RESEARCH ARTICLE

Visual analysis of literatures on Traditional Chinese Medicine treatment of hyperuricemia based on CiteSpace and VOSviewer

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The aim of this study was to thoroughly explore the cutting-edge trends, current status, and hotspots of Traditional Chinese Medicine (TCM) in the prevention and treatment of hyperuricemia (HUA) with a view to providing an innovative direction for the prevention and treatment of HUA with Chinese medicine in the future. Literatures related to the treatment of HUA with TCM published on China Knowledge Network (CNKI), Wanfang Data (Wanfang), and China Biological Literature Service Database (SinoMed) were searched. With bibliometrics as the theoretical support, the literatures were visualized and analyzed in depth for publication year trend, authors, institutions, and keywords with the help of CiteSpace 6.1.R3 and VOSviewer 1.6.R3. Results showed that the search yielded a total of 1,795 relevant documents, among them 1,782 documents were screened and included in the comprehensive study. The total number of authors with 10 or more publications was 9, among which Zhijian Lin was the most prolific author with 23 publications, and the total number of core authors was 164. The number of publications from universities is high, and the core institution is Beijing University of Traditional Chinese Medicine with 61 publications. There was close cooperation among universities. The research hotspots about TCM treatment of hyperuricemia mainly focused on the cutting-edge scientific research areas such as data mining, molecular docking, and network pharmacology. The results suggested that research teams should strengthen academic exchanges and actively integrate traditional therapies of TCM with modern scientific and technological means to promote the modernization of TCM. In addition, in-depth exploration of innovative concepts involved in the literatures such as the integration of personalized medicine and precision drug design in the treatment of hyperuricemia found that they were expected to lead to a new trend in the future of TCM in the prevention and treatment of hyperuricemia.

Keywords: hyperuricemia; Traditional Chinese Medicine (TCM); CiteSpace; VOSviewer; visualization.

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Introduction

Hyperuricemia (HUA) is a clinical disorder caused by abnormal purine metabolism or reduced uric acid excretion and has become a global health problem that cannot be ignored. With the improvement of people's living standard, the change of dietary structure and the change of lifestyle, the number of HUA patients in various countries is increasing [1, 2]. HUA is closely related to obesity, hypertension, coronary heart disease, diabetes mellitus, *etc*., and its clinical manifestations not only include joint redness, swelling and arthritis, but also may be accompanied by renal disease and other serious complications. Especially for asymptomatic HUA

patients, although they do not show symptoms such as arthritis, the existence of HUA also brings certain health risks.

In Chinese medicine, HUA is named as "calendar disease", "heat paralysis", "blood turbidity", *etc*. Commonly used medicines include cypress, Poria cocos, Atractylodes macrocephala, and Psyllium carinatum, *etc*. Commonly used formulas include Si-Miao-San plus reduction, Yu Ping-Feng-San, Gui-Zhi Shao-Yao Zhi-Mu Tang, *etc*. [3-5], Jade Screen Fung San, Gui Zhi Paeoniae Zhi Mu Tang, *etc*. These herbal treatment protocols not only have a long history, but also reflect the profound understanding and treatment experience of TCM for HUA. With the rapid development of big data and computer technology, data mining and other technologies are widely used in various disciplines. The combination of literature study and experimental investigation has become the mainstream of current research, which brings more profound understanding and systematic results for scientific research. The CiteSpace software (https://citespace.podia.com) used in this study is a citation analysis software using Java language. Based on scientometrics and data visualization and analysis, CiteSpace can quantitatively analyze the relevant literature in the field of research, so as to make the evolution of research in the field and the distribution of hotspots clear, and also provide a more intuitive and comprehensive understanding [6, 7].

In this research, CiteSpace and VOSviewer (www.vosviewer.com) software were applied to map the retrieved HUA-related literature into a visualization map, which sought to comprehensively understand the current research status of TCM for HUA in terms of multiple dimensions such as citation relationship, author collaboration network, and keyword distribution. Meanwhile, the in-depth mining of the literature data would help to reveal potential research hotspots and innovative directions, providing a more comprehensive guide for the future in-depth exploration of TCM in the treatment of HUA. The application of this research methodology would help promote the modernization of TCM and better serve human health.

Materials and methods

Data collection

In this research, China Knowledge Network (CNKI) (www.cnki.net), Wanfang Data (Wanfang) (www.wanfangdata.com), and China Biological Literature Service Database (SinoMed) (www.sinomed.com) were systematically searched to incorporate the relevant literature data. The search style of CNKI was adopted as an advanced search with the "subject term = HUA", and the catalogs of the literature classifications were Traditional Chinese Medicine, Traditional Chinese Pharmacy, and Integrative Medicine under Medicine and Health Science and Technology. The cross-library selection was journals, the time range was set from January 1, 2002 to November 1, 2022, and the language restriction was Chinese. A total of 1,795 documents were obtained. In Wanfang database, advanced search was used with "subject = HUA", the document type was journal, subject classification was Chinese medicine, the time span was 2002-2022, and the search results yielded 1,442 documents. In SinoMed, the advanced search with the subject term "HUA", the discipline selection of Chinese medicine, and the time span of 2002-2022 yielded 1,063 documents. Considering the clear correlation between academic quality and research topic, EndNote X9 software (Clarivate, London, UK) was used to screen duplicates, missing documents, and documents that were not related to the research topic, and finally obtained 1,782 documents that met the research criteria. The flow of the literature screening process was shown in Figure 1. Literature was exported *via* Refworks format in the format download of ***.txt. Subsequently, the literature data was converted to Web of Science format using the built-in Data Import/Export function of CiteSpace 6.1.R3 to ensure data normalization. Further analysis was carried out by VOSviewer (version 1.6.18) and CiteSpace 6.1.R3.

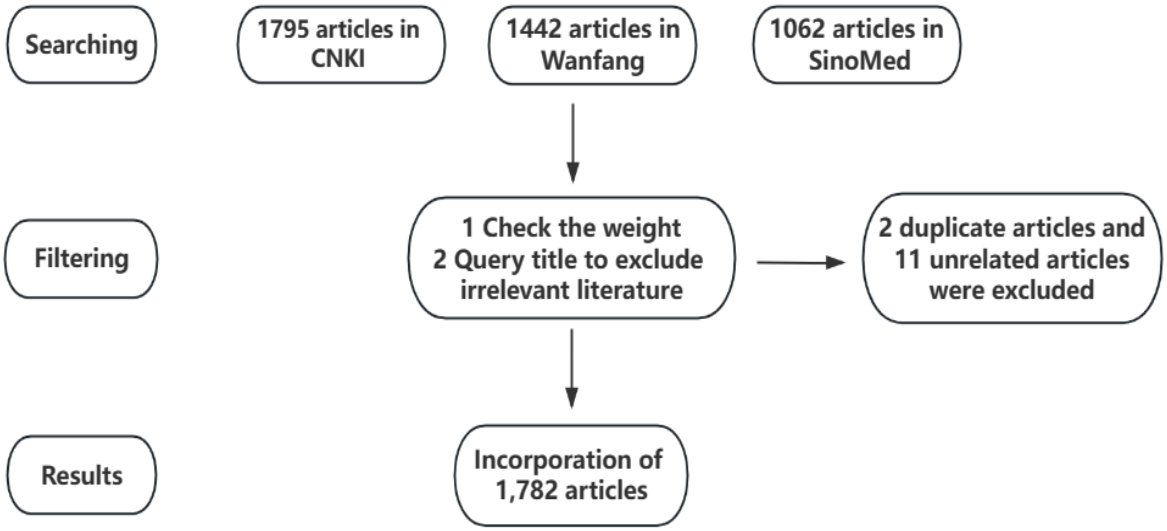

Figure 1. Flowchart for inclusion of literature.

Parameter settings

In the VOSviewer software, author collaboration was selected as the type of analysis. The counting method was complete counting to ensure a comprehensive count of each author's collaborative relationships. The threshold was selected as a minimum literature limit of 4 to filter out authors with a small number of studies. The rest of the parameter settings were adopted as the software default settings. In the CiteSpace software, the time range of 2002-2022 was set to comprehensively cover the time period of the study. The time slice was set to be one time slice per year. The node types included author, institution, and keyword to analyze the study content in depth. The nodes were extracted to analyze the study content in depth. In-depth analysis of the research content, the node extraction threshold was set as top 50 per slice to highlight the top 50 important nodes in each time slice. The pruning option chose pathfinder and purring the merged network to ensure the clarity and accuracy of the network structure.

Results

Trend map of annual postings

From January 2002 to November 2022, a total of 1,782 related papers were retrieved. There were relatively fewer than 50 papers issued between 2002 and 2008, indicating that the field was in its infancy (Figure 2). Subsequently, 2008-2011 experienced a rapid development with a sharp increase in the number of annual publications. 2012-2021 demonstrated a fluctuating increase in the number of publications with the number of publications in 2021 reaching 150, accounting for 8.59% of the total literature (141/1,641). Given that the literature data was only available up to November 2022, it was not possible to determine the change in the number of publications in 2022. This trend reflected an overall solid growth in scientific activity in the field.

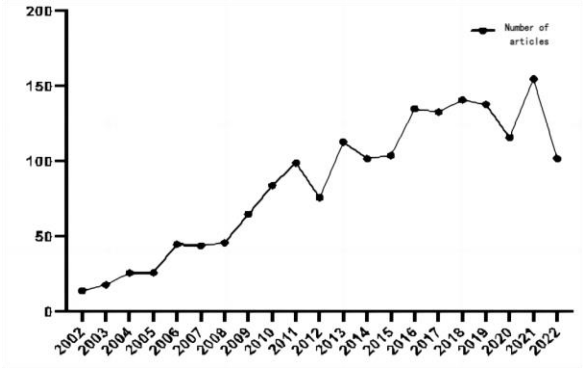

Figure 2. Trend of publications on TCM for HUA 2002-2022).

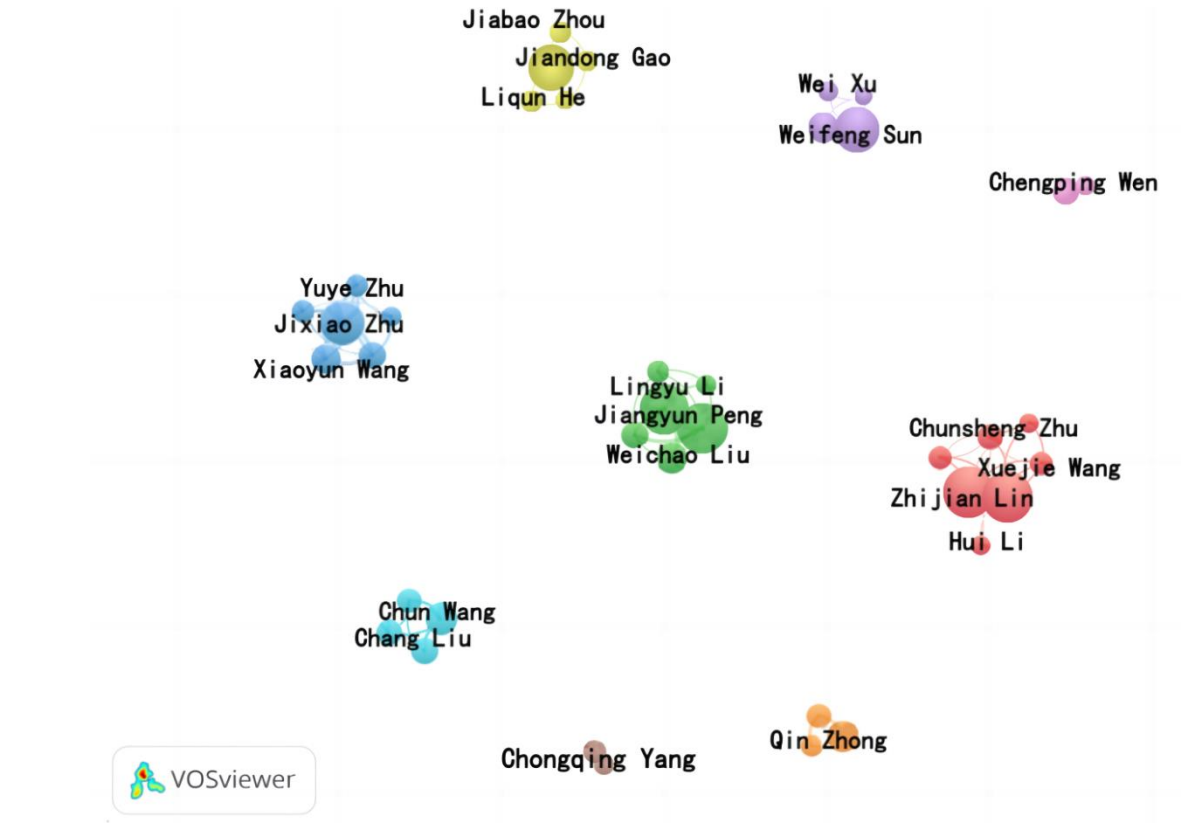

Figure 3. Author collaborations for TCM for HUA (2002-2022).

Author Collaboration

A total of 4,893 authors were covered within the network, and according to Price's theory, the lower limit of the number of articles issued by the core authors could be calculated by the formula $M = 0.749\ N_{max}^{1/2}$ (where M was the lower limit of the number of articles issued by the core authors, and N_{max} was the number of articles issued by the highest-producing authors). Calculated by VOSviewer software, the number of articles issued by the highest-producing authors was 23, from which the minimum value of the number of articles issued by core authors was 4. Under this criterion, the core authors totaled 164, accounting for 3.35% (149/4893) of the total authors, and published a total of 979 papers, accounting for 54.94% (979/1782) of the total papers. The top 10 core authors included Zhijian Lin (23 articles), Bing Zhang (22 articles), Jiangyun Peng (21 articles), Zhaofu Li (21 articles), Weifeng Sun (19 articles), Jiandong Gao (19 articles), Xianmin Wang (18 articles), Jixiao Zhu (17 articles), and Xianxian Zhang (12 articles). It was worth noting that the clustering of authors with more than 6 publications and a link strength of more than 2 resulted in the formation of 9 research teams dominated by Zhijian Lin, Jiangyun Peng, Jiandong Gao, Weifeng Sun, Jixiao Zhu, Chun Wang, Qin Zhong, Chengping Wen, and Chongqing Yang (Figure 3).

Institutional collaboration

Highly productive institutions in the network represent the core strength of scientific research. The visualization and analysis of the issuing institutions by CiteSpace software produced 527 nodes and 268 connecting lines, where the connecting lines indicated the strength of cooperation between institutions. Among them, the institution with the most publications was Beijing University of Traditional Chinese Medicine, which published a total of 61

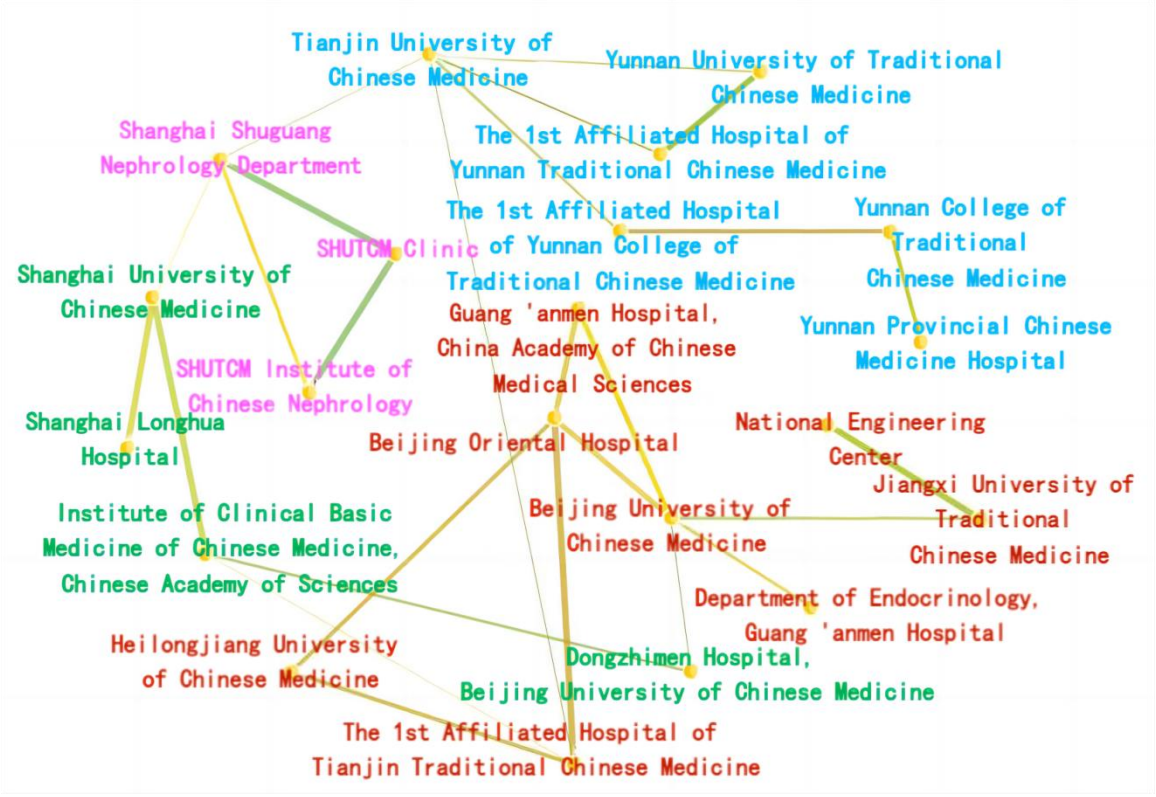

Figure 4. Institutional collaboration map of the literature on TCM for HUA (2002-2022).

documents and maintained collaborative relationships with the China Academy of Traditional Chinese Medicine, Heilongjiang University of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, and Jiangxi University of Traditional Chinese Medicine. The top ten institutions included Beijing University of Chinese Medicine (61 articles), Tianjin University of Traditional Chinese Medicine (29 articles), Zhejiang University of Traditional Chinese Medicine (21 articles), The First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine (19 articles), Yunnan College of Traditional Chinese Medicine (16 articles), Heilongjiang University of Traditional Chinese Medicine (16 articles), Guang'anmen Hospital of China Academy of Traditional Chinese Medicine (15 articles), Yunnan Provincial Hospital of Traditional Chinese Medicine (15 articles), Nanjing University of Chinese Medicine (14 articles), and Guangzhou University of Chinese Medicine (14 articles). The mapping clearly demonstrated the collaborative relationship between the universities and their own affiliates, and also depicted a close network of cooperation among universities geographically, forming a pattern of cooperation in the regions of Beijing, Tianjin, Shanghai, Jiangxi, Heilongjiang, and Yunnan (Figure 4).

Keyword analysis

(1) Co-occurrence analysis

Keywords, as the core content of literature research, refract the distribution of scientific research topics. High-frequency keywords not only represent the hotspots and trends of scientific research, but also occupy an important position in the subject areas to which they belong. Under the criterion of mediated centrality of no less than 0.10, a set of keywords was obtained, among which those with high mediated centrality included gout, blood uric acid, mechanism of action, and rat. By deleting meaningless keywords and combining uniform

Table 1. Keyword frequency table.

Keywords	Frequency	Centrality	Keywords	Frequency	Centrality
Gout	441	0.85	Review	61	0.05
Blood uric acid	130	0.21	Experiences of Famous Doctors	44	0.03
Mechanism of action	110	0.17	Clinical Observations	33	0.07
Chinese medicine	91	0.09	Traditional Chinese Medicine	32	0.04
Rats	63	0.14	Paralysis	30	0.01

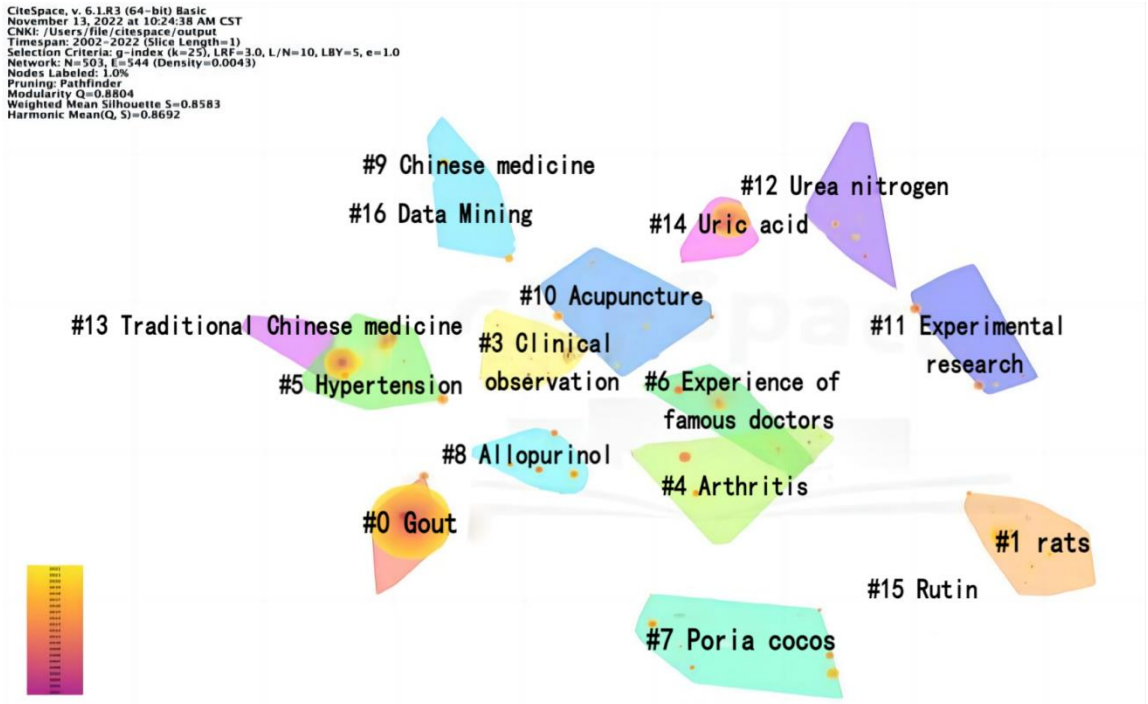

Figure 5. Clustering of keywords in the literature on TCM for HUA (2002-2022).

academic terms such as combining "uric acid" and "hematuric acid" into "hematuric acid", the top 10 keywords in terms of frequency of occurrence were obtained (Table 1).

(2) Keyword clustering

The keywords were then clustered and analyzed using CiteSpace software. 17 clusters were formed, including "#0 gout", "#1 rat", "#2 blood uric acid", and so on (Figure 5). The upper left corner of Figure 5 showed the number of network nodes (N = 503), the number of connectivity (E = 544), the network density (Density = 0.0043), the network modularity (Modularity Q = 0.8804), and the average silhouette value (Mean silhouette = 0.8583), which indicated that each cluster had sufficient similarity and the clustering was reasonable and plausible.

(3) Keyword time-line graph analysis

The time-line diagram analysis of the keywords of TCM treatment of HUA can clearly show the evolution path of each clustered keyword. The results showed that, from 2002 to 2004, gout, arthritis, allopurinol, herbal therapies, reviews, animal experiments, and mechanisms of action were the hot spots of research, especially the

Keywords	Year	Strength	Begin	End
Experimental Research	2002	5. 22	2005	2013
Treatment	2002	4. 73	2007	2010
Arthritis	2002	3. 73	2007	2014
Dendrotoxin	2002	3. 14	2011	2011
Chinese Medicine	2002	3. 95	2015	2016
Research Progress	2002	3. 21	2015	2019
Anti-inflammatory	2002	3. 14	2016	2019
Cure the Future Disease	2002	3. 49	2017	2018
Hypertension	2002	3. 4	2017	2020
Acupuncture	2002	3. 47	2018	2022
Si Miao Pill	2002	3. 35	2018	2022
Inflammatory Factor	2002	3. 84	2019	2020
Creatinine	2002	4. 22	2020	2022
Uric Acid Lowering	2002	3. 73	2020	2022
Potassium Oxonate	2002	3. 2	2020	2022
Molecular Docking	2002	4. 1	2021	2022
Data Mining	2002	3. 55	2021	2022

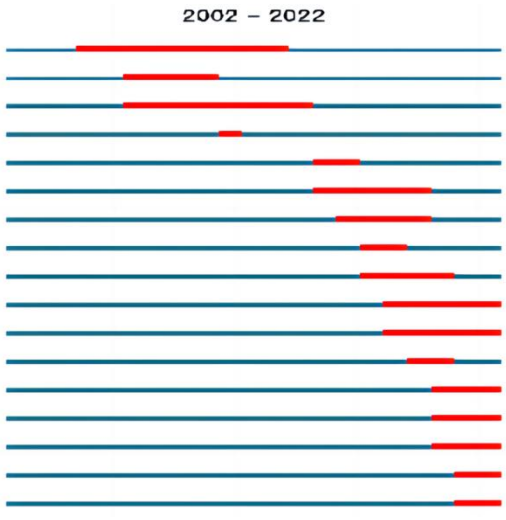

Figure 6. 2002-2022 keyword emergence chart for TCM treatment of HUA.

Chinese medicine chicory was outstanding in the treatment of HUA. From 2005 to 2008, herbal compounding (Poria cocos, Phellodendron Bark, and Xianlingtian), summaries of the experience of famous doctors, and the model of HUA became the focal points of research. From 2009 to 2012, research on TCM compound prescriptions mainly focused on Si Miao San, Yazhi Fang, and gout particles. Meanwhile, pathogenesis, hypertension, inflammatory factors, rhodopsin, quercetin, endothelin, and TCM constitution became new hotspots for research, while treatment methods emphasized treating from the kidney, strengthening the spleen, and removing dampness. From 2013 to 2016, treatment of future diseases, risk factors, meridian formula, intestinal flora, molecular docking, anti-inflammation, signaling pathways, and medication patterns became new focuses of research, while the literature on the HUA research progress was also gradually increasing. Psyllium, Salvia miltiorrhiza, *etc*. became the hotspots of TCM research. From 2017 to 2020, metabolomics, Liujunzi Tang, Sanmiao Pill, oxidative stress, Astragalus, and dandelion became the hotspots of research. From 2021 to the present, the research hotspots were mainly focused on Liujunzi pill, action targets, reevaluation, empirical summarization, and data mining.

(4) Keyword emergence analysis

Keyword emergence analysis is able to detect keywords with high frequency changes in the corresponding time nodes and determine the cutting-edge content of scientific research fields. From 2005 to 2010, it was mainly experimental research on HUA and the treatment of HUA's clinical manifestations. From 2011 to 2016, it was the research on TCM and its components and the summary of the research progress on HUA. From 2017 to 2020, it was research on the metabolic diseases caused by HUA and the treatment of HUA, HUA-induced metabolic diseases, prevention research, research on TCM therapies, and experimental models. Since 2021, the molecular docking data mining emergence, indicating that the emergence of new research tools has brought about breakthroughs in the field of HUA research (Figure 6). Network big data research methods are favored by researchers because of their accuracy, convenience, and quite accessible advantages. The current research focuses on molecular docking, data mining, and network (cyber) pharmacology. Due to the complexity of the pathophysiological mechanisms of HUA, the use of network pharmacology to screen disease targets and action targets is accurate and convenient, which greatly improves research efficiency.

Discussion

Authors

Lin Zhijian's team mainly studied the uric acid-lowering effect of Chinese medicine chicory from the intestinal-renal pathway. The intestinal-renal pathway mediates 99% uric acid excretion and may be an important target organ for lowering blood uric acid and reducing urate deposition [12]. Abnormalities of intestinal-renal uric acid excretion in HUA are associated with oxidative stress-mediated inflammatory injury of intestinal-renal tissues. In this study, chicory extract could improve the oxidative stress-mediated inflammatory injury in the intestinal-renal tissues and promote the excretion of uric acid in the intestinal-renal tissues, thus exerting a uric acid-lowering effect [13]. The team further investigated the mechanism of uric acid-lowering effect of chicory, and found that the components of chicory, such as chrysophanin, chlorogenic acid, and chicoric acid, had the effect of lowering uric acid, and their mechanism of lowering uric acid might be related to the inhibition of xanthine oxidase (XOD) and adenosine deaminase (ADA) activity [14]. Peng Jiangyun's team mainly investigated the mechanism of action of traditional Chinese medicine compound gout granules in the treatment of HUA and found that gout granules were able to reduce the expression levels of TNF-, IL-1, IL-2, IFN-, IL-4, IL-13, and IL-17 in the plasma of rats, and at the same time, reduce the inflammation in renal tissues [15]. According to Prof. Jiangyun Peng, the first step in treating HUA is to prevent the disease before it occurs, advocating tonifying “Qi” and warming “Yang” to dispel blood stasis and resolve phlegm, and making good use of cat's whiskers, corn husk, cinnamon sticks, fine pungent, and coix seed to retreat heat and relieve dampness [16]. Jixiao Zhu's team studied the molecular mechanism of gout and the uric acid level-lowering and mechanism of action of herbal extracts, including the Tibetan medicine rhubarb, the Tibetan medicine long-flowered clematis, the She medicine hemiptera, and plantain. The results showed that single herbs generally reduced gouty attacks by lowering inflammatory factor levels through their effects on inflammatory cytokines. Some herbs reduced HUA by inhibiting inflammatory factor production [17]. For example, she-herbal medicine Half a Bird's Nest specifically acted on the expression of renal urate anion exchanger 1 (URAT1) and glucose transporter protein 9 (GLUT9) mRNA to promote renal uric acid excretion [18]. Jindong Gao's team found that Yazhi Fang not only improved oxidative stress and renal tubular injury in rats, but also regulated lipid metabolism and increased the expression of organic anion transporters (OAT1, OAT3) in renal tissues to promote uric acid excretion [19-22]. Sun Weifeng's team mainly investigated the therapeutic effects of compound Tu Fu Ling granules and Drainage of Turbid and Removal of Paralysis Tang on HUA. The compound Poria cocos granules could reduce the activities of xanthine dehydrogenase (XDH) mRNA and XOD, lower the levels of inflammatory factors such as IL-1 and IL-6, and reduce the production of uric acid [23-25].

Research hotspots

This research summarized and clustered the high-frequency keywords to get 17 categories, in which the research hotspots were mainly concentrated in four aspects including animal experiments, clinical observational research, action mechanism research, and data mining.

(1) Animal experiments

Animal experiment is a common means to verify the action level of TCM components and TCM compound preparations. It is also an important way to study the mechanism of action, as well as being able to help study the pathogenesis and clinical characteristics of HUA. There are many domestic and international studies of rodent models for uricase gene modification and chemical drug-induced type [26]. Recent studies showed that the destruction of the intestinal flora in the animal body could be used as a method of inducing the HUA model [27], and high fructose intake could cause intestinal flora dysbiosis [28]. Currently, potassium oxonate is often used internationally to prepare HUA animal

models by intraperitoneal injection or gavage in SD rats or Wistar rats [26].

(2) Clinical observational studies

Observational study is to observe and record the characteristics of the research subjects in the natural state, and to describe, compare, and analyze the results. The study can be subdivided into three ways, which are descriptive study, case-control study, and cohort study. There are some problems in the current clinical observational study on TCM treatment of HUA, such as small sample size, the measurement indexes of the experimentally derived research effects are not comprehensive enough, and the evaluation of efficacy is not accurate enough, and the observation object combined HUA with other systemic diseases. No high-quality meta-analysis literature has appeared for the observational study of TCM treatment of HUA, which may be due to the lack of data required for the study.

(3) Research on the mechanism of action

Uric acid is the end product of purine metabolism. 2/3 of the uric acid in the body is excreted through the kidneys, while 1/3 is excreted through intestinal decomposition. Xanthine oxidase (XOD) is the key catalytic enzyme for the generation of uric acid, purine metabolism disorders, and excessive uric acid production. Reduced excretion is the basis of the disease. The kidney reabsorbs and resecrets uric acid through uric acid transporters such as ATP binding cassette subfamily G member 2 (ABCG2), GLUT9, and urate anion transporter (URAT1) in the proximal tubule [29]. Intestinal flora and their metabolites are closely related to human uric acid levels, for example, *Escherichia coli* and *Aspergillus* spp. are able to secrete XOD, which promotes the conversion of purines to uric acid, and *Lactobacillus* spp. and allantoinase synthesize uric acid metabolizing enzymes. The metabolites of intestinal flora alleviate and reverse HUA by regulating the proliferation of intestinal epithelial cells to improve purine metabolism, promote uric acid excretion, and reduce inflammation [30]. Single-flavored Chinese medicines are prominent in the treatment of HUA, and their mechanism of action is mainly due to the ability of the active ingredients of Chinese medicines to inhibit XOD activity. Some Chinese medicines reduce blood uric acid content and promote uric acid excretion by inhibiting URAT1 and organic anion transporter protein 4 (OAT4) protein expression and elevating OAT1/3 protein expression [31].

(4) Data mining

With the advent of the information age, data in various industries show explosive growth trends. Data mining technology is a highly applied cross-type technology, closely linked with database technology, statistics, artificial intelligence technology, and computers. Data mining technology is used in the field of TCM to carry out correlation analysis, category analysis, and exception analysis of TCM treatment or disease evidence to study the mechanism of drug action, the law of medication, and the experience of famous doctors.

Research frontiers and future hotspots

From the results of keyword emergence, the current research hotspot is focused on the efficacy and action mechanism verification of acupuncture and prescription in Chinese medicine therapy. Due to the development of internet technology and the arrival of the era of big data, the research on network pharmacology and data mining of HUA has become a research hotspot in recent years. Network pharmacology can screen the common targets of diseases and drugs through the database, which greatly increases the accuracy of target research and provides the direction of clinical precision treatment. The data mining research of HUA provides the ideas and basis for the clinical use of drugs and physician decision-making, which is of great practical significance.

Problems

At present, there are still some problems in the treatment of HUA with TCM. First, the research on TCM is too concentrated on particular drugs. The research focuses on Poria cocos, Phellodendron Bark, and so on. There is less

research on other effective drugs and specialty drugs. Second, there is a lack of communication and cooperation among institutions. Most of the cooperation among institutions is concentrated in universities and their affiliated hospitals and research institutes. The cross-regional research is not close. As patients in different regions have different physiques and different dosages and types of medicinal herbs, communication and cooperation among regions need to be strengthened. Third, the mechanism of HUA treatment by TCM is relatively single. Since single herbs and pairs of herbs have to be combined in formulas to produce effects. The mechanism is more complex, and further in-depth investigation is needed to elucidate the mechanism of action of the formulas in detail.

Conclusion

This study provided an in-depth analysis of the literature on TCM treatment of HUA through CiteSpace and VOSviewer software, which revealed the main research directions and current status in this field. The use of network pharmacology and data mining provided strong support for the realization of clinical precision treatment, as well as theoretical support and guidance for the future development of TCM in the field of HUA treatment. Future research directions should focus on the diversity and synergistic effects of TCM formulas, promote cross-field cooperation, and promote the in-depth study of TCM in the treatment of HUA.

Acknowledgements

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