms between CHMs and GM in glaucoma remain unexplored. This constitutes a major research gap in the current understanding of pathophysiology of glaucoma. To narrow this gap, the present study has integrated data mining, network pharmacology, and Mendelian randomization (MR) analyses (two-sample design) to systematically elucidate how CHMs regulate GM to influence the development and progression of POAG. This integrative approach has not only bridged traditional and modern medical frameworks but also provided innovative evidence for microbiota-targeted CHM therapy in glaucoma management.

2 Data and methods

2.1 Literature search and data collection

(i) Data sources: research on the use of CHMs in POAG treatment was retrieved from Chinese databases including the China National Knowledge Infrastructure (CNKI), Wanfang Data, Chinese Science and Technology Journal Database (VIP), and China Biomedical Literature Database, and English databases including PubMed, Embase, and the Cochrane Library. The included literature primarily consisted of peer-reviewed journal articles and academic dissertations. The data retrieval timeline spanned from the establishment of each database to June 30, 2024.

(ii) Search terms: the data retrieval was conducted using combinations of terms such as (“primary open-angle glaucoma” OR “POAG” OR “primary glaucoma” OR “open-angle glaucoma” OR “glaucoma”) AND (“traditional medicine” OR “Chinese medicine” OR “Han medicine” OR “herbal medicine” OR “herbs” OR “decoction” OR “natural products” OR “TCM formula” OR “Chinese herbal formula”).

Detailed data retrieval strategies and the specifics of the retrieved literature are provided in Supplementary Table S1.

2.2 Diagnostic criteria

The study enrolled patients who were diagnosed with POAG according to the prevailing diagnostic criteria at the time of each publication, which generally followed the Chinese Ophthalmological Society [25] or American Academy of Ophthalmology guidelines [26]. Typical diagnostic features included elevated IOP, optic nerve head damage confirmed by fundus or optical coherence tomography (OCT) examination, and corresponding visual field defects.

2.3 Inclusion criteria

(i) The selected studies included randomized controlled trials (RCTs) and observational clinical studies, featuring at least one group of participants treated with CHMs. (ii) Interventions involved herbal decoctions, granules, or other orally administered CHMs, all with clearly specified herbal dosages. (iii) In the case of duplicate publications, studies with the most detailed clinical data were selected. (iv) Publications were limited to studies published in Chinese or English.

2.4 Exclusion criteria

(i) Case reports, review, conference publications, animal-based studies, and theoretical papers. (ii) Studies involving external TCM therapies such as acupuncture and cupping. (iii) Studies involving non-compound CHM preparations or non-oral administration routes. (iv) Studies with prescriptions lacking detailed descriptions of the main herbal components, such as those only described as modified classical formulas without specifying individual herbs.

2.5 Data extraction and standardization

Two researchers independently reviewed relevant studies and retrieved data from the aforementioned databases. All discrepancies were discussed, and unresolved disagreements were adjudicated by a third reviewer to reach consensus. Information such as article titles, authors, publication dates, prescription details, and dosages were recorded for each study. Botanical medicine names were standardized following the *Pharmacopoeia of the People's Republic of China 2020* [27], while information of CHMs not included in this pharmacopoeia was supplemented from *Chinese Materia Medica* [28] and *Compendium of Materia Medica* [29].

2.6 Frequency and association rule mining of CHMs

To clarify clinical applications of combined medicinal herbs, we conducted frequency count and systematic clustering analysis using IBM SPSS Modeler 18.0. The Apriori algorithm was applied to analyze the associations among high-frequency CHMs (usage frequency $\geqslant 5$), because the average usage frequency across all herbs was 4.02; selecting a slightly above-average value ensured focus on representative herbs while maintaining the complexity of manageable analysis. The Apriori algorithm was used to analyze associations among herbs, with the Support and Confidence thresholds set at 10% and 80%, respectively. These values are commonly adopted in CHM data mining studies to ensure rule relevance and interpretability, following established protocols [30, 31].

2.7 Screening of active herbal components and cross-targets

To further elucidate potential bioactive components, targets, and associated pathways involved in POAG treatment, network pharmacology analysis was conducted on core CHMs identified through association rule mining described above. The active compounds of these core herbs were identified through the Traditional Chinese Medicine Systems Pharmacology Platform (TCMSP, https://old.tcmsp-e.com) and literature review. The screening criteria were oral bioavailability (OB) $\geqslant$ 30% and drug-likeness (DL) $\geqslant$ 0.18 [32].

Targets for these components were collected from the TCMSP database, with additional targets predicted using the SwissTargetPrediction (STP) tool (http://www.swisstargetprediction.ch/) [33].

Species-specific disease gene profiles for "human" were standardized using the UniProt database (http://www.uniprot.org/), where protein names and annotations were matched with the targets of herbal components.

POAG-related targets were identified using GeneCards (relevance score > median value of 6.69), Online Mendelian Inheritance in Man (OMIM), DrugBank, and DisGeNET databases. GM metabolites were retrieved using the GutMGene database (http://bio-computing.hrbmu.edu.cn/gutmgene/), and their potential targets were predicted using the Similarity Ensemble Approach (SEA) (https://sea.bkslab.org/) and STP databases [33, 34]. The combined results from these databases were used to compile a GM metabolite target set (hereafter referred to as GM targets).

2.8 Construction of a GM-based interaction network centered on core targets

The intersection of herbal targets, POAG targets, and GM targets was identified as the potential set of targets through which CHMs acts on POAG via GM. These target data were imported into the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) (https://cn.string-db.org) [35], with the protein species set to *Homo sapiens* and a confidence score threshold of > 0.9.

Isolated targets were excluded to construct a protein-protein interaction (PPI) network. The resulting PPI network was visualized and analyzed using Cytoscape v3.8.2. Network topology was assessed based on degree values (number of connections per node) to identify targets with higher network connectivity.

2.9 Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) enrichment analyses of core targets

To better understand the biological roles of these targets, KEGG pathway and GO functional enrichment analyses were performed using the Metascape platform (https://metascape.org/). The significance threshold was set at $P < 0.05$, and P values were adjusted for multiple testing using the Benjamini-Hochberg false discovery rate correction. The GO analysis encompassed three categories: biological processes (BP), molecular functions (MF), and cellular components (CC).

2.10 Genome-wide association study (GWAS) data sources for MR

GWAS data for GM were obtained from the MiBioGen consortium (https://mibiogen.gcc.rug.nl). This dataset comprises 18 340 individuals from multi-national Eurasian populations, including 122 111 host genetic variants mapped to 211 taxa, spanning 9 phyla, 16 classes, 20 orders, 35 families, and 131 genera [36].

Outcome data for POAG were derived from the GWAS conducted by SHIGA et al. [37] (https://gwas.mrcieu.ac.uk/datasets/bbj-a-75/). This dataset includes East Asian individuals, comprising 3 980 POAG cases and 18 815 controls.

2.11 MR analysis

GM data at the genus level with a significance threshold of $P < 1 \times 10^{-5}$ were selected as exposures [38]. Clumping parameters were set to 500 kb and $r^2 = 0.1$ to exclude linkage disequilibrium single nucleotide polymorphisms (SNPs). Additionally, the F-statistic for each SNP was calculated, and only instrumental variables with an F-statistic greater than 10, which indicated a strong association, were retained [39].

2.12 Sensitivity and horizontal pleiotropy analysis

We applied the inverse-variance weighted (IVW) random-effects model as the primary analysis method, as it accounts for heterogeneity across studies while providing precise, robust, and easily interpretable effect estimates [40]. MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) and MR-Egger were employed to assess potential horizontal pleiotropy [41, 42]. MR-PRESSO identifies outlier variants and adjusts for pleiotropic effects, while MR-Egger accounts for directional pleiotropy through its intercept test. Sensitivity analyses were further performed to evaluate the influence of outliers and the robustness of the causal estimates. Heterogeneity among instrumental variables was assessed using Cochran's Q test.

2.13 Statistical analysis

All statistical analyses were conducted using RStudio 2023.12.0. Data analysis and visualization were performed with the following packages: arules 1.7-7, ggplot2 3.5.1, TwoSampleMR 0.6.1, and MR-PRESSO 1.0. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant.

3 Results

3.1 Frequency distribution of CHMs used in POAG prescriptions

A total of 54 studies were included, involving 46 prescriptions and 104 CHMs (Supplementary Table S2 and S3). Among them, 422 herb-use instances were recorded across all prescriptions. Each prescription contained between 1 and 24 herbs, with an average of 9.17 herbs per prescription. Seventeen herbs were used at least 9 times (a total of 227 instances), accounting for 53.79% of the overall usage frequency (Table 1).

The six most commonly used herbs were Danggui (Angelicae Sinensis Radix), Fuling (Poria), Gouqizi (Lycii Fructus), Danshen (Salviae Miltiorrhizae Radix et Rhizoma), Baishao (Paeoniae Radix Alba), and Chaihu (Bupleuri Radix). Detailed information on frequently used herbs is provided in the Supplementary Table S4.

3.2 Properties, flavors, and meridian tropisms of CHMs used for POAG

A total of 104 CHMs used for POAG treatment were analyzed for their properties, flavors, and meridian tropisms. The results are illustrated in Figure 1. The cumulative frequency of flavors was 169 (Figure 1A). The most common flavors were bitter (56 times, 33.14%), sweet (52 times, 30.77%), and pungent (34 times, 20.12%).

Regarding properties (Figure 1B), a total of 104 occurrences were recorded, and no herbs with hot properties were identified. The most frequently observed properties of the CHMs were cold (42 times, 40.38%), warm (31 times, 29.81%), and neutral (25 times, 24.04%).

A total of 12 meridian tropisms were identified, with 259 cumulative occurrences (Figure 1C). The most frequently involved meridians were the Liver Meridian of Foot Jueyin (66 times, 25.48%), the Lung Meridian of Hand Taiyin (40 times, 15.44%), and the Kidney Meridian of Foot Shaoyin (38 times, 14.67%).

Table 1 Frequently used CHMs for POAG treatment (⩾ 9 instances)

Herb	Frequency	Percentage of POAG prescriptions (%)	Percentage of total herb uses (%)
Danggui (Angelicae Sinensis Radix)	24	52.17	5.69
Fuling (Poria)	23	50.00	5.45
Gouqizi (Lycii Fructus)	16	34.78	3.79
Danshen (Salviae Miltiorrhizae Radix et Rhizoma)	15	32.61	3.55
Baishao (Paeoniae Radix Alba)	14	30.43	3.32
Chaihu (Bupleuri Radix)	14	30.43	3.32
Gancao (Glycyrrhizae Radix et Rhizoma)	13	28.26	3.08
Baizhu (Atractylodis Macrocephalae Rhizoma)	12	26.09	2.84
Cheqianzi (Plantaginis Semen)	12	26.09	2.84
Chuanxiong (Chuanxiong Rhizoma)	12	26.09	2.84
Zexie (Alismatis Rhizoma)	12	26.09	2.84
Gegen (Puerariae Lobatae Radix)	11	23.91	2.61
Juhua (Chrysanthemi Flos)	11	23.91	2.61
Huangqi (Astragali Radix)	10	21.74	2.37
Shichangpu (Acori Tatarinowii Rhizoma)	10	21.74	2.37
Honghua (Carthami Flos)	9	19.57	2.13
Shudihuang (Rehmanniae Radix Praeparata)	9	19.57	2.13

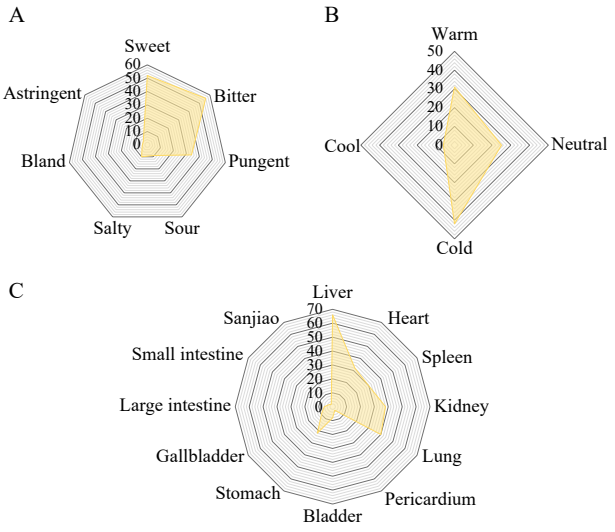

Figure 1 Distribution of flavors, properties, and meridian tropisms of CHMs used for POAG treatment

A, flavors. B, properties. C, meridian tropisms.

3.3 Core herb pairs identified through association rule mining

A total of 11 association rules were identified (Table 2), all with Lift values greater than 3, indicating that all associations were valid. Among these rules, the combinations Shudihuang (Rehmanniae Radix Praeparata)-Gouqizi (Lycii Fructus)⇒Zexie (Alismatis Rhizoma), Gouqizi (Lycii Fructus)-Fuling (Poria)⇒Shudihuang (Rehmanniae Radix Praeparata), Juhua (Chrysanthemi Flos)-Gouqizi (Lycii Fructus)⇒Zexie (Alismatis Rhizoma), and Gouqizi (Lycii Fructus)-Fuling (Poria)⇒Zexie (Alismatis Rhizoma) had the highest Support, all at 15.22%.

The rules Shudihuang (Rehmanniae Radix Praeparata)-Fuling (Poria)⇒Zexie (Alismatis Rhizoma), Shanzhuyu (Corni Fructus)-Gouqizi (Lycii Fructus)⇒Shudihuang (Rehmanniae Radix Praeparata), and Shanzhuyu (Corni Fructus)⇒Shudihuang (Rehmanniae Radix Praeparata) exhibited the highest Confidence at 100%.

The rules Shanzhuyu (Corni Fructus)-Gouqizi (Lycii Fructus)⇒Shudihuang (Rehmanniae Radix Praeparata) and Shanzhuyu (Corni Fructus)⇒Shudihuang (Rehmanniae Radix Praeparata) showed the highest Lift values at 5.11.

The association analysis highlighted that Zexie (Alismatis Rhizoma), Shudihuang (Rehmanniae Radix Praeparata), Gouqizi (Lycii Fructus), Fuling (Poria), Juhua (Chrysanthemi Flos), and Shanzhuyu (Corni Fructus) were the most frequently associated herbs.

3.4 Identification of CHM, GM, and POAG targets and overlapping targets

A total of 112 primary components of CHMs were identified through the TCMSP database and literature searches (Supplementary Table S5). Using the TCMSP and STP databases, 580 target names related to these herbal components were obtained. Additionally, 2 075 POAG-associated genes were retrieved from the GeneCards, OMIM, DrugBank, and DisGeNET databases.

For GM targets, 1 256 targets were identified from the SEA database and 947 from the STP database, resulting in a combined set of 1 535 unique targets after removing duplicate entries.

A total of 172 overlapping targets were identified through Venn diagram analysis of CHM components, GM metabolites, and POAG-related genes (Figure 2A). These overlapping targets represent potential mediators linking CHMs, GM, and POAG.

Table 2 Association analysis of CHMs for POAG treatment

Antecedent	Consequent	Support (%)	Confidence (%)	Lift	Clinical relevance
Shanzhuyu (Corni Fructus)	Shudihuang (Rehmanniae Radix Praeparata)	10.87	100.00	5.11	Tonifies liver and kidney to nourish vision
Shanzhuyu (Corni Fructus)-Gouqizi (Lycii Fructus)	Shudihuang (Rehmanniae Radix Praeparata)	10.87	100.00	5.11	Strengthens liver-kidney synergy to nourish Yin and vision
Gouqizi (Lycii Fructus)-Fuling (Poria)	Shudihuang (Rehmanniae Radix Praeparata)	15.22	85.71	4.38	Supports spleen-kidney interaction and fluid metabolism
Shudihuang (Rehmanniae Radix Praeparata)-Fuling (Poria)	Zexie (Alismatis Rhizoma)	13.04	100.00	3.83	Promotes water metabolism and supports Yin
Shudihuang (Rehmanniae Radix Praeparata)-Gouqizi (Lycii Fructus)	Zexie (Alismatis Rhizoma)	15.22	85.71	3.29	Clears dampness and nourishes liver-kidney Yin
Juhua (Chrysanthemi Flos)-Gouqizi (Lycii Fructus)	Zexie (Alismatis Rhizoma)	15.22	85.71	3.29	Clears liver heat and brightens the eyes
Gouqizi (Lycii Fructus)-Fuling (Poria)	Zexie (Alismatis Rhizoma)	15.22	85.71	3.29	Tonifies liver and regulates fluid metabolism
Shanzhuyu (Corni Fructus)	Zexie (Alismatis Rhizoma)	10.87	80.00	3.07	Stabilizes essence while draining turbidity
Shanzhuyu (Corni Fructus)-Shudihuang (Rehmanniae Radix Praeparata)	Zexie (Alismatis Rhizoma)	10.87	80.00	3.07	Strengthens kidney essence and promotes water flow
Shanzhuyu (Corni Fructus)-Gouqizi (Lycii Fructus)	Zexie (Alismatis Rhizoma)	10.87	80.00	3.07	Nourishes liver and kidney while resolving dampness
Shudihuang (Rehmanniae Radix Praeparata)-Juhua (Chrysanthemi Flos)	Zexie (Alismatis Rhizoma)	10.87	80.00	3.07	Nourishes liver-kidney Yin and promotes fluid elimination

Antecedent and Consequent represent herb pairs identified by association rules. Support shows rule frequency, Confidence the conditional probability, and Lift the association strength.

3.5 Enrichment analysis of potential therapeutic targets

To further illustrate their inter-connections, a tripartite CHM-GM-POAG network was constructed (Figure 2B), revealing shared regulatory targets. Among them, the top-degree nodes in the PPI network—interleukin (IL)-6, protein kinase B (AKT1), tumor protein p53 (TP53), IL-1β, epidermal growth factor receptor (EGFR), B-cell lymphoma 2 (BCL2), estrogen receptor 1 (ESR1), caspase-3 (CASP3), proto-oncogene tyrosine kinase Src (SRC), and hypoxia-inducible factor-1α (HIF1A)—were identified as key enriched targets (Figure 2C).

KEGG pathway analysis revealed significantly involved pathways such as phosphatidylinositol 3 kinase-protein kinase B (PI3K-Akt), advanced glycation end products-receptor for the advanced glycation end products (AGE-RAGE), mitogen-activated protein kinase (MAPK), tumor necrosis factor (TNF), IL-17, and lipid metabolism/atherosclerosis signaling pathways (Figure 2D). CC analysis highlighted enrichment in components including membrane rafts, membrane microdomains, and receptor complexes (Figure 2E). MF enrichment showed significant involvement of protein kinase activity, kinase binding, and protein tyrosine/serine-threonine kinase activity (Figure 2E). BP analysis indicated enrichment in processes such as responses to hormone, responses to inorganic or xenobiotic stimuli, and positive regulation of cell migration or motility (Figure 2E).

3.6 GWAS summary statistics for GM and POAG

In the genetic data analysis of GM, under the conditions of a significance threshold of $P < 1 \times 10^{-5}$ and the exclusion of linkage disequilibrium, a total of 1 563 SNPs were identified. The *F*-statistic varied between 14.58 and 88.42, all surpassing the threshold of 10.

Detailed information for the instrumental SNPs used in the MR analysis, including microbial taxa, SNP identifiers, effect alleles, β coefficients, effect allele frequencies (EAFs), *P* values, and sample sizes, is provided in Supplementary Table S6.

3.7 MR-based causal effects between GM and POAG

The MR analysis identified six GM taxa significantly associated with POAG, in the IVW analysis (Figure 3). Specifically, *Ruminiclostridium 6* [odds radio (OR) = 0.73, 95% confidence interval (CI): 0.58 – 0.92, $P = 0.007$], *Ruminococcaceae UCG-002* (OR = 0.77, 95% CI: 0.63 – 0.96, $P = 0.018$), *Ruminococcus torques* group (OR = 0.71, 95% CI: 0.57 – 0.90, $P = 0.004$), and *Victivallis* (OR = 0.82, 95% CI: 0.70 – 0.96, $P = 0.016$) were negatively associated with POAG, suggesting potential protective effects. Conversely, *Actinomyces* (OR = 1.34, 95% CI: 1.06 – 1.68, $P = 0.013$) and *Blautia* (OR = 1.39, 95% CI: 1.01 – 1.90, $P = 0.042$) were positively associated with POAG risk.

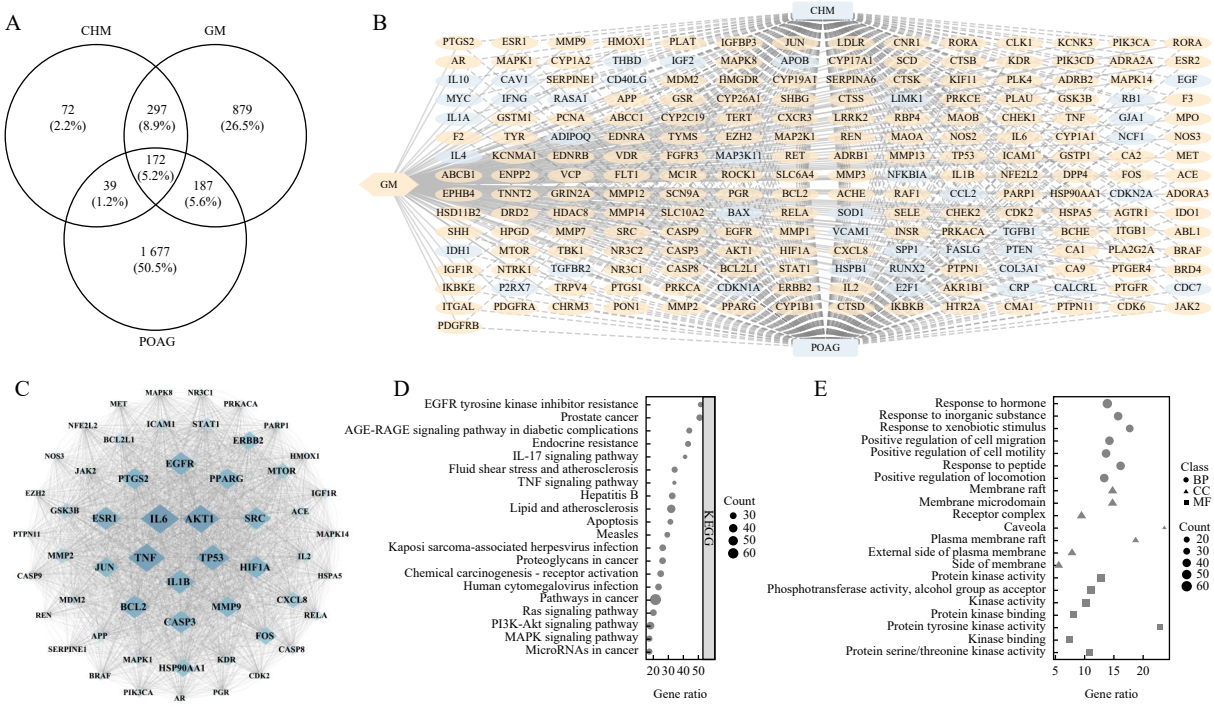

Figure 2 Network construction and enrichment analysis of CHM-GM-POAG targets

A, the intersection of CHMs, GM, and POAG-related targets. B, tripartite network of CHMs, GM, and POAG targets. Nodes represent 211 POAG-related targets linked to CHMs and/or GM; among which the orange nodes (n = 172) denote overlapping targets potentially regulated by CHMs via GM. Edges indicate associations between targets and CHM components, GM taxa, or POAG. C, PPI network of the 172 shared targets. Node size is proportional to degree centrality, with larger nodes indicating more interactions. D, KEGG pathway enrichment analysis for shared targets ralated to CHMs, GM, and POAG. E, GO enrichment analysis for CC, MF, and BP.

Heterogeneity was assessed using Cochran's Q test, and no significant heterogeneity was observed. MR-Egger intercept tests yielded P values > 0.05, indicating no evidence of directional pleiotropy.

Figure 3 – 5 summarize the MR results for these six taxa. In Figure 3, the IVW and MR-Egger estimates showed consistent effect directions across most SNPs. Figure 4 presents the regression lines from multiple MR methods, demonstrating stable associations without major outliers. Figure 5 shows largely symmetrical funnel

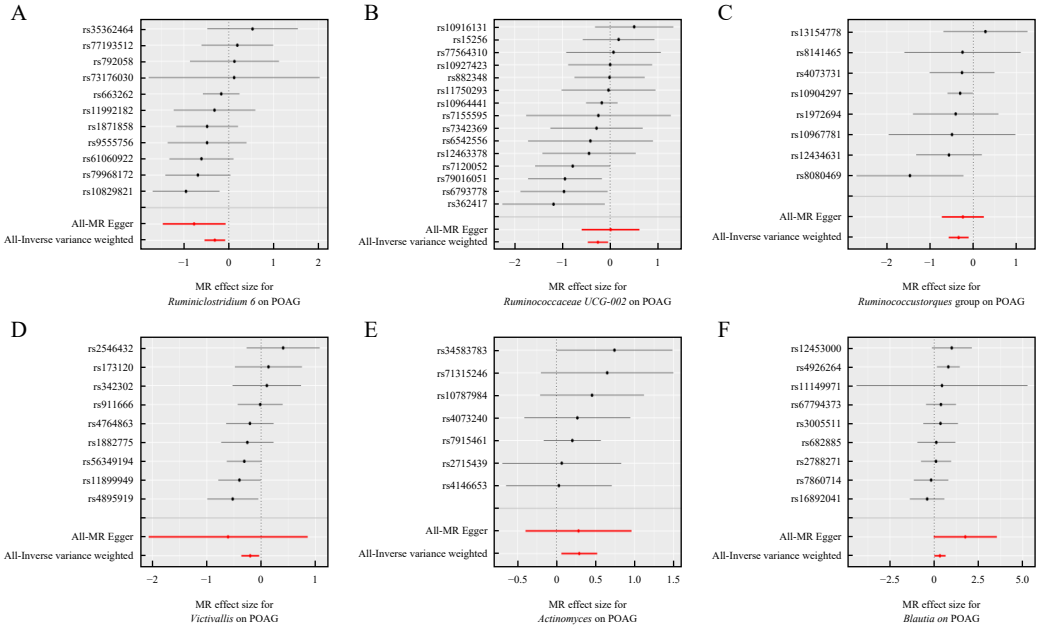

Figure 3 Forest plots of MR estimates between GM and POAG

A, *Ruminiclostridium 6*. B, *Ruminococcaceae UCG-002*. C, *Ruminococcus torques* group. D, *Victivallis*. E, *Actinomyces*. F, *Blautia*. Each panel presents SNP-level causal estimates obtained using IVW and MR-Egger methods. Red lines indicate the overall effect estimates from IVW and MR-Egger analyses, while black lines represent 95% CI of individual SNPs.

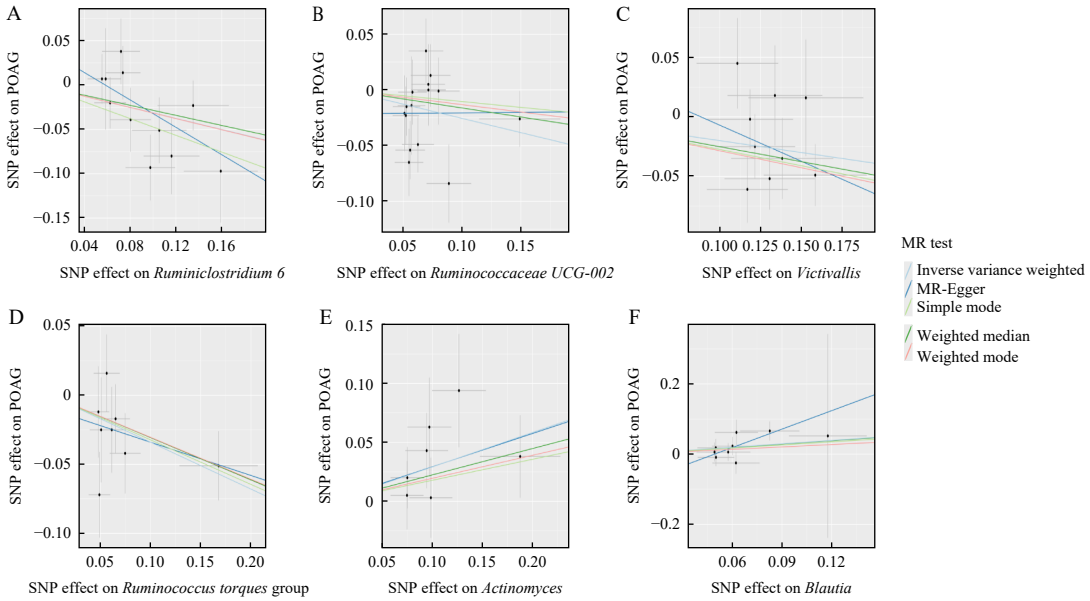

Figure 4 Scatter plots of SNP effects on GM and POAG

A, *Ruminiclostridium 6*. B, *Ruminococcaceae UCG-002*. C, *Ruminococcus torques* group. D, *Victivallis*. E, *Actinomyces*. F, *Blautia*. Each panel shows the scatter plots of MR analyses for GM taxa significantly associated with POAG. Dots represent individual SNPs, and colored lines correspond to causal estimates derived from different MR methods.

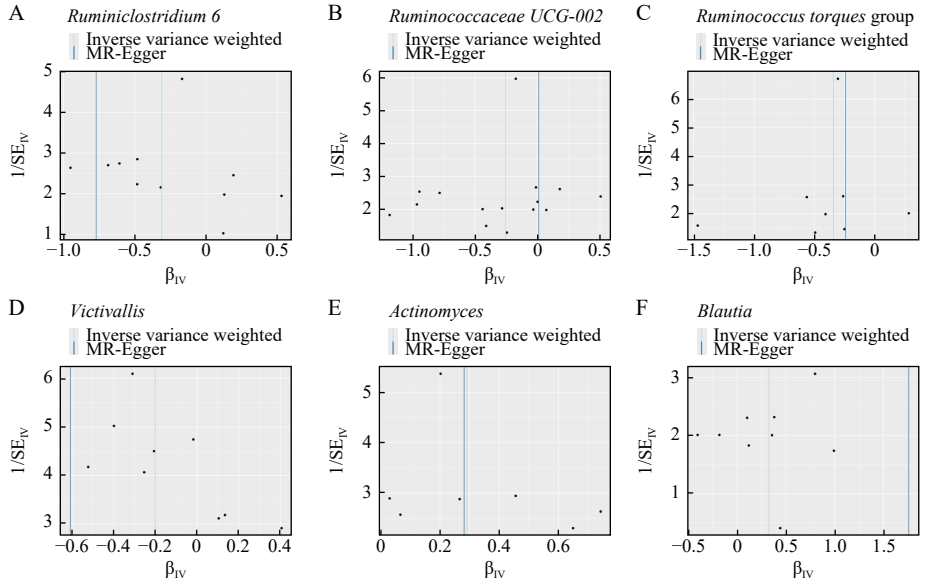

Figure 5 Funnel plots for assessing horizontal pleiotropy in MR analyses

A, *Ruminiclostridium 6*. B, *Ruminococcaceae UCG-002*. C, *Ruminococcus torques* group. D, *Victivallis*. E, *Actinomyces*. F, *Blautia*. Each panel shows funnel plots of SNP-level estimates for GM taxa included in the MR analyses. Dots represent individual SNPs, and vertical lines indicate causal estimates derived from the IVW and MR-Egger methods.

plots, suggesting no substantial horizontal pleiotropy and supporting the robustness of the causal effects.

Detailed results of heterogeneity (Cochran's *Q*), directional pleiotropy (MR-Egger intercept), global pleiotropy (MR-PRESSO global test), and leave-one-out (LOO) analyses are provided in Supplementary Table S7 – S12. Overall, these sensitivity analyses showed no significant heterogeneity, no evidence of horizontal pleiotropy, and no influential SNPs affecting the causal estimates.

4 Discussion

4.1 Integrative insights into CHM, GM, and POAG: contextualization within previous studies

Unlike previous studies focusing merely on herbs or clinical correlations, this work integrates computational, network-based, and causal-inference methods to construct a holistic framework linking CHMs, GM, and POAG.

The medication patterns identified in this study align well with TCM theories such as “the liver opens into the eyes” “the liver and kidney share the same origin” and “ocular disorders arise from disturbed water metabolism”. In clinical practice, CHM treatments for POAG commonly focus on soothing the liver and regulating Qi to restore energy flow, promoting blood circulation to improve ocular microcirculation, and resolving dampness to alleviate fluid retention. These therapeutic strategies aim to enhance ocular blood supply, reduce optic nerve compression, and slow visual function decline. The commonly used herbs are characterized by bitter, sweet, and pungent flavors and moderate cold or warm properties, reflecting a balanced principle of “combining cold and warm” and “addressing both the root cause and manifestations”. These therapeutic strategies provide a theoretical basis for individualized treatment of POAG, emphasizing flexible herbal combinations tailored to the patient’s constitution and disease pattern to enhance efficacy and slow disease progression.

In Western medicine, POAG is considered a neurodegenerative disease characterized by inflammation, oxidative stress, and immune dysregulation. Evidence from key CHMs identified in the association rule analysis suggests that many of these herbs exert biological effects through GM modulation.

First, several herbs demonstrate GM-mediated anti-inflammatory and metabolic regulatory effects. Zexie (Alismatis Rhizoma) has anti-atherosclerotic effects potentially related to the reduction of GM-derived metabolite trimethylamine N-oxide (TMAO) [43]; Gouqizi (Lycii Fructus) polysaccharides improve glucose and lipid metabolism and attenuate intestinal inflammation through reshaping GM regulation [44, 45]; Juhua (Chrysanthemi Flos) extracts alleviate hepatic oxidative stress and inflammation via GM regulation and activation of PPAR-related pathways [46].

Second, tonic herbs enhance gut barrier integrity through GM effects. Polysaccharides from Shudihuang (Rehmanniae Radix Praeparata) strengthen epithelial barrier function and improve GM composition [47]; the combination of Shudihuang (Rehmanniae Radix Praeparata) and Shanzhuyu (Corni Fructus) promotes gut barrier protection and regulates GM in kidney-related metabolic disorders [48]; polysaccharides from Fuling (Poria) exert immunomodulatory effects partly through GM modulation [49].

From a system biology perspective, network pharmacology analysis identified putative targets and pathways associated with CHM-GM co-regulation in POAG, primarily involving inflammatory responses, apoptosis, signal transduction, and metabolic regulation. KEGG enrichment further suggested that CHMs may suppress POAG progression mainly by modulating ocular metabolism through anti-inflammatory and antioxidative mechanisms. These findings indicate that CHM-GM interactions may act through multiple biological processes, including inflammation, oxidative stress, apoptosis, and metabolism.

Further supporting this hypothesis, our MR analysis identified genetic-level associations between specific GM taxa and POAG risk. Protective taxa, including *Ruminiclostridium 6*, *Ruminococcaceae UCG-002*, *Ruminococcus torques* group, and *Victivallis*, are primarily involved in cellulose degradation and short-chain fatty acid production, both crucial for maintaining intestinal homeostasis and regulating immune responses [50-54]. Conversely, *Actinomyces*, a genus associated with mucosal inflammation [55], showed a positive association with POAG risk, aligning with the concept of immune dysregulation in the gut-eye axis. Existing GM-ocular MR studies provide additional contextual support: *Ruminiclostridium 9* was linked to glaucoma susceptibility [56], while in the MR research of LIU et al. [57], *Ruminococcaceae UCG-011* was associated with an increased risk of diabetic retinopathy. Additionally, the abundance of *Ruminococcus* species in the GM of patients with Graves’ ophthalmopathy was significantly reduced compared with healthy individuals [58]. Although direct causal evidence remains limited, these findings have strengthened the biological plausibility of microbiota-mediated mechanisms in POAG pathogenesis and align with the gut-eye axis hypothesis.

Overall, these findings suggest that modulating GM may be one of the mechanisms underlying the therapeutic effects of CHMs in POAG. This integrated perspective bridges traditional medical theory and modern biomedical evidence, offering new insights into the gut-eye axis and providing a theoretical basis for future microbiota-targeted CHM strategies.

4.2 A proposed CHM-GM-eye axis mechanistic model

While not intended to establish a definitive causal chain, this study has proposed a hypothesis-driven CHM-GM-eye axis framework for POAG based on integrative analyses and literature evidence. The network pharmacology results suggested that core CHMs might influence POAG through signaling pathways that overlap with those influenced by specific GM, implying a potential indirect link between CHM activity and GM-mediated metabolic or immune regulation. In parallel, MR analysis identified several GM taxa with potential causal effects on POAG risk, highlighting microbial targets that could participate in CHM-responsive pathways.

Although this study did not directly demonstrate a causal interaction between CHMs and GM, previous pharmacological studies have shown that certain CHM components can reshape gut microbial composition and modulate metabolites such as short-chain fatty acids and trimethylamine-N-oxide. Integrating these findings, we

proposed a conceptual model in which CHMs might influence POAG pathophysiology partly through GM-related mechanisms involving immune regulation, oxidative stress, and vascular homeostasis.

From TCM perspective, this model aligns with the theory that "the liver opens into the eyes" and that the liver's regulation of Qi is closely associated with the spleen and stomach. The gut-liver-eye axis thus represents a convergence of TCM's holistic view of organ coordination and modern biomedical understanding of intestinal-hepatic-retinal interactions. This integrative framework offers a biologically plausible yet exploratory hypothesis for future mechanistic validation.

4.3 Limitations and future research directions

Regardless, this study has several limitations. First, the GWAS data used in the MR analysis were region-specific, and differences in genetic background, diet, and GM composition between exposure and outcome populations may limit the study's generalizability. Second, the causal link between GM effects on POAG and the influence of CHM components has not been experimentally validated. Future work should integrate multi-omics approaches, such as metagenomics and metabolomics, in larger and more diverse POAG cohorts to clarify these interactions.

To verify the proposed CHM-GM-POAG pathway, *in vivo* glaucoma models could assess whether key CHM pairs modulate IOP, optic nerve health, and GM composition, while *in vitro* microbial co-culture studies may identify direct microbiota-herb effects. These findings should be further confirmed through metabolomics and clinical studies combining CHM interventions with GM monitoring.

Minor heterogeneity in POAG diagnostic criteria among literature sources may exist, but since this study focused on identifying treatment patterns rather than assessing treatment efficacy, its impact is likely limited. Moreover, although environmental factors such as long-term medication or diet may affect GM composition, the MR approach minimizes such confounding by using randomly assigned genetic variants as instrumental variables, approximating a natural experiment that allows directional inference from GM to POAG.

5 Conclusion

This study systematically integrated data mining, network pharmacology, and Mendelian randomization to elucidate the potential interactions among CHM, GM, and POAG. The findings identified characteristic herb profiles, shared molecular pathways, and genetically predicted causal GM taxa related to POAG risk, suggesting that GM-mediated anti-inflammatory, antioxidative, and metabolic mechanisms may contribute to the therapeutic effects of CHMs. These results provide mechanistic clues that bridge CHM practices with modern microbiome science. Beyond revealing these associations, this study highlights the need for rigorous experimental and clinical validation. Future research should incorporate metagenomics, metabolomics, and controlled CHM interventions to clarify causal pathways and evaluate whether microbiota-targeted CHM strategies can translate into meaningful clinical benefits. Overall, this work offers a conceptual framework and research direction for advancing microbiota-based CHM approaches in glaucoma management.

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Competing interests

Qinghua PENG is an editorial board member for *Digital Chinese Medicine* and was not involved in the editorial review or the decision to publish this article. All authors declare that there are no competing interests.

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中药调节肠道菌群对原发性开角型青光眼的作用机制：数据挖掘、网络药理学与孟德尔随机化研究

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【摘要】目的 探讨中药通过调节肠道菌群影响原发性开角型青光眼（POAG）发生发展的潜在机制。**方法** 采用数据挖掘、网络药理学及双样本孟德尔随机化（MR）相结合的方法，系统研究中药–肠道菌群–POAG 三者之间的关联。通过文献数据挖掘识别 POAG 常用中药及其药对，并分析其性味与归经特征。进行靶点预测与通路富集分析，以揭示中药成分、肠道菌群及 POAG 间的共同分子通路。MR 分析用于评估特定菌群分类单元与 POAG 风险之间的遗传因果关系。**结果** 数据挖掘结果显示，POAG 治疗中常用中药主要具有苦、甘味，寒性，以归肝、肺、肾经为主，主要功效包括疏肝理气、活血利水。代表性药对包括熟地黄–枸杞配泽泻，枸杞–茯苓配熟地黄，菊花–枸杞配泽泻。网络药理学揭示了抗氧化、抗炎及代谢调控等共同作用通路。MR 分析结果表明，瘤胃梭菌 6 [比值比（OR）= 0.73，95% 置信区间（CI）: 0.58 ~ 0.92，P = 0.007]、瘤胃球菌 UCG-002（OR = 0.77，95% CI: 0.63 ~ 0.96，P = 0.018）、扭链瘤胃球菌组（OR = 0.71，95% CI: 0.57 ~ 0.90，P = 0.004）和长壁菌属（OR = 0.82，95% CI: 0.70 ~ 0.96，P = 0.016）的相对丰度升高与 POAG 风险降低相关，而放线菌属（OR = 1.34，95% CI: 1.06 ~ 1.68，P = 0.013）和布劳氏菌属（OR = 1.39，95% CI: 1.01 ~ 1.90，P = 0.042）与 POAG 风险升高相关。**结论** 本研究揭示了肠道菌群与 POAG 之间的潜在因果联系，并提供了中药可能通过调节肠道菌群发挥神经保护作用的综合证据。研究结果为肠–眼轴的理解提供了新的整合性视角，并为青光眼中基于微生物靶向的中药干预策略奠定了理论基础。

【关键词】中药；原发性开角型青光眼；肠道菌群；数据挖掘；网络药理学；孟德尔随机化