

CiteSpace-based visualization of Chinese medicine for uric acid nephropathy

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Abstract: *Objective:* To analyze the research status and trend of Chinese medicine for the treatment of uric acid nephropathy in the past 30 years. *Methods:* The database of China Knowledge Network (CNKI) was searched, and CiteSpace analysis software was used to visualize and analyze the annual number of articles, authors, institutions, key words and emergent words. *Results:* A total of 767 relevant research papers were included. The number of annual publications showed a stable increasing trend; teams with close cooperation, such as Jiakai Hu's team, Dongdong Li's team, Nietao Guo's team and Fengxian Meng's team, were formed. A cluster of core research institutions including Beijing University of Traditional Chinese Medicine, Shuguang Hospital affiliated to Shanghai University of Traditional Chinese Medicine and Tianjin University of Traditional Chinese Medicine has been formed. *Key words related mapping showed.* *Conclusion:* Chinese medicine research on uric acid nephropathy is being developed and improved, and the combination of Chinese and Western medicine is highly valued. Basic experimental research on oxidative stress, inflammatory response, and disease prevention may be a hot spot for future research. Interdisciplinary, interdisciplinary and talent exchange and cooperation need to be strengthened, and further explored at the microscopic level through research in order to exploit the advantages of TCM in disease treatment.

Keywords: CiteSpace; Chinese medicine; uric acid nephropathy; visual analysis; knowledge graph

1. Introduction

Uric acid nephropathy (UAN) has gradually become one of the most important problems threatening human health due to the development of society and the improvement of living standards [1]. UAN is the increase of blood uric acid level due to the disorder of purine metabolism, excessive production of uric acid (UA) or reduced excretion, and the deposition of urate crystals in the renal medulla, interstitial or distal collecting duct, causing interstitial inflammatory reaction, renal tubular obstruction and loss of nephron [2-3]. The clinical manifestations can be divided into intra-renal and extra-renal manifestations. The intra-renal manifestations are lumbago, nocturia, decreased urine specific gravity and osmolality, hematuria, proteinuria, and urinary calculi; the extra-renal manifestations are mainly nocturnal joint redness, swelling and heat pain, and unfavorable flexion and extension [4-5]. Hyperuricemia (HUA) is the biochemical basis of UAN and an independent risk factor for the development and exacerbation of chronic kidney disease [6]. The incidence of chronic kidney disease in the HUA population was 32.7% higher than that with normal uric acid 16.2% [7]. Studies have shown that UA can damage the kidney through inflammatory mechanisms, impairment of endothelial function, oxidative stress and activation of the RAS system [8]. The name "UAN" is not recorded in Chinese medical texts, but modern medical practitioners have classified it as "gout", "kidney paralysis", "deficiency labor", "paralysis", and "calendar disease" according to its clinical manifestations [9-10].

According to Chinese medicine, this disease is the result of a combination of internal and external factors, such as external exposure to wind, cold, dampness and heat, combined with poor diet or emotional disorders, resulting in the imbalance of the body's yin and yang and the malfunction of the internal organs. At the same time, due of dampness, stasis, toxic internal injury, phlegm obstruction, eventually for this disease [10]. Western medicine often uses diet control, oral administration of

febuxostat, benzbromarone, allopurinol and other drugs to reduce UA production, thus increasing the solubility of monosodium urate in urine, but long-term use of allopurinol and other drugs tend to increase the risk of kidney damage, with large side effects, and UA levels are very likely to rebound after stopping the drugs, with a poor long-term prognosis^[11]. Chinese medicine has its own unique features in the treatment of UAN, and its multi-target and multi-pathway action pathways are promising in reducing UA and delaying the progression of kidney disease, with definite clinical efficacy and low toxic side effects, good safety and low price^[12]. As the research of Chinese medicine for UAN continues to develop, therefore, it is significant to deeply explore the current research status and hot spots in this field to guide clinical practice, scientific research and the promotion of a healthy China.

CiteSpace is a software based on data mining and metrological analysis developed by Professor Chaomei Chen's team, which can analyze disciplinary trends and detect hot spots and frontiers of disciplinary development by drawing visual knowledge graphs for bibliometric analysis^[13]. Therefore, based on the current research background of TCM treatment UAN, this study conducted data statistics and visual analysis of relevant research literature based on Cite Space 6.1.R6 software to sort out the current research status and development of the field, analyze and predict the hot spots and frontier trends related to the field, and provide a basis for the subsequent research in this field.

2. Information and Methods

2.1. Search Strategy

Taking the relevant literature of CNKI Journal database as data source, the search library was limited to "academic journals" and "dissertations", and the search strategy: Advanced search: Subject = "uric acid nephropathy + uric acid renal disease + uric acid renal impairment + hyperuricemia nephropathy + hyperuricaemic renal disease + gout nephropathy + gout nephropathy + gouty renal disease + gout nephropathy + gouty kidney"; the time span was from January 1, 1993 to December 31, 2022; "Chinese medicine", "traditional Chinese medicine", and "combined Chinese and Western medicine" were selected for the literature classification.

2.2. Inclusion and exclusion criteria for literature screening

Literature inclusion criteria: (1) Closely related to the subject matter; (2) Academic journals and dissertations involved in the field.

Literature exclusion criteria: (1) Literature inconsistent with the content of the research topic; (2) Conferences, newspapers, yearbooks, standards, achievements, books, academic journals; (3) Missing literature with incomplete author data; (4) Repeated publication of the literature.

2.3. Data Processing

1056 relevant documents were retrieved, selected and those that did not meet the standards were selected and excluded, the documents were exported in NoteExpress format and de-duplicated them, and 767 articles were exported in Refworks format, data conversion was conducted using CiteSpace 6.1.R6 software, and the authors, institutions and keywords were visually analyzed respectively. The parameters are set to: From January 1, 1993 to December 31, 2022, For each 1 year to partition, Node types is the Keywords, author Author, Institution; Threshold parameter setting (Top N perslice) = 50, (TopN%) 10%; Co-occurrence selection of g-index (k=10), A TopN threshold selection of 50, The shear method (Pruning) parameter is set to "Pathfinder, Pruning sliced networks and Pruning the merged network" trimming mode for simplified processing, All other settings are the default settings. Manually edit the citespace. alias folder to combine synonyms, such as "hyperuricemia nephropathy", "hyperuricemia renal damage" and "gouty nephropathy" into "uric acid nephropathy". And standardize the name of the research institutions, the lower institutions unified to the superior institutions, such as the "basic medical school of Yunnan university of Chinese medicine" as "Yunnan university of Chinese medicine", "dawn hospital affiliated to Shanghai university of Chinese medicine kidney department" "shuguang hospital affiliated to Shanghai university of Chinese medicine renal medicine", unified as "shuguang hospital affiliated to Shanghai university of Chinese medicine", the unified name update to the current name.

3. Results

3.1. Analysis of post volume

In this paper, the statistical analysis of the number of relevant literature in this field in the past 30 years using Excel shows that although there are intermittent fluctuations in the number of papers published in this field, the overall trend of steady growth, especially in recent years, shows a peak, indicating that the research in this field has gained some attention and its research results are gradually remarkable. (Figure 1)

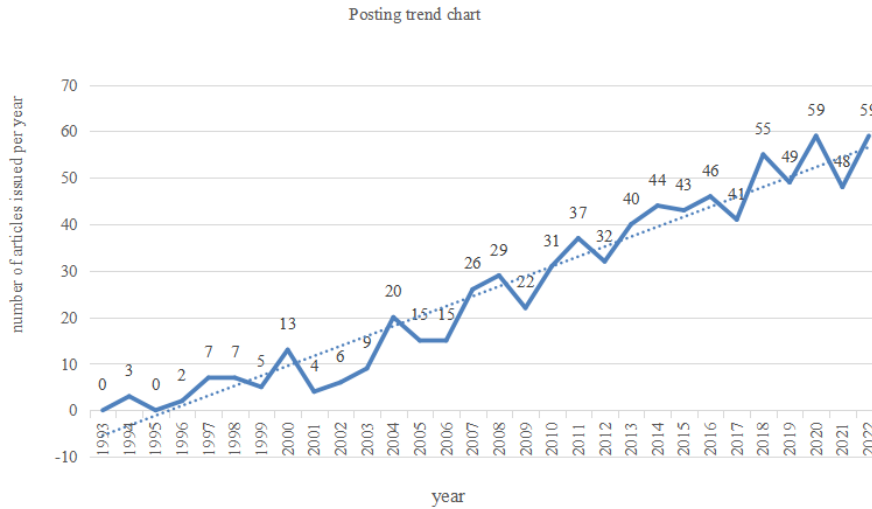


Figure 1: Trend chart of the treatment of uric acid nephropathy in recent 30 years

3.2. The author collaborated on the analysis

As shown in Figure 2, from 1993 to 2022, the collaborative network of researchers in this field contains 281 nodes, 290 links, and a network density Density of 0.0074, in which the authors with the most publications are Jiakai Hu (16) and Jiandong Gao (15). The top 9 authors are shown in Table 1. nodes represent authors, and the larger the node, the greater the number of articles published by the author, and the existence of collaboration or connection between authors is indicated by a link [14]. Most of the authors formed their own teams and published multiple articles, among which mainly the teams of Jia-Cai Hu, Dong-Dong Li, Nie-Tao Guo and Feng-Xian Meng were the core, and according to the map, these teams were closely connected within each other, but the cooperation between teams was less.



Figure 2: Core authors of UAN research literature in recent 30 years

Table 1: Author of the top 9 publications

Serial number	Author	Number of articles	Year
1	Jiacai Hu	16	2000
2	Jiandong Gao	15	2012
3	Qing Ni	9	1997
4	Fengxian Meng	9	2012
5	Fan Wu	9	2000
6	Kaiming Ren	8	2000
7	Enfeng Song	7	2004
8	Dongdong Li	7	2020
9	Jianyong Zhang	7	2003

3.3. Institutional cooperation analysis

The institutional cooperation map forms 164 nodes with 67 links, see Figure 3. The nodes in the figure represent the agencies. The more publications, the larger the nodes, and the more connections, the stronger the regional connection. Density=0.005, the small knowledge map density indicates the overall dispersion of institutions and the weak connection between institutions. Among them, Beijing University of Chinese Medicine has issued the most articles, with 40 articles, followed by Shuguang Hospital of Shanghai University of Chinese Medicine (24), Guangzhou University of Chinese Medicine (19), and Tianjin University of Chinese Medicine (18). Photo Gallery shows that issuing Institution is given priority to with regional aggregation, research institutions cooperation mainly for the university of Chinese medicine and its hospital exchanges and cooperation, regional research independence, cross-regional cooperation and communication, scattered, is not conducive to promoting the development of discipline, so the next step should strengthen cooperation and communication between cross-regional, institutions, promote grassroots institutions level, realize the breakthrough in the field.



Figure 3: Co-occurrence chart of core institutions of TCM treatment in the past 30 years

3.4. Keyword analysis

3.4.1. Keyword co-occurrence analysis

The keywords are the core summary of the relevant papers, which is the main idea of the whole article, with the help of high-frequency keywords to deeply explore the distribution and development of different research hotspots in the field [15]. The keywords in this field were analyzed visually by CiteSpace software and the knowledge graph of keyword co-occurrence was drawn, see Figure 4. 240 keyword nodes were formed, with 358 connections and a network density of 0.0125. Excluding the topic keywords, the top 10 high-frequency keywords in this research field are shown in Table 2, including hyperuricemia (170 times) and Traditional Chinese Medicine Therapy (108 times). The frequencies of these two keywords were much higher than the latter. In addition to being used to assess the importance of the literature, centrality can also reflect the ability of a node to act as a mediating bridge, and nodes with high centrality are likely to suggest research hotspots and trends in the field [16].

In the graph, a node wrapped by a purple ring represents a node with high mediated high centrality. By calculation, the top 5 keywords of centrality in this research field are Therapy of combing traditional Chinese and Western medicine (0.51), Hyperuricemia (0.5), Kidney damage (0.42), Clinical research (0.38), Gout (0.31), which represent hot research topics with high influence and attention in this research field.

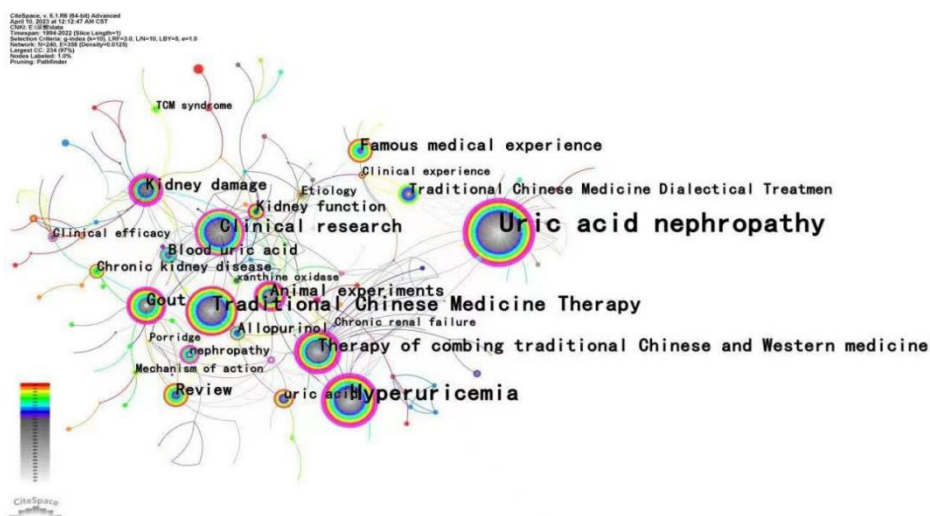


Figure 4: Keyword co-occurrence map

Table 2: Keyword frequency ranking table (top 10)

Serial number	Keywords	Frequency	Centrality
1	Hyperuricemia	170	0.5
2	Traditional Chinese Medicine Therapy	108	0.2
3	Clinical research	62	0.38
4	Therapy of combing traditional Chinese and Western medicine	53	0.51
5	Gout	48	0.31
6	Famous medical experience	41	0.07
7	Animal experiments	39	0.29
8	Kidney damage	34	0.42
9	Review	34	0.06
10	Kidney function	28	0.16

3.4.2. Keyword clustering analysis

Keyword clustering is the integration and classification of closely linked keywords, which leads to the formation of highly generalized clustering clusters and generates clustering labels, which are used to analyze and illustrate the research structure and hotspots in the field through each cluster^[17]. The clustering module value Modularity Q value > 0.3 indicates that the graph clustering is valid^[18]; the closer the average profile value Silhouette S value is to 1 indicates better network homogeneity, S > 0.5 results are reasonable and S > 0.7 is highly credible^[19]. After clustering all keywords, Q=0.8331(>0.3), S=0.9406(>0.7) were obtained, suggesting that the clustering is valid and credible, and can well show the research characteristics of the field. The 10 meaningful keyword clustering labels with the most clustered keywords were selected and shown in Figure 5, and the specific labels are shown in Table 3. The 10 clusters can be divided into 3 categories: #2, #3, #5 and #8 are clinical studies, containing the keywords "Blood uric acid", "Clinical research", "Clinical efficacy", "Wuzi Chengqi Soup", "Angelica pain pills", etc.; #4, #6, #7 are basic research, including keywords "Oxidative stress", "Molecular docking", "Quercetin", "Porridge", etc.; #0, #1, #9 are clinical diagnosis and treatment, including keywords "Famous Medical Experience" "Dialectical Treatment". (Table 3)

CiteSpace, v. 5.1.R6 (64-bit) Advanced
 Date: 10/03/2023 09:12:12:47 AM CST
 Class: g-index
 Timespan: 1994-2022 (Slice Length=1)
 Selection Criteria: g-index (w=1), LRF=1.0, L/N=10, LBY=5, w=1.0
 Network: N=240, E=7508 (Density=0.126)
 Labels: CC: 238 (97%)
 Nodes Labeled: 176
 Pruning: Pathfinder
 Modularity Q=0.7472
 Weighted Mean Silhouette S=0.9406
 Harmonic Mean Q+S=0.8311

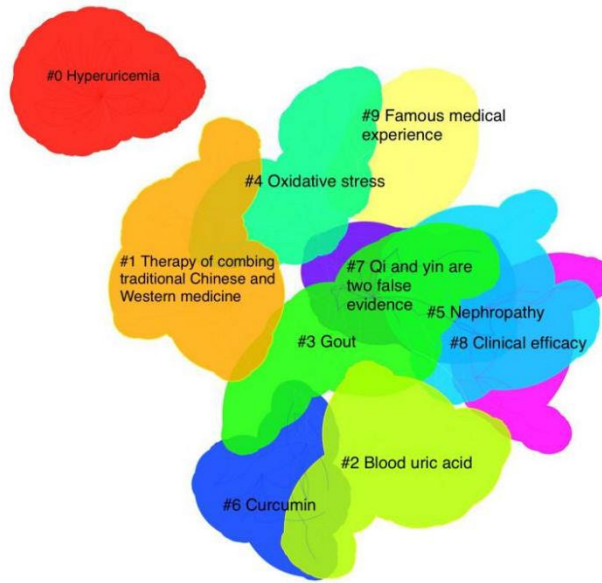
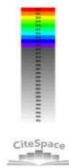


Figure 5: Keyword cluster map

Table 3: Keyword clustering table

ID	Number of nodes	Profile value	Year	Clustering Tags
#0	37	0.998	2004	Hyperuricemia; Syndrome differentiation; Uric acid nephropathy; Gouty nephropathy; Treat
#1	34	0.922	2005	Hyperuricemia; Integrative medicine therapy; Chronic renal failure; Uric acid nephropathy; Therapy of combing traditional Chinese and Western medicine
#2	25	0.885	2010	Blood uric acid; Kidney function; Inflammatory factors; Acute gouty arthritis; Goko Chengqi soup
#3	24	0.962	2007	Gout; clinical research; Clinical efficacy observation; Angelica Pain Pills ; Clinical features
#4	21	0.957	2012	Oxidative stress; Quercetin; Kidney protection; Kidney injury; Inflammation
#5	21	0.921	2005	Nephropathy; Uric acid; Traditional Chinese Medicine Therapy; Primary hyperuricemia; Chinese medicine
#6	21	0.897	2010	Curcumin; Herb capsules; molecular docking ; Connective tissue growth factor intestinal flora
#7	17	0.941	2001	Qi and Yin deficiency; Porridge; Chinese Medicine Research; raw astragalus; Whitening
#8	13	0.977	2016	Clinical efficacy; Chronic kidney disease; Adverse reactions; nitrogen lowering decoction; Dispel humidification and turbidity
#9	8	0.893	2007	Famous medical experience; Hongfang Liu ; CHEN Yiping; Clinical experience; Zhengsheng Shi

3.4.3. Keyword timeline analysis

Timeline view shows the development status and historical span of each cluster, the horizontal axis is the time, the vertical axis is the cluster label, through CiteSpace software to draw keyword timeline mapping, to understand the dynamic development trend of the field research within a certain time period [20]. UAN was proposed after 1994, and from 1998 onwards, research on group therapy such as Shenfukangzishentang, Lijieshenlingbaizhusan, and Xingqi lihuitang, as well as single-agent treatment of UAN such as Tufuling and Donggua pi has developed rapidly. Animal experiments, randomized controlled treatment observation, network pharmacology molecular docking, mate analysis and other research methods have been continuously applied in the field of research, while some healers have adopted combined treatment with Chinese medicine therapies such as herbal enema and blood pricking therapy, as well as many famous masters and clinical workers have accumulated a large amount of personal treatment experience. From 2020 to the present, researchers have enhanced their research in immunological and cellular molecular biology perspectives, such as NLRP3 signaling pathway and NF-KB signaling pathway. Chinese medicine treatment for UAN is also evolving toward more precise

and effective.

3.4.4. Keyword occurrence analysis

Burst words refer to high-frequency hot words within a certain period of time, through which we can understand the development and changes of research hotspots, trends and frontier dynamics within a certain time node [21]. In this study, a total of 15 emergent words were detected, see Figure 6, in which Strength represents the emergent strength, with larger values indicating greater influence; Begin and End represent the beginning and end of the emergent time, respectively [22]. In this paper, the overall hotspot shift is obvious, and the one with the highest emergence intensity is "combined Chinese and Western medicine treatment", as shown in the figure, from 1996 to 2009, in the early 1990s, the renal lesions caused by hyperuricemia attracted the attention of clinical workers, and the clinical treatment of UAN was mainly based on combined Chinese and Western medicine, which was considered to be mainly qi-yin Both deficiency evidence; 2009-2016, related clinical research began to increase, the development of Chinese medicine compound preparations, as well as the accumulation of experience exploration of Chinese medicine workers; after 2017, we began to pay attention to the study of early prevention and long-term healing, such as uric acid levels, kidney function levels, the prevention of chronic kidney disease, and related basic experimental research gradually increased, and in recent years, the main research direction is to pre-disease intervention treatment and disease pathogenesis, drug action mechanism research, such as high uric acid on the kidney oxidative stress and inflammatory response, and according to Figure 6, its research direction is still potentially popular between the future period.

Top 15 Keywords with the Strongest Citation Bursts

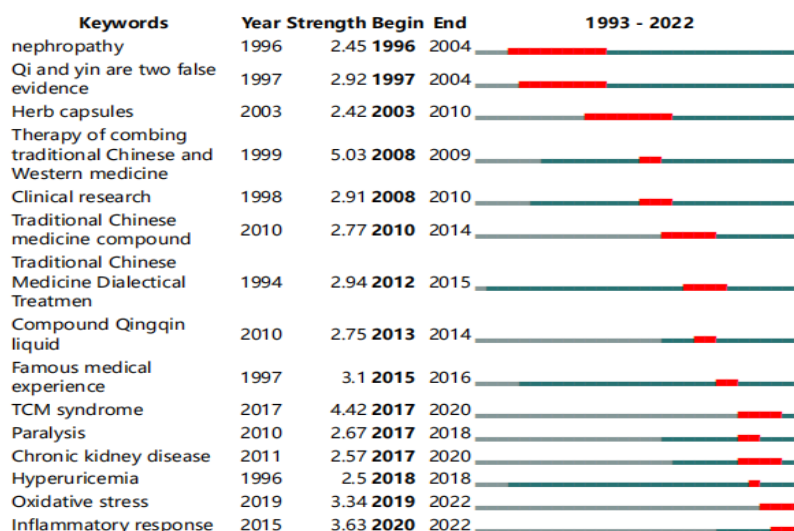


Figure 6: Keyword emergent map

4. Discussion

In this study, we analyzed 767 literature on Chinese medicine treatment of UAN in CNKI database in the past 30 years through Cite Space 6.1.R6 software, and visualized and analyzed them by drawing a knowledge map to visually and effectively reveal the current status and hot trends of relevant research in this field, with a view to play a role in advancing the development of the discipline in this field in the future.

The annual volume of publications shows that the volume of publications in this field is relatively stable, with an overall trend of steady increase. It is at the peak level in recent years, so it can be predicted that the research in this field will remain popular for some time in the future and is worthy of further study by scholars.

The analysis of the authors of the publications shows that the authors with the largest number of publications are Jiakai Hu and Jiandong Gao, while a collaborative team of authors represented by Hu Jiakai, Li Dongdong, Guo Nietao and Meng Fengxian was formed. Hu Jiakai's team mainly studied the

clinical control and basic research on the treatment of UAN with Wei Cao Capsules ^[23], Wei Cao Tang ^[24] and the single herbal medicines Wei Ling Xian ^[25], Huang Bai ^[26] and Da Huang ^[27] to observe the therapeutic effects and explore the mechanism of action to slow down the degree of kidney damage. Li Dongdong's team mainly studied the clinical formula "uric acid-lowering formula" and investigated the mechanism of action of uric acid-lowering formula on kidney damage in UAN rats at the molecular level through basic experimental studies ^[28-29]. Guo Nietao's team focused on the clinical efficacy of UAN and the relationship between the disease and sex hormone levels in the body ^[30-31]. Meng Fengxian's team mainly investigated the effects of compound Qing Qin Liquid ^[32] and Qin Ling Liquid ^[33] on renal function and renal histopathology in rats with uric acid nephropathy UAN, as well as the effects on AMPK/INOS signaling pathway at the molecular level through basic animal experimental studies ^[34].

Through the analysis of the issuing institutions, the field has formed a cluster of core research institutions such as Beijing University of Traditional Chinese Medicine, Shuguang Hospital affiliated to Shanghai University of Traditional Chinese Medicine, Guangzhou University of Chinese Medicine and Tianjin University of Traditional Chinese Medicine, etc. The cooperation of research institutions is mainly based on the exchange and cooperation between each TCM university and its affiliated hospitals, and there is a cross-regional cooperation trend between Guangdong, Shanghai and Henan institutions, and between Beijing and Anhui institutions, but the overall cooperative linkage still shows scattered and insufficient. Therefore, it is recommended that each high-level core team play a leading role in promoting the strengthening of talent exchange and regional cooperation, giving full play to the strengths of each team and the resources of each region, complementing each other, strengthening the improvement of grassroots research institutions, and jointly promoting innovation in the development of disciplines in this field in China.

The analysis of keywords shows that the type of research in this field is mainly clinical research, basic research on animal experiments and experience of famous doctors, and there are also related literature research and data mining articles published, which aim to organize and summarize the research status in a certain period of time, and lay the foundation for the theoretical and practical development of the discipline in the subsequent field. A large number of scholars have developed a series of TCM preparations through clinical research, which have opened up clinical treatment tools, such as Qingrexiezhuofang ^[35], Tongfengshentaifang ^[36], and Qubixiaozhengyishenfang ^[37]. The experience of famous doctors is of great significance to the inheritance and development of traditional Chinese medicine as well as the research and development in this field. Many doctors have accumulated a lot of treatment experience in clinical treatment. For example, Liu Hongfang believes that the pathogenesis of UANN is kidney yuán deficiency, kidney complex obstruction. To fuzheng quxie as the treatment, to cultivate yuán luo as the treatment ^[38]. Dr. Cao Enze, the chief physician, has been engaged in TCM kidney disease for nearly 50 years. According to the characteristics of UAN, he adopted the method of stage differentiation (acute onset and stable period), and established differentiation and treatment of Traditional Chinese medicine like "Qingbu method", "Huayutongluo method" ^[39]. Dr. Cheng Jinguo, chief physician of Zhejiang Province, in his long-term clinical evidence, classified them into four categories according to their clinical symptoms and signs: spleen-stomach qi deficiency with dampness, damp-heat internalization, phlegm-dampness obstruction, and liver-kidney yin deficiency, and proposed the specific treatment methods of "raising yang and benefiting qi, transforming dampness and clearing the middle, and passing down turbidity" ^[40]. In recent years, new ideas have also emerged regarding the study of signaling pathway mechanisms at the molecular level through. For example, Lei Huan ^[41] and Zhang Shanhua ^[8] investigated the targets and pathways related to the treatment of UAN by herbal drugs and herbal compound from the molecular biological level of modern medicine through the relationship of "drug-target-disease" according to the research method of network pharmacology, and explored the scientific mechanism of action. According to the chart, it can be seen that in 2020 research about molecular biological mechanisms began to take off, and the current research in this area involves less, which shows that there is still more room for future research development in this field. In the future, it is expected to combine with modern medicine to deeply explore the pathogenesis and therapeutic targets from the molecular biological and metabolomic levels, and provide basic theoretical support to further promote the development of UAN in Chinese medicine treatment. From the keyword clustering time diagram and the emergent keyword diagram, we can see that the current research in general shows a development toward modernization and diversification. Clinical research has become more scientific and rigorous, shifting the level of clinical research to basic experimental research from macroscopic treatment to microscopic molecular biological mechanism of action; in literature research from simple experience summaries to data mining; in treatment, shifting from treatment-oriented to "prevention before illness" and "prevention of existing

illness", reducing disease risk factors in advance and considering patients' long-term prognosis. Western medicine and Chinese medicine both have their own advantages, the combination of traditional medicine and modern medicine, for the characteristics of the disease mechanism, to achieve the objective of both the symptoms and the root cause, therefore, the combination of Chinese and Western medicine treatment is the inevitable trend of future development.

5. Conclusion

Based on Citespace to visually reflect the current research status and development trend of Chinese medicine for UAN in the past 30 years, we aim to provide reference for subsequent disciplinary research in this field. However, there are also certain limitations, the study of this paper only screened the literature of China Knowledge Network (CNKI) database, selected domestic papers for analysis, did not include papers from other databases, lack of comparison with foreign studies, in addition, this study only listed the high-frequency keywords required for the study for analysis, making some of the vocabulary with low frequency of existing and newly emerged words that have significance for future research were not included in the analysis and description, all these make the study have certain shortcomings.

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