


The Traditional Chinese Medicine in Treating Diabetic Nephropathy: A Bibliometric Analysis

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Background: Diabetic nephropathy (DN) is one of the most common complications of diabetes mellitus, causing a serious economic burden worldwide. Traditional Chinese Medicine (TCM) is playing an increasingly important role in the treatment of DN. The purpose of this study was to comprehend the main themes and developments in relevant research throughout the last 11 years.

Methods: We looked for publications in the Web of Science Core Collection database (WOS) and the Chinese National Knowledge Infrastructure (CNKI) between 2013 and 2024. CiteSpace 6.3.R1 software was used to analyze the co-authorship of countries/regions, organizations, and co-occurrence of keywords. In addition, burst detection was applied to predict research hotspots and future trends.

Results: A total of 530 articles were included. The overall trend of published articles is increasing. China is the country with the highest number of publications and the highest impact. The research institutions are relatively scattered, with Beijing University of Traditional Chinese Medicine having the highest number of publications. The cooperation among institutions is mainly between universities of traditional Chinese medicine and their affiliated hospitals, and the cross-regional cooperation is not common. The research hotspots are the efficacy of TCM on DN and its mechanism of action, the exploration of TCM and formulas related to the treatment of DN, and the identification and typing of DN in TCM. The research frontiers lie in the control of oxidative stress and the effects of TCM on gut microbiota. In addition, the use of network pharmacology to explore the targets of Chinese herbal formulas for the treatment of this disease has also become popular.

Conclusion: TCM provides more possibilities for the treatment of DN. Researchers can refer to the research hotspots and trends in this paper for future research direction, on the one hand, they can focus on the study of the clinical efficacy of TCM and its improvement of renal function, on the other hand, they can also start from the pharmacological mechanism of TCM for the treatment of DN. Among them, improving oxidative stress in human body and regulating gut microbiota are the directions that can be studied.

Keywords: diabetes nephropathy, traditional Chinese medicine, citespace, bibliometric analysis, visualization

Introduction

Diabetes mellitus, as a common chronic non-communicable disease, has become a public health problem of global concern. The incidence of diabetic nephropathy (DN) has increased in tandem with the growth in the prevalence of diabetes mellitus in recent years. DN is the most important and common microvascular complication of diabetes mellitus, and the main cause of end-stage renal disease.¹ In clinical practice, when there is an irreversible decline in renal function, patients rely on renal transplantation or dialysis for renal replacement therapy. These expensive treatments not only cause economic losses and depletion of health resources for the country, but also impose a heavy financial burden on the whole society, patients and families.² At present, the main methods of treating DN are hypoglycemia,³ antihypertensive,⁴ diuretic,⁵ lipid regulation⁶ and other treatments. Standardized western medical treatment can improve the clinical indicators of patients, but still cannot stop the progression of the disease. A significant number of people in China suffer from diabetes, and with the growth of traditional Chinese medicine (TCM) in recent years, TCM has emerged as a key tool in the fight against diabetes. Some studies^{7,8} have found that TCM can delay the progression of DN and has significant advantages in maintaining blood glucose homeostasis, improving clinical symptoms, and increasing patient compliance. Therefore, increasing the application rate of TCM in the treatment of DN deserves further investigation.

Although the application of TCM in this field has received a certain extent, and the number of articles is increasing year by year, progress is slow, the total amount of literature is relatively small, and there is a lack of systematic and comprehensive literature analysis. In addition, some published studies have faced a variety of problems such as unscientific study designs, irrational interventions, and insufficient quality control, resulting in a lower quality of literature. It is evident that conducting well-designed clinical trials or performing quantitative literature analysis on published studies to explore the therapeutic effects of TCM on this disease is meaningful. The study quantitatively and intuitively analyzes the research findings in this field, explores the research hotspots and challenges, investigates the development trajectory and research frontiers, aiming to provide suggestions and references for future research and to fill existing gaps.

Materials and Methods

Data Source

On March 27 2024, online literature data was collected from WOS and CNKI using a search strategy consisting of the following terms: (WOS) Topic=(“diabetic nephropath*” OR “diabetic kidney disease*”) AND Topic=(“Chinese traditional medicine” OR “Zhong Yi Xue” OR “Traditional Chinese medicine”). The language was limited to English. (CNKI) Topic: “diabetes nephropathy” AND Topic:“traditional Chinese medicine”. The article source category is limited to core journals. Article types are limited to “reviews” and “articles” only. As shown in Figure 1, excluding 78 noncompliant articles, we finally obtained 530 articles.

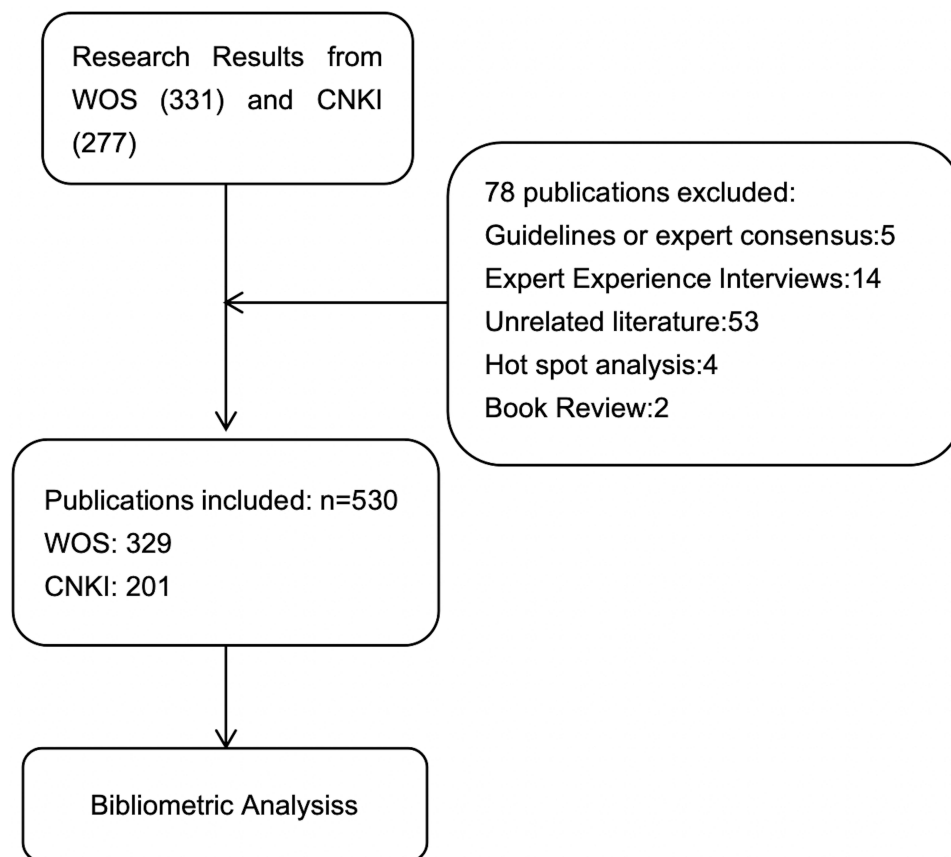


Figure 1 Retrieval process flowchart for the research.

Statistics and Analysis

According to the number of articles published annually by CNKI and WOS, the frequency is used to count the trend of articles published in this research field. Use CiteSpace 6.3.R1 software to draw a network graph of countries/region and institutional cooperation and a keyword co-occurrence network in this field. The retrieved literature data will be checked, filtered, and transformed before being entered into the software. The time span is set to 2013 to 2024, and the time slice is set to 1, forming 12 time periods. In the knowledge graph, the size of nodes represents the frequency of nodes, and the thickness of the lines between nodes represents the degree of their connection and cooperation.⁹ The centrality of intermediary is an indicator for evaluating the importance of nodes in the visualized knowledge graph, and the centrality of nodes ≥ 0.1 is marked as purple, which indicates that it is the more popular and important research in this field.¹⁰ In the clustering map, the module value $Q > 0.3$ indicates that the clustering structure is significant, the average profile value $S > 0.5$ indicates that the clustering is reasonable, and $S > 0.7$ means that the clustering effect is credible.¹¹ Set the display option to “Burstness” to get the emergent words, and the red line segment in the emergence map indicates the explosive years of emergent words.

Results

Annual Publication Analysis

530 articles from 2013 to 2024 were included in our study. Figure 2 shows the trend of changes in the number of publications. The trend of cumulative publications in Chinese studies and foreign language studies are both increasing. Combining the two databases, there were over 20 relevant articles in 2013, while by 2022, there were 87 articles. Currently, research on the relationship between DN and TCM is receiving increasing attention.

Countries/Region Analysis

The data shows that from 2013 to 2024, 15 regions had conducted relevant research. Table 1 shows the top five regions in terms of article output, with the People’s Republic of China ranking first with 312 articles. In the table, China has the highest centrality at 1.46, followed closely by Australia (0.26) and the USA (0.04). The United States ranks second with 16 articles published, while Taiwan Province has 11 articles published, ranking third. Australia has published 7 articles, although its publication volume is relatively small, its centrality is relatively high, indicating a high level of influence.

Spatial Distribution Analysis

More and more institutions contributed to this area. In terms of CNKI, 325 institutions were identified as participating in research on TCM and DN. As shown in Table 2, a total of 5 institutions have published five or more Chinese literature. There are Beijing University of Chinese Medicine (10 articles), Affiliated Hospital of Liaoning University of Traditional Chinese Medicine (8 articles), Guang’anmen Hospital of the Chinese Academy of Traditional Chinese Medicine (6

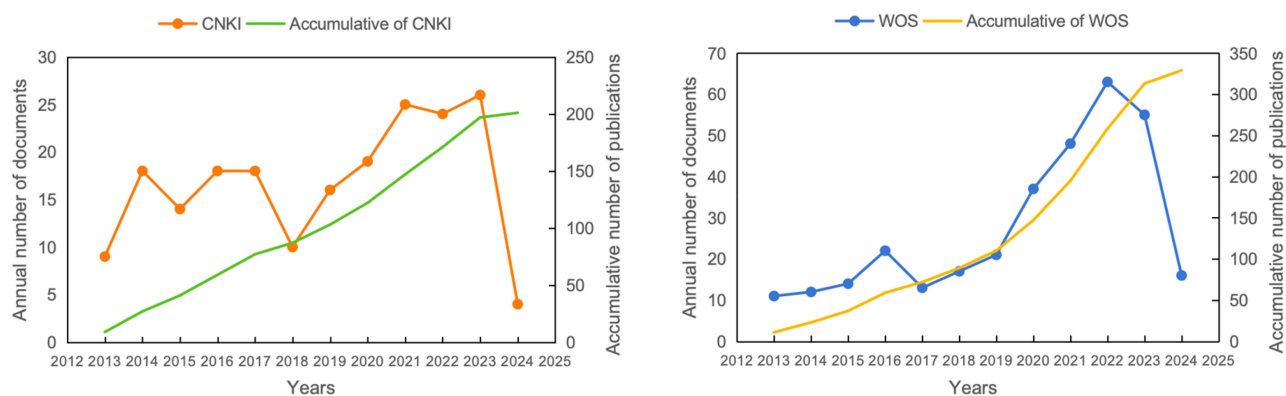


Figure 2 Trends in publication annually.

Table 1 Top 5 Regions with the Most Publications

Ranking	Countries	Centrality	Year	Publications
1	PEOPLES R CHINA	1.46	2013	312
2	USA	0.04	2016	16
3	TAIWAN	0.00	2013	11
4	AUSTRALIA	0.26	2014	7
5	JAPAN	0.00	2020	3

Table 2 Top 5 Institutions with the Most Publications

Database	Ranking	Institutions	Centrality	Year	Publications
CNKI	1	Beijing University of Chinese Medicine	0.04	2014	10
	2	Liaoning University of Traditional Chinese Medicine Affiliated Hospital	0.01	2013	8
	3	Guang'an men hospital China Academy of Chinese Medical Sciences	0.04	2013	6
	4	Liaoning University Of Traditional Chinese Medicine	0	2017	6
	5	Dongzhimen hospital Beijing university of Chinese Medicine	0.01	2014	5
WOS	1	Beijing University of Chinese Medicine	0.31	2014	37
	2	China Academy of Chinese Medical Sciences	0.22	2013	25
	3	Nanjing University of Chinese Medicine	0.13	2013	21
	4	Shanghai University of Traditional Chinese Medicine	0.07	2014	16
	5	Changchun University of Traditional Medicine	0.06	2017	15

articles), Liaoning university of Traditional Chinese Medicine (6 articles), and Dongzhimen Hospital of Beijing University of Traditional Chinese Medicine (5 articles).

In WOS, 388 institutions were identified as participating in related research. Table 2 also illustrates 5 institutions with a publication volume of fifteen or more. The top 5 institutions are Beijing University of Chinese Medicine (32 articles), China Academy of Chinese Medical Sciences (21 articles), Nanjing University of Chinese Medicine (21 articles), Shanghai University of Traditional Chinese Medicine (16 articles), and Changchun University of Traditional Medicine (15 articles). The Figure 3a and b shows a trend of cooperation within institutions. For example, Liaoning university of Traditional Chinese Medicine and Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, Beijing University of Chinese Medicine and China Academy of Chinese Medical Sciences have established stable internal cooperation networks using their geographical advantages, both of which are high volume institutions. The cross-regional cooperation is not common.

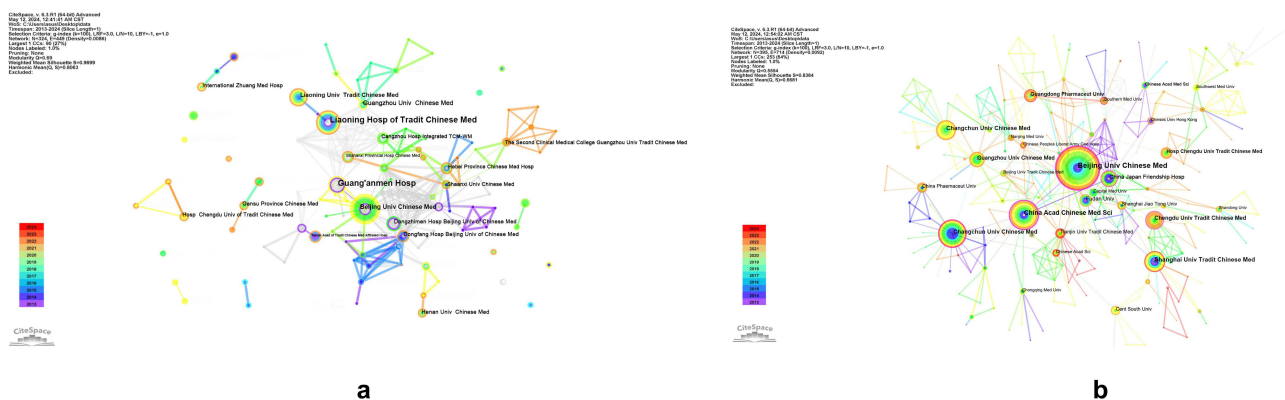


Figure 3 Institutions cooperation network in CNKI (a) and WOS (b).

Keywords Analysis

The 530 articles included in this analysis had 591 keywords. To present the results more intuitively, we excluded “DN” and “TCM”, and combined keywords with the same meaning but different expressions, such as “diabetic nephropathy” and “diabetic kidney disease”. As can be seen in Figure 4a, the top three keywords based on frequency are ‘clinical efficacy’, early diabetic nephropathy”, ‘deficiency of both qi and yin’. In terms of intermediary centrality, the phrase ‘Yiqi Yangyin Tongluo formula’ came in first place, followed by the words ‘Tangshen formula’, and ‘clinical efficacy’. Figure 4b shows in foreign studies, ‘network pharmacology’, ‘renal fibrosis’ and ‘inflammation’ appear more frequently. Among them, the centrality of “inflammation” is the highest.

In general, TCM believes that the cause of this disease lies in the deficiency of both Qi and Yin. At the same time, exploring the targeted mechanisms of traditional Chinese medicine through network pharmacology has become a hot topic.

Keywords Clustering Analysis

Figure 5a and b shows that 10 cluster labels were obtained for both Chinese and foreign studies. The silhouette value indicates good homogeneity and reasonable clustering among clusters. The smaller the cluster number, the larger the cluster size and the more keywords it contains.¹² The clustering results show that Chinese research can be roughly divided into three research directions, one is to explore the mechanism of TCM treatment of the disease, one is to explore the safety of TCM treatment, and the other is to study the effect of TCM treatment of different periods and types of DN.

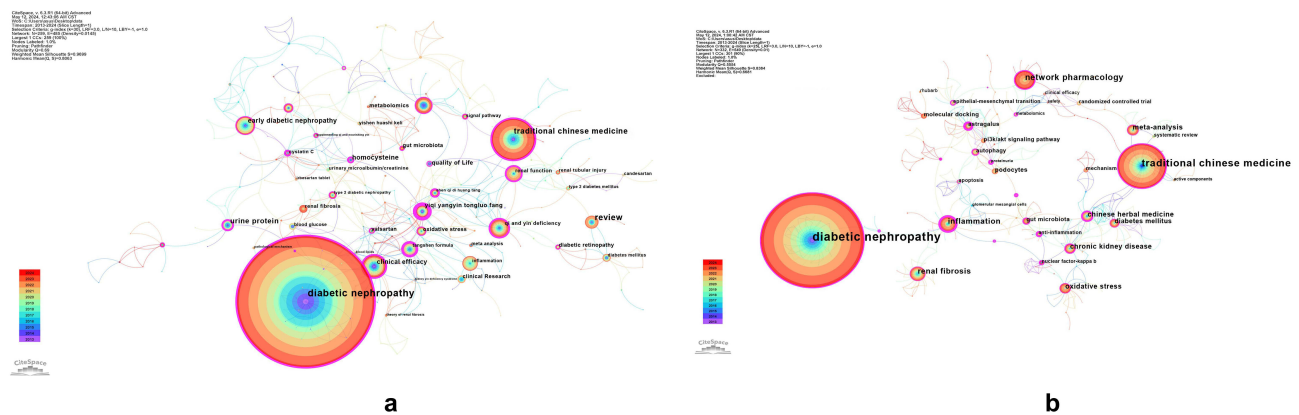


Figure 4 Visualization of keyword cooccurrence in CNKI (a) and WOS (b).

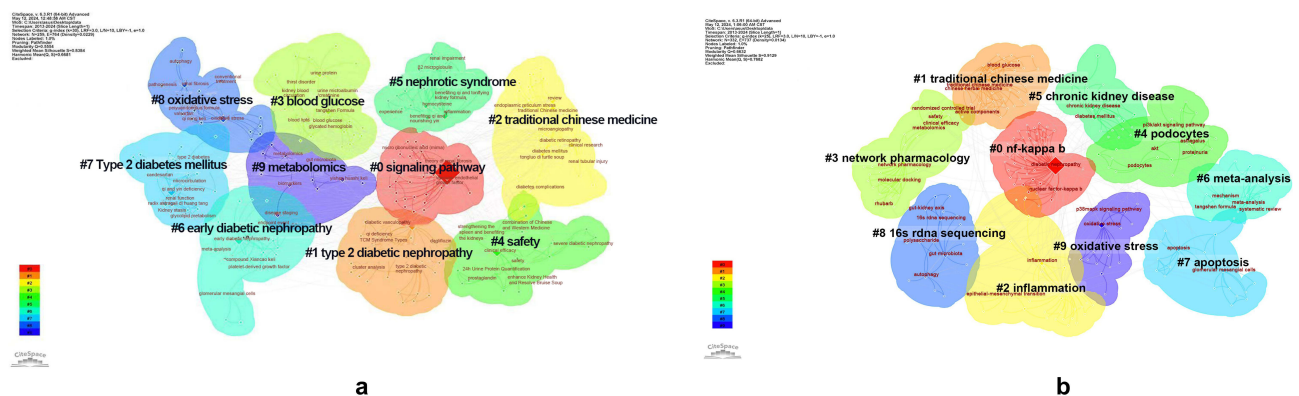


Figure 5 The map of keyword clustering in CNKI (a) and WOS (b).

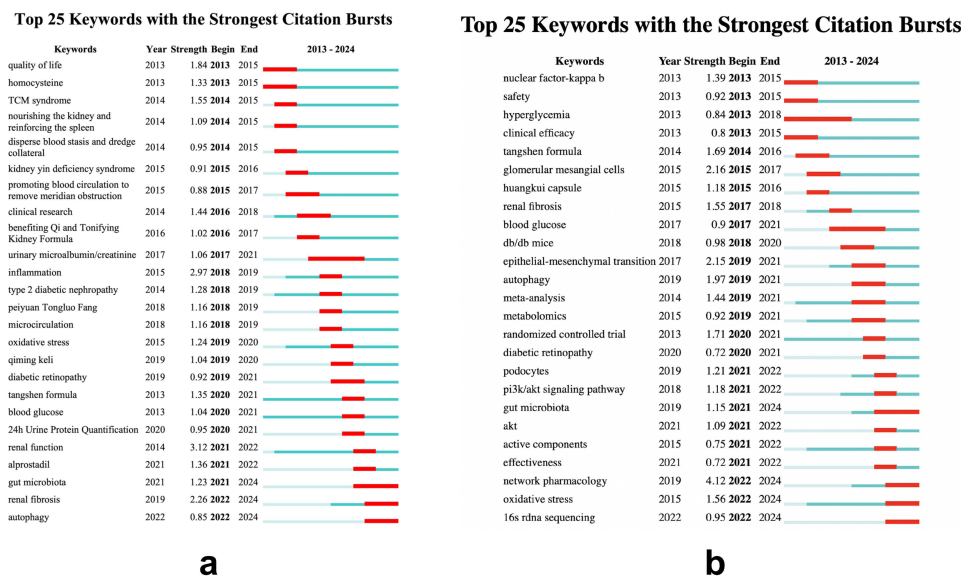


Figure 6 Visualization of Keyword Bursts in CNKI (a) and WOS (b).

The research direction of foreign language research is also divided into three main fields. First, the study of the pathogenesis of DN; second, the exploration of the mechanisms of TCM; and third, most related research in this field is presented in the form of meta-analysis.

Visualization of Keyword Bursts

Keyword emergence analysis refers to the identification of words that appear frequently and are growing rapidly. These words can help us understand the areas of high interest in research, analyze research hotspots, and identify development trends.¹³ “Begin” represents the start time of the sudden appearance, “end” represents the end time, and “strength” represents the intensity of the keyword’s mutation. The higher the intensity, the greater the impact.

Figure 6a and b shows the top 25 terms in this field with the most intense outbreaks. In Chinese studies, the explosive intensity of keywords such as “kidney function”, “inflammation”, “renal fibrosis”, “quality of life”, “TCM syndrome” exceeds 1.5. In foreign studies, words like “network pharmacology”, “glomerular mesangial cell”, and “epithelial-mesenchymal transition” have outbreak intensities exceeding 2.0. Keywords like “gut microbiota”, “network pharmacology”, “oxidative stress”, “16s rDNA sequencing” and “renal fibrosis” have surfaced in the past two or three years.

Discussion

This work is a bibliometric evaluation of DN and TCM research, providing important data in this field for the upcoming researchers. A total of 201 records were included from CNKI and 329 records were included from WOS.

We first look at publishing trends. From 2013 to 2024, many relevant articles are published every year. After 2019, there is a significant increase in foreign publications. After 2021, there is an obvious surge in Chinese publications, which may be related to the important role of TCM in the prevention and treatment of the COVID-19. More and more scholars in the field have focused their attention on TCM, starting to explore the relationship between DN and TCM, and expecting that TCM can also play an important role in the treatment of DN. Secondly, although previous studies have shown that TCM has unique advantages and good prospects in the prevention and treatment of DN, many of them have limitations, such as high risk of bias in outcome indicators, lack of standardization in the evaluation of the efficacy of TCM, neglect of end-point indicators, and under-reporting of safety events, and so on. To compensate for these shortcomings, several studies have been conducted by different scholars.

Over the past 11 years, China has published 321 studies, making it the most influential country with the largest number of publications. Australia and the United States are countries with relatively high publication numbers and

intermediary centrality, and are also important positions for related studies. In China, TCM has been used in the treatment of diseases for more than a thousand years. However, research on its pharmacological mechanisms and clinical applications started relatively late, but developed rapidly, making it the first in the total number of publications. Li Qing et al¹⁴ found that it plays a protective role by affecting the cellular pyrolysis pathway. Li Yanfang et al¹⁵ found that TCM regulates the level of autophagy in podocytes through the mTOR signaling pathway and thus prevents DN. In addition, the TLR4 signaling pathway has become an important target for the prevention and treatment of DN by TCM, which was reported in the study of Gao Yali et al.¹⁶

The spatial distribution analysis results show that the intermediary centrality of research institutions in this field is generally low, and that their influence needs to be improved. Many institutions take advantage of geography to work closely with institutions in the same region, but cross-regional cooperation is not common, which to some extent limits the development of this field and is not conducive to academic research. The top 5 research institutions in terms of publication volume are all located in China, indicating that China has extensive research and more authoritative institutions in this field.

The main pathological changes in DN are thickening of the glomerular basement membrane, hypertrophy of glomerular cells, and damage to podocytes. Podocytes are an important component of the glomerular filtration barrier and are crucial for ensuring the filtration function of the glomerulus. The normal functioning of podocyte cells heavily relies on the regulation of intracellular calcium signaling. Excessive influx of Ca^{2+} can lead to the fusion and disappearance of podocyte foot processes, as well as cell apoptosis, ultimately resulting in damage to the glomeruli.¹⁷ At present, the focus of Chinese research is mainly on the improvement of renal function of early DN by TCM, focusing on the clinical efficacy of TCM treatment. The early clinical symptoms of patients with DN are atypical, mainly manifested as a small amount of proteinuria, which is easy to be ignored. However, proteinuria is the most direct and primary manifestation of DN, and the onset of proteinuria is closely related to the damage of podocytes.¹⁸ For early DN, if it can be diagnosed and treated in time, the damage of renal function can be reversed and the progression of the disease can be delayed. Otherwise, once it reaches stage IV or V, the renal function will continue to decline and even develop into renal failure.¹⁹ Therefore, early diagnosis and treatment of diabetes nephropathy is very important. Professor Lin Lan, a Chinese scholar, believes DN begins with a deficiency of both qi and yin and develops into a deficiency of both yin and yang at a later stage. Based on years of clinical experience, she believes that the key period for treatment is the period of Qi Yin deficiency. Effective treatment methods can prevent the further development of diseases. In the treatment, she emphasizes that the treatment method should benefit qi and nourish yin.²⁰ Foreign studies have focused mainly on oxidative stress response, cellular damage and network pharmacology. The pathogenesis of DN involves the interaction of multiple factors. Angiotensin, inflammation, and oxidative stress are a few of the pathways that contribute to the onset and development of DN. Oxidative stress is the most noticeable of them.²¹ Chronic hyperglycemia increases the production of reactive oxygen species, damages DNA and proteins due to oxidative stress, lowers antioxidant capacity, and triggers the immune system to release inflammatory mediators and cytokines that alter the structure and function of glomerular capillaries and tubules.²² All of these effects exacerbate systemic injury and renal cell damage.²³ TCM includes decoction treatment, traditional Chinese patent medicines and simple preparations treatment, external treatment of traditional Chinese medicine and other methods.²⁴ It has the advantages of small adverse reactions and individualized medication. However, due to the large number of components of Chinese medicine, the target of action is not clear. As a new tool in the field of Chinese medicine research, network pharmacology²⁵ puts an end to the traditional drug development model of “one drug, one target, one disease” and opens up a new research model of complex network relationship between multiple targets and multiple diseases.²⁶ Phosphatidylinositol 3-kinase (PI3K) and 16s rDNA sequencing are the main research directions of foreign journals. PI3K/protein kinase B (AKT) is a classic signaling pathway that inhibits cell apoptosis and promotes survival.²⁷ Inhibition of this pathway can control glucose and lipid metabolism, alleviate pathological damage such as basement membrane thickening, mesangial dilation, and renal interstitial fibrosis.²⁸ 16s rDNA sequencing is an important method for detecting the composition of gut microbiota. TCM believes that the gastrointestinal tract interacts with the kidneys, and the gastrointestinal tract has a regulatory effect on kidney function.^{29,30} Utilizing multi-component, multi-target, and multi-effective traditional Chinese medicine to act on the intestinal tract can not only regulate the intestinal microbiota, but also treat renal diseases.³¹ By detecting the

intestinal flora composition of DN in different periods, it was found that the abnormal flora structure occurred in the early stage of diabetes with kidney disease.³² In addition, evaluating the differences in the composition of gut microbiota in different disease states can help to establish indicators of differences in different renal diseases.³³ Visualization of Keyword Bursts shows that renal function, network pharmacology, gut microbiota, and renal fibrosis are still hot research trends in the future.

At present, clinical treatment of DN is mainly based on measures such as lowering blood glucose, regulating lipids, decreasing blood pressure, etc. Although the disease progression is slowed down to a certain extent, the therapeutic effect is not very satisfactory. In recent years, with the continuous development of TCM, good results have been achieved in the treatment of DN, which can significantly improve the prognosis and quality of life of DN patients. However, there are still some shortcomings, such as the lack of clinical experimental studies, the lack of necessary TCM theoretical guidance for the study of single-flavored TCM extracts and TCM compound therapy, which is not conducive to giving full play to the advantages of TCM, and the fact that the specific pathogenesis of DN is still under further investigation, and the related mechanism of action needs to be more in-depth and detailed excavation. Therefore, in future research, we should innovate the research approach for treating DN, fully explore and leverage the advantages and potential of TCM in the treatment of DN, benefiting a wide range of DN patients.

Strengths and Limitations

This article conducts a bibliometric analysis of relevant literature on the topic. We used systematic retrieval and quantitative statistical analysis, so the bibliometric research in this article is more comprehensive than literature review. However, our research also have some disadvantages. Although the WOS and CNKI databases contain most of the research, the information may not be complete. In addition, regarding the application effect of citespace, the analysis of our study is relatively single, and we did not include new analysis functions, which is one of the goals of our subsequent efforts.

Conclusion

At present, there are not many review articles on bibliometric analysis in the field related to TCM treatment of DN, and our study fills the relevant gap to some extent. We used citespace6.3.R1 to evaluate 530 publications on DN and TCM research from 2013 to 2024. Related research on DN and TCM treatment has increased over the past 11 years, with the most significant increase occurring in the past 3 years. TCM treatment of diabetes has important research value and broad application prospects. This study demonstrates that China is a leader in this field. Among the research institutions, Beijing University of Traditional Chinese Medicine has the most number of publications and the greatest impact. Different countries and institutions need to strengthen cooperation and communication. The research on the treatment of DN by TCM mainly focuses on oxidative stress, network pharmacology, and gut microbiota. Researchers can refer to the relevant conclusions of this paper and take oxidative stress and gut microbiota as an entry point to focus future research in this area, which is a good choice. In addition, utilizing network pharmacology technology to deeply explore the effective active ingredients and their mechanisms of action can also provide new research ideas for the prevention and treatment of DN by TCM.

Abbreviations

DN, Diabetic nephropathy; TCM, Traditional Chinese medicine; WOS, Web of Science Core Collection database; CNKI, Chinese National Knowledge Infrastructure.

Ethics Approval and Informed Consent

The Ethics approval and informed consent is not necessary for our study.

Acknowledgments

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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