RESEARCH ARTICLE

Analysis of medication pattern of famous Chinese medicine practitioners in treating hyperuricemia based on network pharmacology

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The objectives of this study were to explore the prescription and medication rules of famous and old Chinese medicine practitioners in the treatment of hyperuricemia (HUA) and the targets and pathways of high-frequency medication in combination with network pharmacology, so as to provide ideas for clinical justification and prescription. We searched CNKI, Wanfang, VIP, and CBM for literatures related to famous and old Chinese medicine practitioners and "hyperuricemia" and performed association rule analysis and cluster analysis with the help of SPSS Modeler18 and SPSS Statistics21. TCMSP was used to screen the active ingredients of HF medicines, GeneCards and OMIM databases were used to collect disease targets, and STRING and DAVID websites were used to analyze protein interactions (PPI) and GO and KEGG enrichment pathways. A total of 25 papers were included in the study including 58 prescriptions and involving 170 flavors of traditional Chinese medicine. The high-frequency drugs included *Coix* seed, *Rhizona atractylodes macrocephala*, Indian bread, *Poria cocos*, and *Rhizoma dioscoreae tokoro*. The core constituents were quercetin, naringenin, loksinoside, stigmasterol, and steroidal alcohol. The core targets were TNF, IL6, TP53, and IL-1. The efficacy of the drug is to diuretic and seepage of dampness, while the medicinal properties are cold and bitter, and most medicines are attributed to the liver meridian. The combination of drug pairs was the strongest with the association of *Rhizoma atractylodis macrocephalae-Poria cocos*, *Radix clematidis-Rhizoma dioscoreae tokoro*, Indian Bread-*Rhizoma dioscoreae tokoro*, Indian bread-*Coix* seed, and *Rhizoma atractylodis macrocephalae-Astragalus*. The results showed that treatment of HUA by famous Chinese medicine practitioners was based on diuresis and seepage of dampness, clearing heat, and removing toxins. *Coix* seed, *Atractylodes macrocephala*, and *Poria cocos* were the most commonly used in the treatment process. The core components were quercetin, naringenin, and luo xinwuoside, which agonized the lipid and atherosclerotic pathways, TNF signaling, and other pathways, and worked together to treat HUA.

Keywords: hyperuricemia; data mining; famous doctors' experience; network pharmacology; medication patterns.

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Introduction

Hyperuricemia (HUA) is a metabolic disease in which the extracellular fluid is supersaturated with urate due to excessive production of uric acid in the body or impaired renal excretion. Under normal dietary conditions, HUA can be diagnosed when the fasting blood uric acid level is higher than 420 μmol/L in men and 360 μmol/L in non-menopausal women on two occasions not on the same day [1]. The incidence of HUA in China has shown a significant increase and low age trend in recent years and has now reached 13.3% with more than 120 million patients,

making it another common disease after diabetes mellitus [2]. Modern medical treatment of HUA mostly use allopurinol, benzbromarone, febuxostat, and other drugs to inhibit uric acid production and promote uric acid excretion. When the increase in uric acid caused by acute gouty arthritis attacks, the use of non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, glucocorticoids, and other drugs for anti-inflammatory treatment of long-term use may cause gastrointestinal discomfort, peptic ulcers, and even liver and kidney dysfunction and other side effects [3, 4].

In contrast, the treatment of HUA with Chinese medicine or the combination of Chinese and Western medicine has the unique advantages of low cost, small side effects, and obvious effects [5]. Although there is no specific disease name for HUA in Chinese medicine according to its symptoms, HUA can be categorized under the categories of "blood turbidity", "paralysis", and "calendar disease". Chinese medicine theory believes that the external wind, dampness, heat, cold, and other evils, wantonly eat fat, sweet, thick, and greasy will result in the spleen and stomach transportation disorder, or congenital deficiency of the spleen and kidneys, transportation and drainage of turbid disorder, dampness and turbidity, phlegm and dampness stagnation in the body, which causes the Qi and blood run poorly, resulting in blood stasis, blood heat, meridians and collaterals inaccessible, and therefore developing this disease. Traditional Chinese medicine clinically clears heat and dampness, phlegm and blood stasis, strengthen the spleen and kidney drainage, and uses other treatments to support the positive and eliminate the evil, which are supplemented by dietary control to achieve a more satisfactory therapeutic effect to a certain extent and supplemented by the shortcomings of modern medicine [6]. Therefore, drawing on the rich clinical experience of famous and old Chinese medicine practitioners is an important link to improve the clinical level of Chinese medicine and an urgent need to promote the inheritance and innovation of Chinese medicine. In this study, we collected the literature on the treatment of HUA by famous and old Chinese physicians and explored their treatment and medication laws, aiming to provide ideas for clinical medication and new drug development.

Materials and Methods

Research method

Using the key words of “State Medical Masters”, “National Famous Traditional Chinese Medicine Practitioners (TCMPs)”, the fifth batch of National Famous Elderly TCMPs, and the term "hyperuricemia" as the searching terms, and the names of authors and article titles as the searching fields, we searched the China Network of Knowledge (CNKI), Wanfang, VIP, and the Chinese Biomedical Literature Service System (CBM), respectively, and screened literatures on the experiences and medical cases, or data-mined literatures related to HUA treatment by various Famous Elderly TCMPs. HUA experience, medical cases or data mining literature, and the search period was from the establishment of the database to December 31, 2022. Inclusion criteria were (1) clinical experience or medical cases of national famous old Chinese medicine practitioners in the treatment of HUA, (2) drugs taken orally in the form of internal Chinese medicines and tonics, (3) literatures from multiple studies by the same author with the same composition of the same drugs, and only one of them would be included (the basic formula). The exclusion criteria included (1) literature with no clear drug composition, (2) literature that was not treated solely with internal Chinese medicine, (3) literature with no medical case support for review, (4) literature with HUA combined with other systemic diseases.

Network pharmacological methods

1. Active ingredient search

Through Traditional Chinese Medicine Integrated Database (TCMSP), the main active ingredients of *Coix lacryma*, *Atractylodes macrocephala*, *Poria cocos*, *Dioscorea villosa*, and their

pharmacokinetic parameters of absorption, distribution, metabolism, and excretion (ADME) were searched, respectively. The searching conditions were set to screen the drugs with oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18. The selected active ingredients were searched through TCMSP database for the corresponding target of action. All targets were normalized by Uniport, a universal protein database, to obtain a list of standard gene names of active ingredients and their corresponding targets.

2. Retrieval of disease therapeutic targets

Using "hyperuricemia" as the searching term, we searched the relevant disease gene information of hyperuricemia from GeneCards database (https://www.genecards.org/) and the database of Mendelian Inheritance in Man (OMIM) (https://www.omim.org/) to obtain a list of potential therapeutic target genes for hyperuricemia.

3. Construction of protein-protein interactions (PPI) network

The intersection of active ingredient targets and disease targets was calculated by the Venny 2.1 analysis platform, which is the potential target of drug for hyperuricemia. The target list was uploaded to the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (https://string-db.org/), while the species was selected as "Homo sapiens", and the interaction score was set to ≥ 0.7 to obtain the PPI network diagram. The tsv file provided by the platform was downloaded and imported into the database. Cytoscape 3.7.1 software (https://cytoscape.org/) was used to analyze the key targets.

4. GO biofunctional annotation and KEGG pathway enrichment analysis

A total of 63 targets were uploaded to Database for Annotation, Visualization and Integrated Discovery (DAVID) (https://david.ncifcrf.gov/) for KEGG and GO Biological process, GO Cellular component, GO Molecular function analysis.

Data standardization

In order to ensure the accuracy and reliability of data analysis, the names of the Chinese medicines included in the study were normalized. Based on the "Traditional Chinese Medicine" and "Chinese Pharmacopoeia", the same specification was made for those with different names of the same kind of traditional Chinese medicine tablets in the included literature.

Statistical analyses

To establish a database of hyperuricemia treatments, formulas, and patients' four diagnostic data, all data were entered into Microsoft Excel 2020 (Microsoft, Redmond, WA, USA) including the frequency of treatments, the frequency of drugs, and the statistics of drug flavors. SPSS 26.0 (IBM, Armonk, NY, USA) was used to perform clustering analysis of cures. The high-frequency drugs were analyzed by association rules of SPSS Modeler 18 software.

Results and discussion

Incorporation of expert composition

A total of 25 medical practitioners met the inclusion criteria, involving 56 papers. Among them, there were 3 masters of national medicine, 14 instructors of national famous Chinese medicine experts in succession of academic experience and their successors, and 8 provincial famous Chinese medicine practitioners (Table 1).

Analysis of the frequency of medicines used by famous doctors

Involving a total of 170 flavors of medicines, the top 20 medicines in terms of frequency were shown in Table 2. The medicines with a frequency of more than 20 were *Coix* seed, *Rhizoma atractylodes macrocephala*, and *Poria cocos*. The medicinal properties of the drugs were most cold and bitter. The drugs attributed to the liver meridian were the most (Figure 1).

Drug cluster analysis

Cluster analysis of drugs yielded two main categories including group Ⅰ: Indian breads,

Table 1. Incorporation of the classification of experts.

Physician Honors	Physician's name
National Master of Chinese Medicine	Liangchun Zhu [7], Tietao Deng [8], Xin Zheng [9]
National Famous Elderly Chinese Medicine Experts Experience Succession Instructor or Successor	Xiaolin Tong [10], Yinqi Hu [11], Yiping Chen [12], Yaoguang Wang [13], Zhilong Zhang [14], Xiaotang Qiu [15], Shaojie Wang [16], Mengyong Wang [17], Mingshuang Zhu [18], Mingquan Li [19], Jinguo Cheng [20], Huilin Li [21], Shaorong Fan [22], Peichu Peng [23]
Provincial Famous Chinese Medicine Practitioner or other experts engaged in kidney disease research	Dinghua Zhang [17], Genping Lei [24], Weifeng Sun [25], Pingdong Zheng [26], Jianyong Zhang [27], Huazhen Liu [28], Jinghua Ye [29], Xiaowen Chen [30]

Table 2. Frequency of high-frequency drugs.

No.	Drug	Frequency	Percentage	No.	Drug	Frequency	Percentage
1	*Coix* Seed	21	3.49%	11	*Alisma*	13	2.16%
2	*Rhizoma Atractylodis Macrocephalae*	20	3.32%	12	*Radix clematidis*	12	1.99%
3	Indian Bread	20	3.32%	13	*Achyranthes bidentata*	11	1.83%
4	*Poria Cocos*	19	2.66%	14	*Peach Kernel*	11	1.83%
5	*Rhizoma Dioscoreae Tokoro*	16	2.33%	15	*Edible tulip*	10	1.67%
6	*Atractylodis Macrocephalae*	14	2.16%	16	*Codonopsis pilosula*	9	1.5%
7	*Rhubarb*	13	2.16%	17	*Rehmannia*	9	1.5%
8	*Salvia miltiorrhiza*	13	2.16%	18	Chinese Yam	9	1.5%
9	*Phellodendron Bark*	13	2.16%	19	Dodder Seed	9	1.5%
10	*Astragalus*	13	2.16%	20	*Scutellaria baicalensis*	8	1.33%

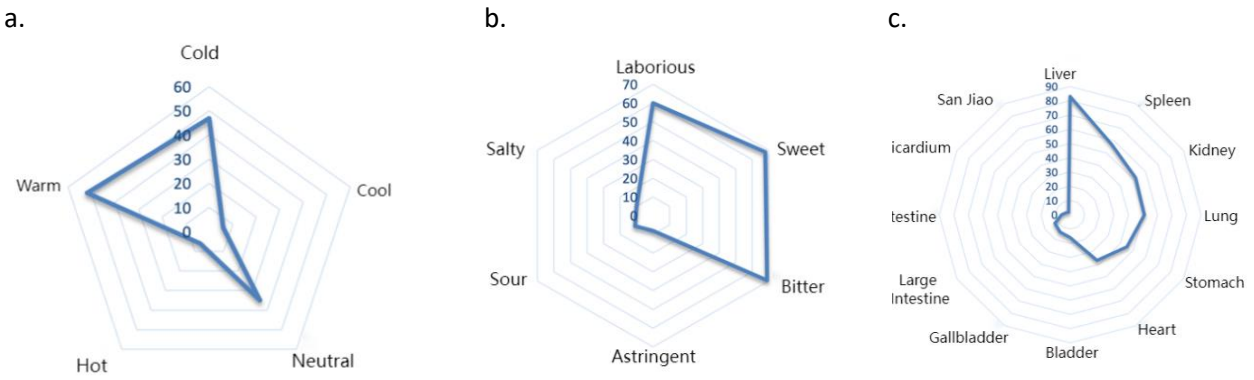

Figure 1. Statistical chart of drug properties (a), medicinal flavors (b), drug categorization (c).

Rhizoma dioscoreae tokoro, *Radix clematidis*, *Edible tulip*, *Salvia miltiorrhiza*, *Atractylodis macrocephalae*, *Phellodendron Bark*, *Coix* seed, *Achyranthes bidentatae*, *rhubarb*, *Scutellaria baicalensis*, and II: *Rehmannia*, Chinese yam, Dodder Seed, *Poria cocos*, *Alisma*, *Rhizoma*

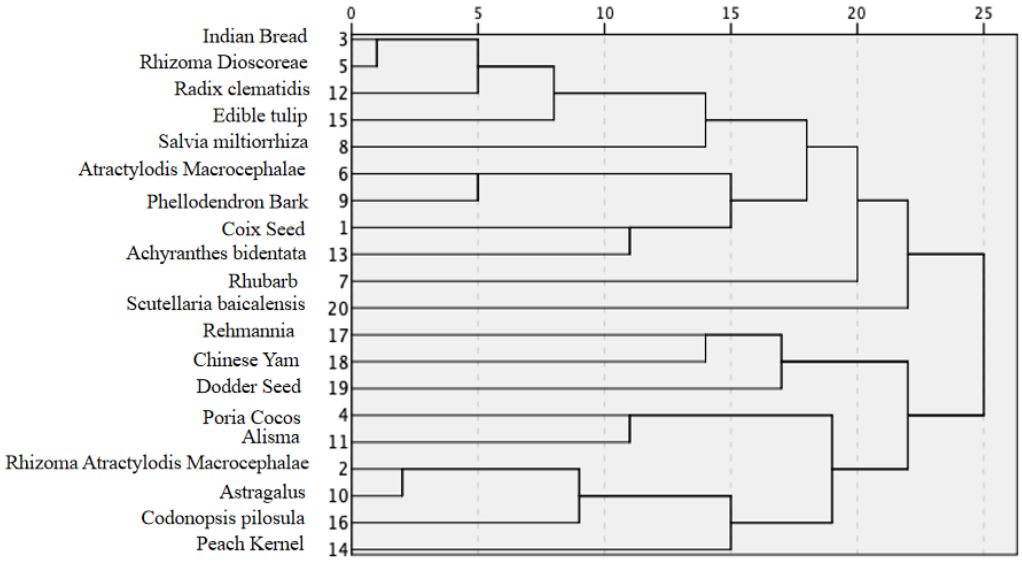

Figure 2. Drug clustering diagram.

Table 3. Formulary of drugs.

Association	Example	Support (%)	Confidence (%)
Rhizoma dioscoreae tokoro → Indian bread	16	27.59	87.5
Astragalus → *Rhizoma atractylodis macrocephalae*	13	22.41	92.31
Radix clematidis → *Rhizoma dioscoreae tokoro*	12	20.69	83.33
Edible tulip → Indian bread	10	17.24	80.00
Eupatorium → Indian bread	7	12.07	85.71
Szechuan Lovage Rhizome → Peach Kernel	6	10.34	83.3
Coix seed + *Rhizoma dioscoreae tokoro* → Indian bread	12	20.69	100.00
Rhizoma atractylodis macrocephalae + Indian bread → *Astragalus*	9	15.51	88.89
Phellodendron Bark + *Coix* seed → *Atractylodis Macrocephalae*	7	12.07	100
Radix clematidis + *Rhizoma dioscoreae tokoro* + *Coix* seed → Indian bread	7	12.07	100
Achyranthes bidentata + *Atractylodis Macrocephalae* → *Coix* seed	5	8.62	100
Eupatorium + Edible tulip → *Coix* seed	5	8.62	100
Eupatorium + *Astragalus* + *Rhizoma atractylodis macrocephalae* → *Coix* seed	5	8.62	100
Eupatorium + *Astragalus* + *Rhizoma atractylodis macrocephalae* → Edible tulip	5	8.62	80

atractylodis macrocephalae, *Astragalus*, *Radix et rhizoma*, *Salvia miltiorrhiza*, Peach kernel (Figure 2).

Analysis of the pattern of prescription formation of each famous doctor

SPSS modeler was used to analyze the medications used, and a total of 22 groups of drug pairs with a confidence level of 100% were obtained (Table 3). The strength of the association between Chinese medicines was shown in Figure 3, in which the thickness of the

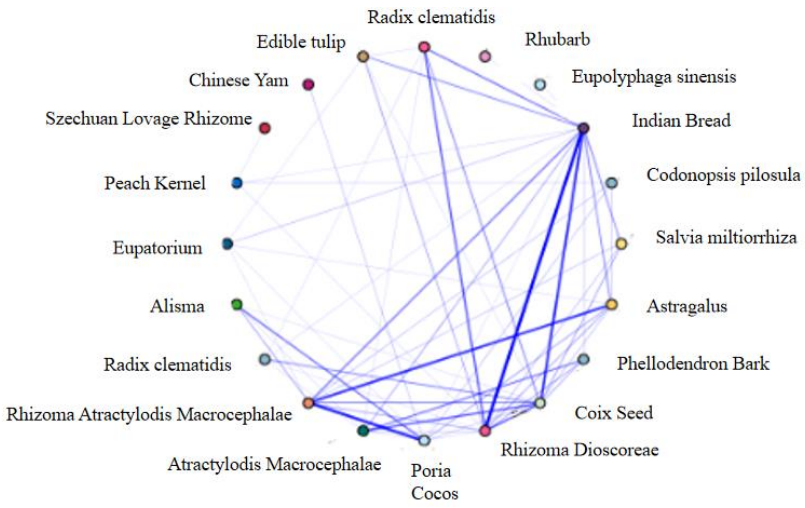

Figure 3. Drug use association mapping.

connecting lines represents the strength of the association between the medicines, and the strongest pairs of medicines with the strongest strength of the association were *Rhizoma atractylodis macrocephalae-Poria cocos*, *Radix clematidis-Rhizoma dioscoreae tokoro*, Indian Bread-*Rhizoma dioscoreae tokoro*, Indian bread-*Coix* seed and *Rhizoma atractylodis macrocephalae-Astragalus*, respectively.

Screening of drug components

Coix seed, *Rhizoma atractylodis macrocephalae*, *Poria cocos*, Indian bread, and *Rhizoma dioscoreae tokoro* were entered into the "Herb Name" search field of TCMSP database, respectively, to preliminary their active ingredients and their ADME parameters. According to the screening conditions of OB ≥ 30% and DL ≥ 0.18, a total of 45 active ingredients meeting the requirements were finally obtained.

Prediction of potential targets of drugs

By searching TCMSP and STITCH databases, a total of 135 targets corresponding to the above 45 active ingredients were predicted. Using "Hyperuricemia" as the search term, we searched for the therapeutic targets of related diseases through the databases GeneCards and OMIM, respectively, of which 843 targets were obtained by using relevance score ≥ 1 as the selection criterion in the database GeneCards. Venny 2.1 online platform was used to draw the Wayne diagram of the intersection between drug targets and disease targets and 63 intersecting targets were obtained (Figure 4).

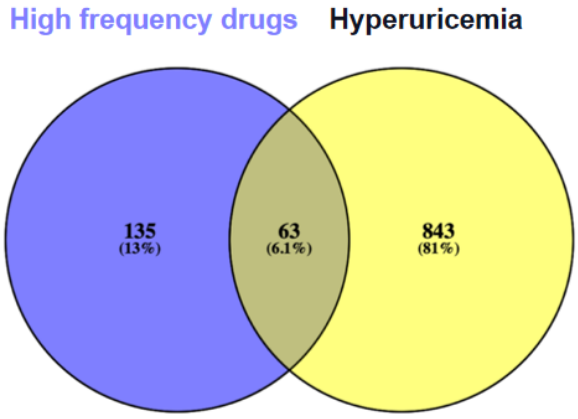

Figure 4. Wayne diagram.

Construction and analysis of PPI network

By uploading 63 targets to the protein interaction analysis platform (STRING) and setting the species (Organization) as "Homo sapiens", the interaction score ≥ 0.4, the nodes with no interactions were hidden, and the rest of the parameters were set as default, the PPI network diagram was drawn by using the Cytoscape 3.9.1 software (Figure 5), and analyzed by Network

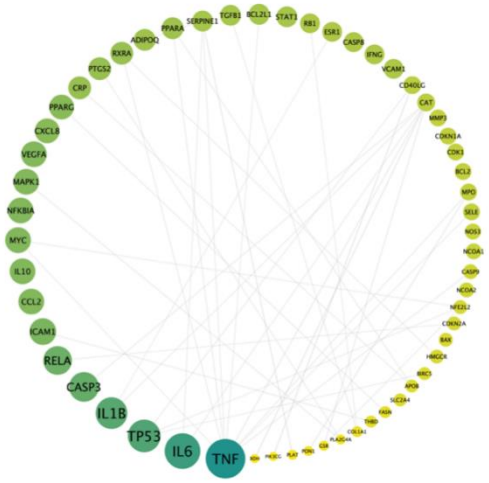

Figure 5. PPI network diagram for high frequency targets.

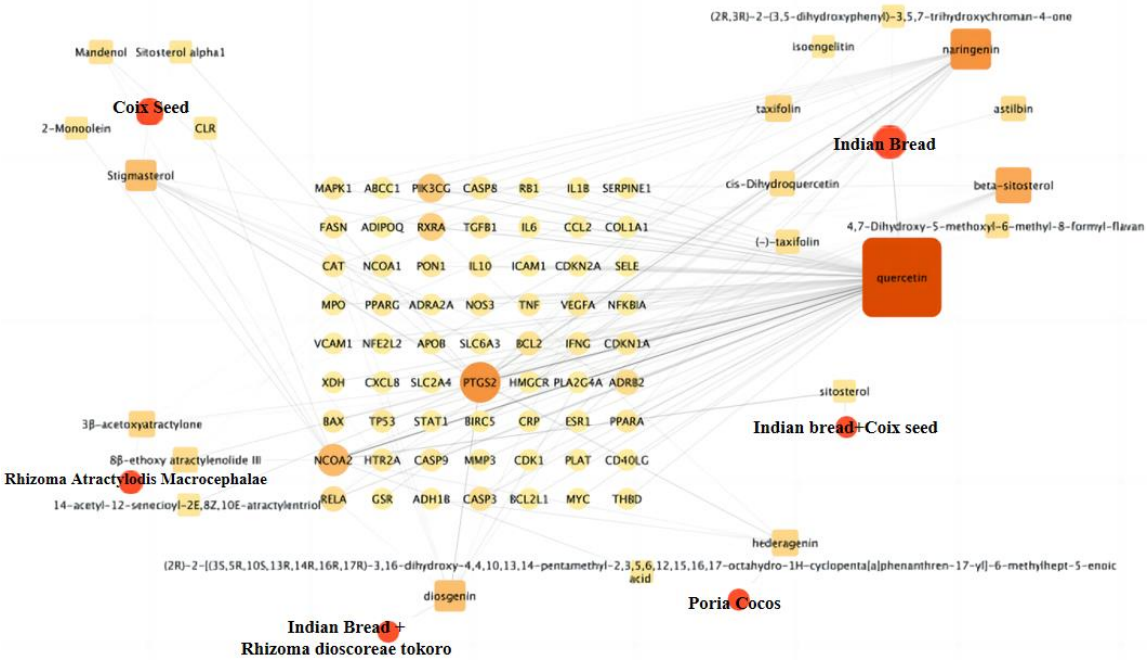

Figure 6. Drug-ingredient-target mapping.

Analysis plug-in. The results showed that the targets of TNF, IL6, TP53, and IL-1 were the core proteins for the treatment of HUA. The network of TCM-active ingredients-targets was constructed with the network graph consisting of 91 nodes and 150 edges with an average of 3.29 neighboring nodes per node (Figure 6). The degree in the network referred to the number of edges associated with the node, i.e., the higher the degree indicated the more interactions at that point. The results suggested that the targets of PTGS2, NCOA2, and PIC3CG might be the core targets of the drugs for the treatment of HUA, and that quercetin, naringenin, stigmasterol, sitosterol, and stigmasterol might be the core targets for the treatment of HUA with quercetin as the most important target (Table 4).

Table 4. List of active ingredients of drugs.

MOL ID	Ingredient	Name	OB (%)	DL	Origin
MOL001323	Sitosterol alpha1	α1-Sitosterol	43.28	0.78	Coix Seed
MOL001494	Mandenol	Ethyl linoleate	42	0.19	Coix Seed
MOL000449	Stigmasterol	Soy sterol	43.83	0.76	Coix Seed
MOL000049	3β-acetoxyatractylone	Acetoxycanthone	274.39	3.39	Rhizoma Atractylodis Macrocephalae
MOL013117	4,7-Dihydroxy-5-methoxyl-6-methyl-8-formyl-flavan	4,7-Dihydroxy-5-methoxy-6-methyl-8-formylxanthane	314.36	2.69	Indian Bread
MOL000358	beta-sitosterol	β-Sitosterol	414.79	8.08	Indian Bread
MOL004328	naringenin	Naringin	272.27	2.3	Indian Bread
MOL004575	astilbin	Naringenin	450.43	0.63	Indian Bread
MOL004576	taxifolin	Dihydroquercetin	304.27	1.49	Indian Bread
MOL000546	diosgenin	Diosgenin	414.69	4.63	Indian Bread、Rhizoma Dioscoreae Tokoro
MOL000098	quercetin	Quercetin	302.25	1.5	Indian Bread
MOL000296	hederagenin	Quercetin	414.79	8.08	Poria Cocos
MOL000359	sitosterol	Sterol	414.79	8.0	Indian Bread、Coix Seed
MOL000072	8β-ethoxy atractylenolide III	8β-Ethoxylated atractylenolide-III	276.41	3.68	Rhizoma Atractylodis Macrocephalae
MOL001736	(-)-taxifolin	Dihydroquercetin	304.27	1.49	Indian Bread
MOL000022	14-acetyl-12-senecioyl-2E,8Z,10E-atractylentriol	14-Acetyl-12-chiridonoyl-8-cis-orthotriol	356.45	3.54	Rhizoma Atractylodis Macrocephalae
MOL008121	2-Monoolein	2-Octadecenoic acid monoglycerides	34.23	0.29	Coix Seed
MOL004580	cis-Dihydroquercetin	Dihydroquercetin	304.27	1.49	Indian Bread
MOL013129	(2R,3R)-2-(3,5-dihydroxyphenyl)-3,5,7-trihydroxychroman-4-one	Dihydromorin	304.27	1.49	Indian Bread
MOL004567	isoengelitin	Isoxanthoside	434.43	0.89	Indian Bread
MOL000953	CLR	Clr	37.87	0.68	Coix Seed
MOL000273	(2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-6-methylhept-5-enoic acid	9-Dehydroporanic acid	470.76	5.41	Poria Cocos

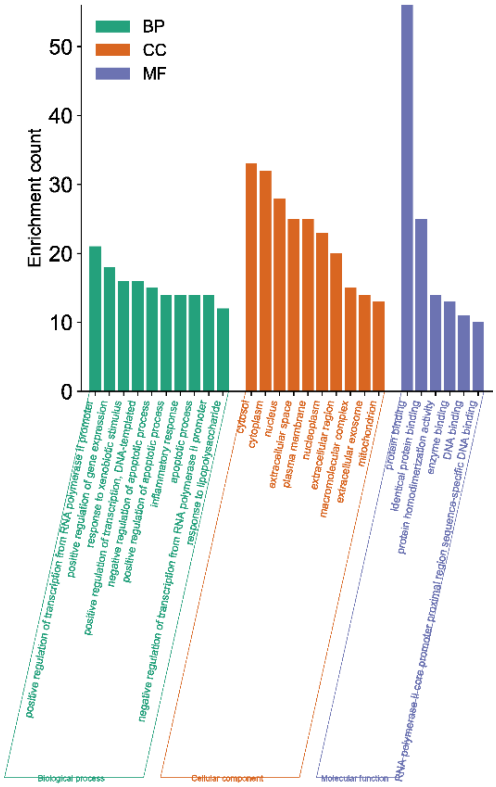

Figure 7. Key target GO analysis graph.

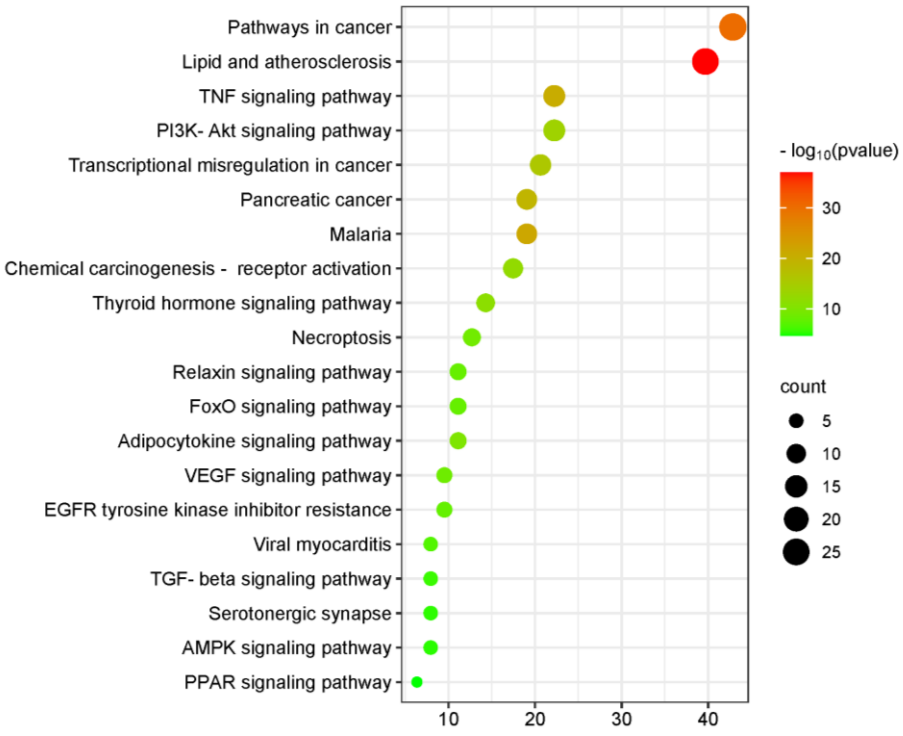

Figure 8. Enrichment analysis of KEGG pathway for key targets.

GO biofunctional annotation and KEGG pathway enrichment analysis

The 63 predicted targets were loaded to the David database for GO biological function annotation and KEGG pathway enrichment analysis. In the Biological Process (BP) category, it involved transcriptional regulation of RNA polymerase II promoter, apoptosis regulation, and response to lipopolysaccharides, among others. For the Cellular Component (CC), it included cytoplasm, extracellular matrix, exosome, and mitochondria, among others. In the Molecular Function (MF) category, it covered protein homodimer activity, protein binding, RNA polymerase II core promoter, and more (Figure 7). The KEGG pathway analysis revealed prominent pathways such as the lipid and atherosclerosis pathway, the AGE-RAGE signaling pathway in diabetic complications, and cancer pathways, among others (Figure 8).

Discussion

Medicines

The results of the study showed that the five Chinese medicines with the highest frequency of use in the treatment of hyperuricemia had obvious diuretic effects, among which *Coix* seed was often used in paralysis contracture and edema caused by dampness with anti-inflammatory and analgesic effects. Indian bread belongs to the heat-cleansing medicine with detoxification, dehumidification, and joint facilitation. It contains resveratrol that can inhibit the expression of mRNA related to xanthine oxidase, thus reducing the production of uric acid. It can also inhibit the secretion of IL-1 and reduce the level of NF-B expression [31], thus reducing the production of inflammatory factors and chemokines and inflammatory cell infiltration and alleviating the inflammation and pain of acute attack of gout caused by HUA. From the results of drug clustering, it was found that the drugs used to treat HUA could be classified as diuretics, expectorants of blood stasis, and tonic drugs. Because the main pathogenic factors of HUA are dampness, turbidity, phlegm, blood stasis, and deficiency, which need to be treated in phases according to the clinical symptoms and the development of the disease, for example, a master of the State Medical College classified the hyperuricemia into four phases as the stage of spleen and kidney Qi deficiency, the stage of dampness and turbidity aggregation, the stage of dampness and toxicity infiltration, and the stage of dampness and blood stasis mutual conjugation, and planed resolving turbidity and dampness, activating blood circulation, and removing stasis as therapeutic means [9]. The protein interaction network diagram of key drug targets demonstrated that TNF, IL6, TP53, IL-1 were the key targets for the treatment of HUA. Indian bread has the effect of inhibiting the secretion of IL-1 and lowering the level of inflammatory factors such as IL-1, IL-6, *etc*., therefore, could be the core of the formula for HUA treatment in Chinese medicine. In addition, the aqueous extract of *Rhizoma dioscoreae tokoro* also down-regulated the gene expression of tumor necrosis factor (TNF-α) in the kidney [32], which reduced the inflammatory response during hyperuricemia. Quercetin, naringenin, and stigmasterol all have anti-inflammatory effects with quercetin regulating inflammatory responses through the signaling pathway of IL-6, naringenin reducing inflammation by inhibiting the expression of TNF-α, *etc*., and stigmasterol interfering mitogen-activated protein kinase 3 (MAPK3), PRKACA mRNA, and protein expression, regulating cytokine release and exerting anti-inflammatory effects [33-35]. Another active ingredient is astilbin, a main components of Indian bread, which has been shown to have diuretic and analgesic as well as anti-inflammatory effects [36]. Go and KEGG analyses showed that the biological processes and pathways involved were RNA polymerase II promoter transcriptional regulation, apoptosis regulation and response to lipopolysaccharides, protein homodimerization, lipid and atherosclerosis pathways, sclerosis pathway, TNF signaling pathway [37], PI3K-Akt signaling pathway, lipocytokine pathway, AMPK, and PPAR signaling pathway. Atherosclerosis is associated in the lipid cytokine pathways with lipocalin

reducing plasma glucose and free fatty acids. Cardiovascular disease has been found to be one of the risk factors for increased blood uric acid [38].

Formulas

Many previous studies mentioned the use of Si Miao Pill with additional reductions in the treatment of hyperuricemia [18, 19, 21, 22, 38]. This formula consists of four herbs including *Atractylodes macrocephala*, *Phellodendron bark*, *Achyranthes bidentata*, and *Coix* seed, which have the effects of clearing heat and inducing dampness, removing paralysis, relieving pain, and expelling blood stasis and promoting menstruation, and have been used in the case of hyperuricemia with internalized dampness-heat. In the formula, *Atractylodes macrocephala* and *Phellodendron bark* have the efficacy of clearing heat and drying dampness, and *Achyranthes bidentata* strengthens the muscles and bones, and draws *Atractylodes macrocephala* and *Phellodendron bark* into the lower Jiao so that the heat can go down from the lower Jiao. *Coix* seed is used into the foot Yangming stomach meridian of the light seepage of dampness, clearing heat and removing paralysis, soothing the tendons, and activating the collaterals, and there is a "treatment of impotence to take the yangming alone" meaning. Xiaolin Tong academician clinically commonly used Indian Bread, *Rhizoma dioscoreae tokoro*, *Radix clematidis* to form a three-flavored small formula [39]. The three drugs can be used to facilitate the removal of dampness and turbidity to facilitate the joints, against hyperuricemia dampness, and turbidity within the effect is remarkable. *Rhizoma dioscoreae tokoro* has therapeutic effect on "cream drench" and "white turbidity" and may reduce the reabsorption of uric acid in renal tubules by down-regulating the expression of uric acid salt transporter 1 (URAT1) gene and protein [40]. *Rhizoma dioscoreae tokoro* can decrease the uric acid reabsorption in hyperuricemia [41]. The aqueous extract of *Rhizoma dioscoreae tokoro* can lower the uric acid level [42], reduce the level of monocyte chemotactic protein-1 (MCP-1) in the serum of hyperuricemia rat model, and down-regulate the gene expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)[32], which have a certain alleviating effect on gouty arthritis caused by hyperuricemia. Weifeng Sun formulated his own compound formula Indian Bread Granules with Indian Bread as the monarch and *Rhizoma dioscoreae tokoro*, Indian Bread, Wang Bu Liuhang, and *Achyranthes bidentata*, which has the effect of clearing heat and dampness, resolving phlegm and dispersing blood stasis [25]. It was found that compound Indian Bread granules could inhibit the activities of xanthine dehydrogenase (XDH) mRNA and XOD, reduce the levels of inflammatory factors such as IL-1 and IL-6, and decrease the production of uric acid [41-43].

Conclusion

This study explored the new therapeutic ideas and potential mechanisms of hyperuricemia treatments by analyzing the medications used by famous Chinese medicine practitioners. The main therapeutic methods included inducing dampness, resolving blood stasis, draining turbidity, clearing heat, and tonifying the spleen and kidney. Commonly used medicines included *Coix* seed, *Rhizoma atractylodis macrocephalae*, Indian bread, *Poria cocos*, and *Rhizoma dioscoreae tokoro* with most of them belonging to the liver meridian and spleen meridian, and sweet and bitter drugs. The main drug pairs were *Rhizoma atractylodis macrocephalae* - *Poria cocos*, *Radix clematidis* - *Rhizoma dioscoreae tokoro*, Indian bread - *Rhizoma dioscoreae tokoro*, Indian bread - *Coix* seed, and *Rhizoma atractylodis macrocephalae* - *Astragalus*. This study mainly focused on the action mechanisms of Indian bread and *Rhizoma dioscoreae tokoro*, which were down-regulation of the expression level of inflammatory factors, reduction of uric acid absorption to promote uric acid excretion, and many other aspects. Future studies of the other active ingredients, targets, and pathways of action of Chinese medicines in the treatment of hyperuricemia are needed, which will not only

help to promote the modernization and scientification of traditional Chinese medicine, but also provide useful references for the development of new therapeutic methods and drugs for hyperuricemia, offering more possibilities for the treatment of the disease, and will also help to integrate the unique therapeutic advantages of Chinese medicine with modern medicine to provide patients with a more comprehensive healthcare solution.

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