Woody International Publish Limited
An Multidisciplinary Academic Journal Publisher

Journal of Theory and Practice in Clinical Sciences, Volume 1, 2024
https://www.woodyinternational.com/

CiteSpace-based Visualization of Xanthone Capsule for Diabetic Nephropathy Treatment

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Abstract: ***Objective:*** ***To conduct a visual analysis of research hotspots and trends in the treatment of diabetic kidney disease (DKD) with Huangkui Capsule using CiteSpace visualization software.*** ***Methods:*** ***Relevant literature on the treatment of DKD with Huangkui Capsule was retrieved from China National Knowledge Internet (CNKI). Co-occurrence and clustering analyses were performed on keywords, authors, and publishing institutions. Additionally, burst analysis and timeline visualization were applied to keywords, and a visual analysis of annual publication volume was conducted to explore research hotspots and development trends.*** ***Results:*** ***A total of 289 articles were included in this study. The annual publication volume showed an upward trend from 2007 to 2010 and from 2013 to 2017, with a decline after 2020. However, the overall trend before 2020 was an increase in annual publications. Author collaborations, exemplified by Liu Rongjuan, Wan Yigang, and Sun Wei, were prevalent. Inter-institutional collaborations were less pronounced. The clustering of keywords yielded eight clusters labeled as adverse reactions, proteinuria, valsartan, renal function, oxidative stress, clinical efficacy, treatment group, and targets. Burst analysis identified 78 burst terms, among which urea nitrogen, dapagliflozin, inflammatory markers, adverse reactions, signaling pathways, and targets emerged as new research hotspots.*** ***Conclusion:*** ***The primary research focus on the treatment of DKD with Huangkui Capsule centers on clinical randomized controlled trials, particularly those combining Huangkui Capsule with valsartan, dapagliflozin, liraglutide, or traditional Chinese medicine formulations. Clinical studies remain the dominant research type. Currently, there is a lack of in-depth basic research, and more standardized clinical and basic research is needed to provide evidence-based medical support in this field. Incorporating the expertise of renowned practitioners with Chinese medicine characteristics can offer additional insights for clinical treatment.***

Keywords: Diabetic kidney disease (DKD); Huangkui Capsule; Research hotspots; Visual analysis; CiteSpace.

Cited as: Feng, X., & Liu, L. (2024). CiteSpace-based Visualization of Xanthone Capsule for Diabetic Nephropathy Treatment. *Journal of Theory and Practice in Clinical Sciences*, *1*, 11–19. Retrieved from https://woodyinternational.com/index.php/jtpcs/article/view/37.

1. Introduction

Diabetic Kidney Disease (DKD): DKD is a chronic complication of diabetes, manifesting as a chronic kidney disease caused by diabetes. It is characterized by a urine albumin-to-creatinine ratio (UACR) >30 mg/g and/or glomerular filtration rate (GFR) <60 ml/min/1.73m² for three months or longer [1]. DKD, driven by a chronic hyperglycemic environment, is clinically marked by persistent albuminuria and/or progressive decline in eGFR, which can progress to end-stage renal disease (ESRD). Large-scale studies in Europe and the United States have reported that 20%-40% of diabetic patients develop DKD [2][3]. In some regions of China, the prevalence of DKD is similar to that in these countries [4][5][6]. Retrospective studies abroad have found that type 2 diabetes mellitus (T2DM) is more likely to progress to DKD compared to type 1 diabetes mellitus (T1DM) [7]. DKD is the leading cause of death in T1DM patients and second only to cardiovascular and cerebrovascular complications in T2DM. Western medical treatments primarily involve 1) nutritional control, such as total calorie, protein, sodium, and potassium intake; 2) exercise management; 3) weight control and surgical weight reduction; 4) the use of kidney-beneficial hypoglycemic drugs like SGLT2i (e.g., dapagliflozin), which significantly reduces renal composite endpoints in clinical studies; 5) lipid-modifying therapy; and 6) the use of drugs to delay proteinuria, such as RAAS inhibitors. Most of these treatments are non-pharmacological or symptomatic. SGLT2i, represented by dapagliflozin, is a newly marketed drug that effectively controls blood glucose while protecting the heart and kidneys, offering high safety and efficacy but imposing significant economic burdens on patients. Huangkui Capsule, whose main ingredient is Abelmoschus manihot flower, clears heat and dampness, detoxifies, and reduces swelling, making it suitable for treating damp-heat syndrome in chronic nephritis. It is recommended as a Class Ia (strong recommendation) drug in the 2022 Guidelines for the Combination of Disease and Syndrome Treatment

of Diabetic Nephropathy for treating damp-heat syndrome in chronic nephritis [8].

2. Materials and Methods

2.1 Literature Retrieval

The data for this study were sourced from the China National Knowledge Infrastructure (CNKI) database. The search query was constructed using the following terms: (subject: "diabetic nephropathy" + "elderly type 2 diabetic nephropathy") AND (subject: "Huangkui Capsule").

2.2 Inclusion Criteria

All literature related to the treatment of diabetic nephropathy (DN) with Huangkui Capsule was included in the analysis.

2.3 Exclusion Criteria

Documents such as conference proceedings, master's and doctoral theses, call for papers, newspaper articles, yearbooks, and case reports were excluded.

2.4 Data Processing

The retrieved 289 documents were exported from CNKI in Refworks format and imported into the CiteSpace 6.1.R6 visualization software. The time slicing was set from January 2005 to December 2023, resulting in 288 documents meeting the search criteria. The software was then configured to analyze Authors, Institutions, and Keywords separately by sequentially selecting each option under Node Types.

3. Results

3.1 Keyword Co-occurrence Analysis

Keywords provide a concise summary of a paper's main research objectives and approach, directly reflecting its research direction. The keyword co-occurrence map illustrates the research hotspots and knowledge structure in the field of Huangkui Capsule treatment for DN. By setting the time slicing from January 2005 to December 2023, the analysis revealed 336 keywords and 688 co-occurrence links, with a network density of 0.0122. (see Figure 1)

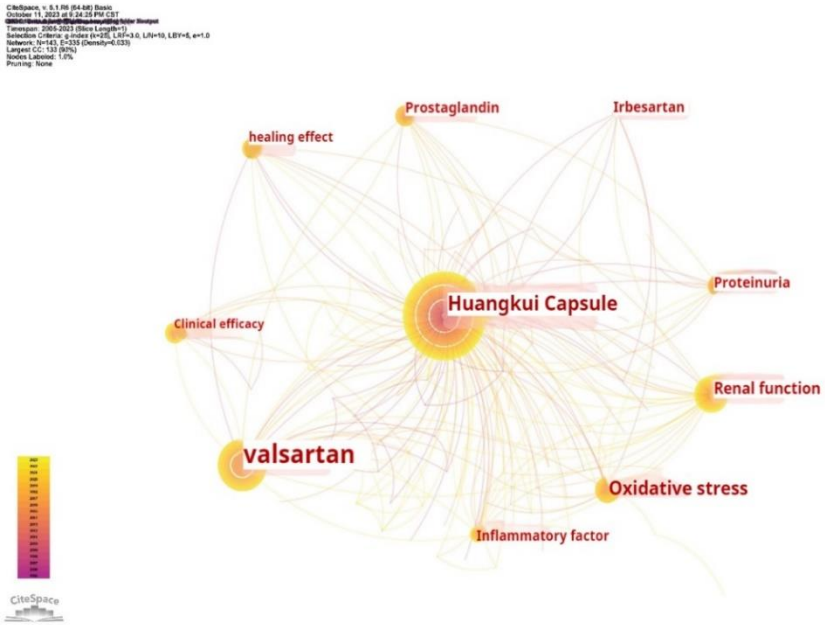


Figure 1: Keyword co-occurrence analysis of xanthone capsule for diabetic nephropathy

The top ten most frequent keywords were Huangkui Capsule (257 occurrences), valsartan (62), renal function (28), efficacy (21), proteinuria (16), oxidative stress (15), clinical efficacy (12), irbesartan (11), alprostadil (11), and inflammatory factors (11). These findings indicate that research on Huangkui Capsule for DN primarily focuses on clinical trials, animal experiments, and basic research.

Sorted	Frequency	Keywords
1	257	Huangkui capsule
2	62	valsartan
3	28	kidney function
4	21	healing effect
5	16	proteinuria
6	15	oxidative stress
7	12	Clinical efficacy
8	11	Irbesartan
9	11	prostaglandin
10	11	inflammatory factor

Figure 2: Keyword frequency ranking chart of huangqi capsule for the treatment of diabetic nephropathy

3.2 Keyword Cluster Analysis

The keyword cluster analysis yielded eight clusters (#0-#7), representing distinct research topics in the field (see Figure 3). These clusters were labeled as #0 adverse reactions, #1 proteinuria, #2 valsartan, #3 renal function, #4 oxidative stress, #5 clinical efficacy, #6 treatment group, and #7 targets. Each cluster represents a hot topic in the research on Huangkui Capsule for DN, revealing trends in the development of this treatment. The clustering could be broadly categorized into clinical efficacy studies and pharmacological research. The modularity Q-value (0.4595, >0.3) and mean silhouette value (S = 0.8507, >0.7) indicate a robust and reliable clustering structure.

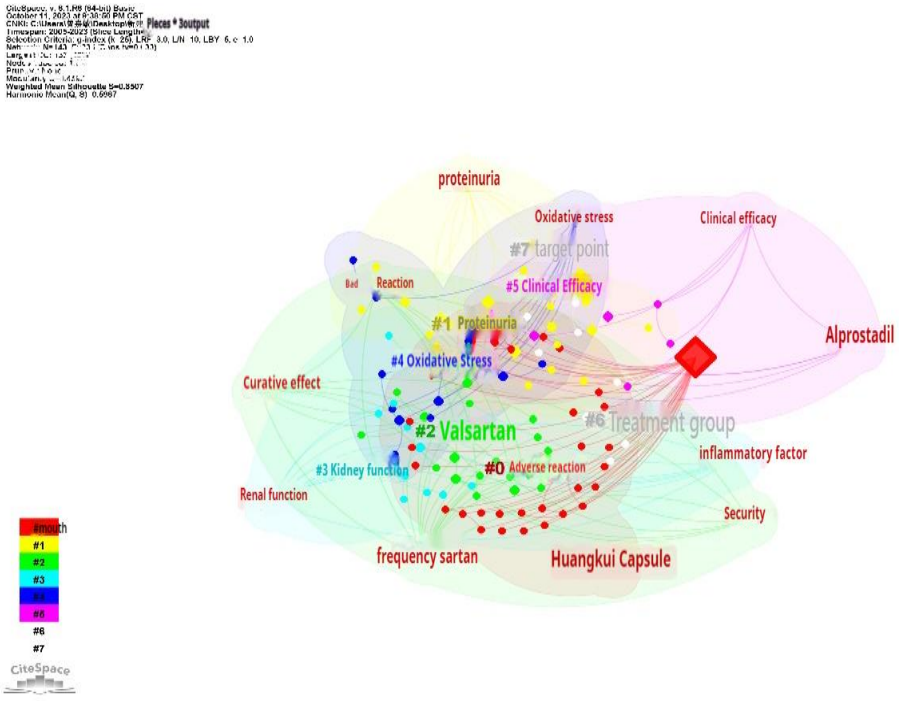
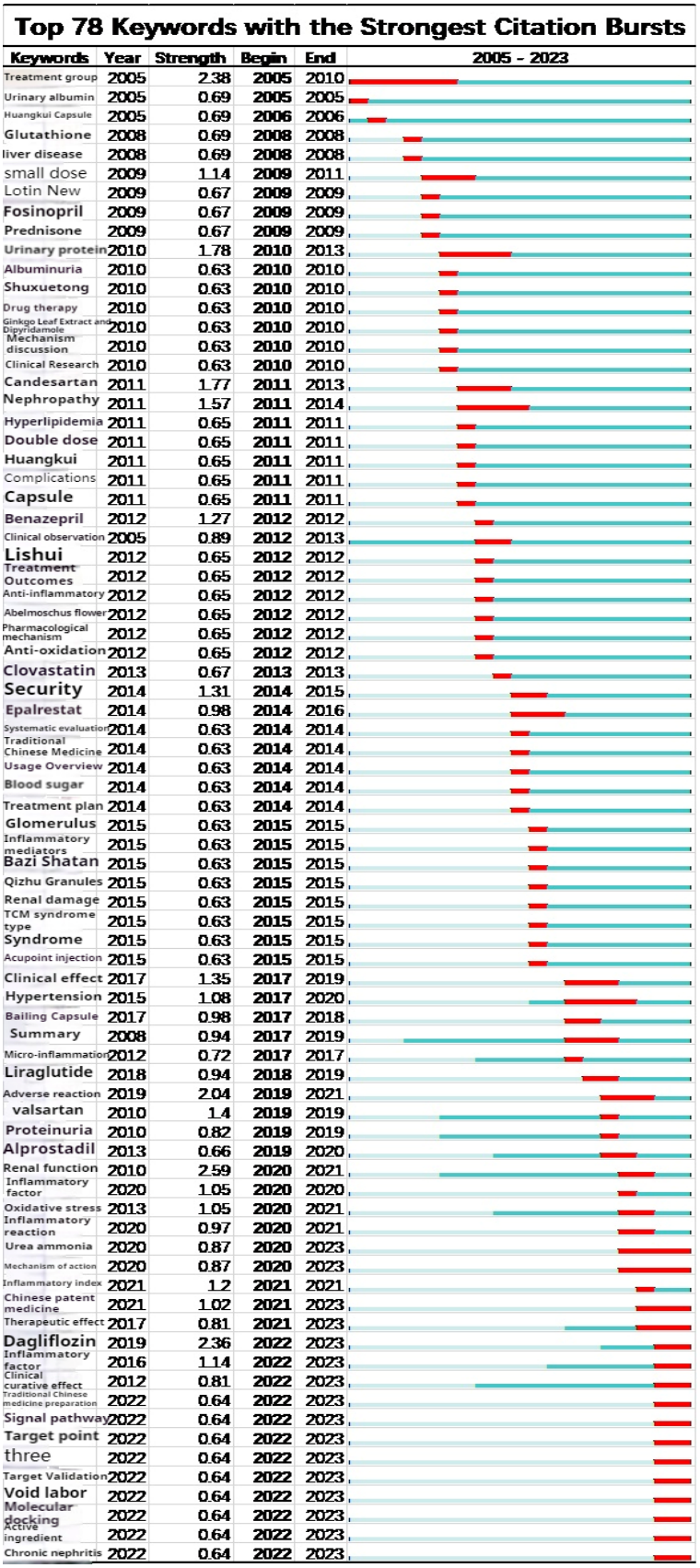


Figure 3: Clustering mapping of keywords for the treatment of diabetes mellitus with Huangwai capsule

3.3 Burst Analysis

Burst analysis identifies evolving research trends in the field. From 2005-2015, research focused on urinary protein, low doses, treatment groups, candesartan, safety, and nephropathy. From 2015-2023, the focus shifted to dapagliflozin, inflammatory markers, oxidative stress, renal function, adverse reactions, urea nitrogen, targets, and signaling pathways (see Figure 4).



Notably, during 2005-2015, articles under the keyword "treatment group" often explored clinical studies combining Huangkui Capsule with compound formulations for DN.

3.4 Timeline Analysis

The timeline analysis revealed that Cluster #0 (adverse reactions) spanned the longest duration (2002-2022), while Cluster #7 (targets) was the most recent (2019-2021). Clusters #1 (proteinuria), #2 (valsartan), and #3 (renal function) maintained sustained interest, while #4 (oxidative stress), #5 (clinical efficacy), and #7 (targets) emerged as new research hotspots.

3.5 Author Co-occurrence Analysis

The analysis of author co-occurrence identified collaborative teams led by authors such as Su Qingmin, Wan Yigang, and Sun Wei, who have published multiple articles in close collaboration. In contrast, most other authors published independently, with a limited number of collaborations. Among the authors, only 19 had published two or more articles, and six had published three or more. This suggests that while the overall number of publications is high, author collaboration is relatively scarce. Applying Lotka's Law, the minimum number of publications for a core author (M) was calculated as $M \approx 0.74$.

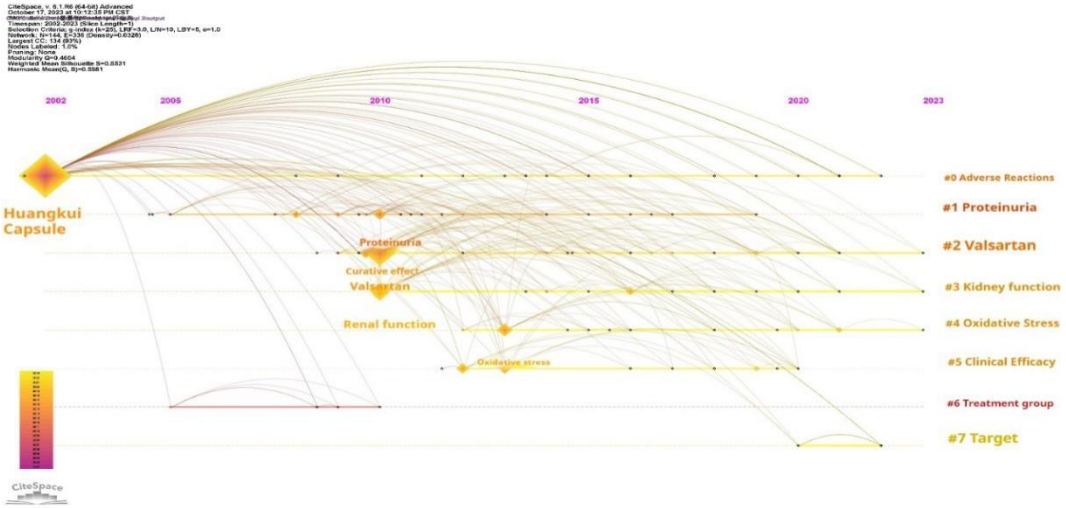


Figure 5: Mapping of keyword emergence in the treatment of diabetes mellitus by Huangwai capsule

3.6 Visualization and Co-occurrence Analysis of Publishing Institutions

The visualization analysis of publishing institutions reveals the prominent research entities in this field, facilitating the grasp of research hotspots and trends. The figure below (see Figure 7) depicts institutions with a publication count of two or more articles, totaling 16 institutions. Among them, the institutions with three or more publications include Hebei Youai Hospital, the Department of Traditional Chinese Medicine, Drum Tower Hospital, Medical School of Nanjing University, Neiqiu County People's Hospital of Hebei Province, and the Nephrology Department, Shaoxing People's Hospital of Zhejiang Province.

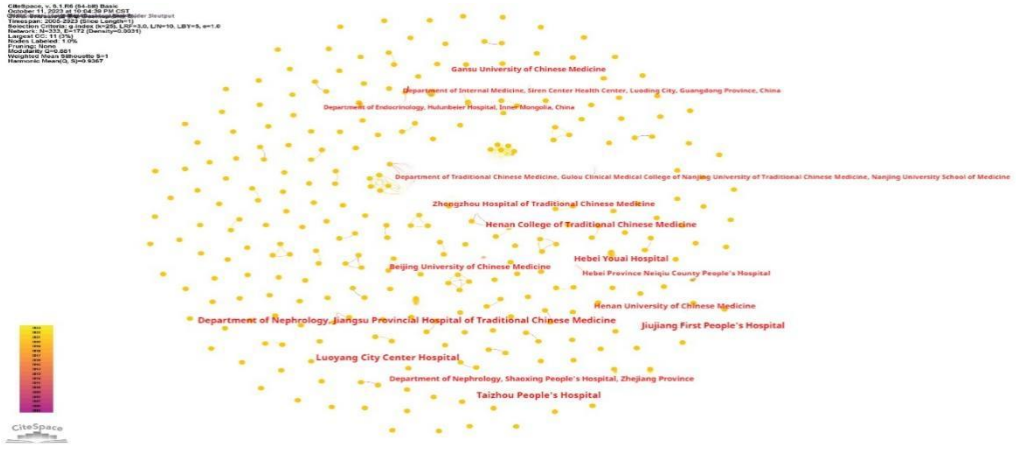
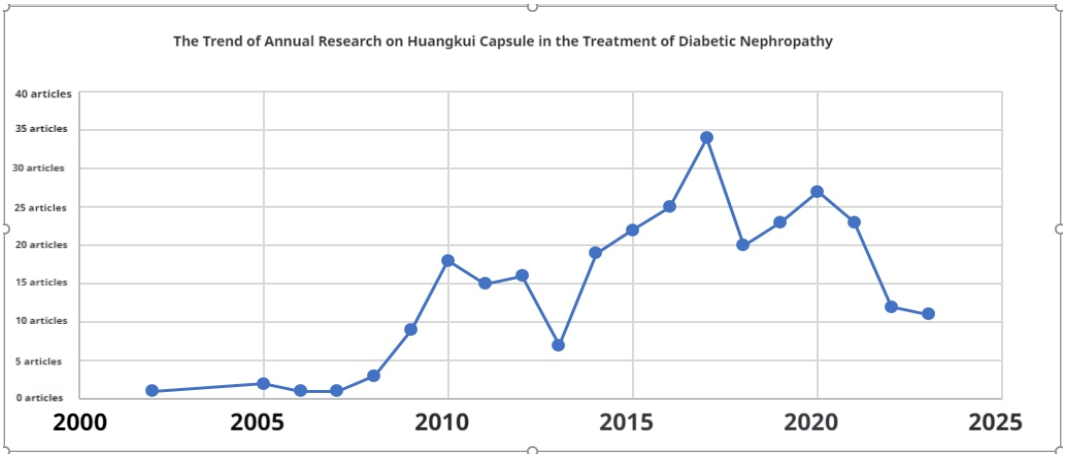


Figure 6: Author co-occurrence visualization map

3.7 Visualization and Co-occurrence Analysis of Annual Publications



This graph indicates that the number of publications in this field exhibited an upward trend in 2006-2010, 2013-2017, and 2018-2020, suggesting that Huangkui Capsule's treatment of diabetic nephropathy gradually emerged as a research hotspot during these periods. The peak year was 2017, with 34 publications, while the lowest years were 2006 and 2007, each with one publication. The number of publications slowed down in 2022-2023, indicating a gradual deepening of research in this area.

4. Discussion

This study utilizes Citespace software to provide an intuitive visual analysis of Huangkui Capsule's treatment of diabetic nephropathy since 2002. Through keyword co-occurrence, clustering, burst analysis, timeline analysis, author and institution co-occurrence, and annual publication volume, we reveal the research hotspots and trends in this field.

4.1 Analysis of Publications by Authors and Research Teams

In the field of Huangkui Capsule's treatment of diabetic nephropathy, collaborative teams led by Su Qingmin, Wan Yigang, and Sun Wei have emerged. These researchers hail from: 1) Su Qingmin (Neiqiu County People's Hospital), 2) Wan Yigang (Drum Tower Hospital, Medical School of Nanjing University), and 3) Sun Wei (Affiliated Hospital of Nanjing University of Chinese Medicine). Su Qingmin focuses on clinical research, exploring Huangkui Capsule's renal protective effects, vascular endothelial function, inflammatory response, and blood lipid impacts in diabetic nephropathy patients [9][10][11]. Wan Yigang's work is primarily based on fundamental research, investigating Huangkui Capsule's targets, signaling pathways, and the mechanisms of Huangkui flower preparations in treating renal diseases [12][13][14]. Sun Wei's research combines statistical analysis (Meta-analysis) with fundamental research, focusing on Huangkui Capsule's mechanisms and signaling pathways in diabetic nephropathy and its efficacy when combined with ACEI/ARB [15][16][17]. Collaborations among these teams are limited, with Wan Yigang and Sun Wei having some collaborations. Publications mainly originate from local hospitals and university-affiliated hospitals, primarily in Nanjing. Small teams dominate, with minimal inter-team cooperation. Future efforts should strengthen intra-city, intra-provincial, inter-provincial, and inter-team collaborations, sharing research methods and theories to establish standardized clinical trial evaluation metrics, further advancing research in this field.

Since 2007, research publications on Huangkui Capsule's treatment of diabetic nephropathy have shown a fluctuating growth trend, maintaining over 20 publications annually after 2014, albeit with a slight decline in 2022 and 2023. This indicates increasing attention and research efforts towards Huangkui Capsule, a traditional Chinese medicine, in treating diabetic nephropathy.

4.2 Research Hotspots

4.2.1 Clinical Efficacy of Huangkui Capsule in Treating Diabetic Nephropathy

As shown in Figure 3's keyword clustering analysis, "#0 Adverse Reactions," "#1 Proteinuria," and "#3 Renal

Function" reflect the clinical research hotspots of Huangkui Capsule in treating diabetic nephropathy. Clinical studies reveal that Huangkui Capsule's adverse reactions are lower or unchanged compared to Western medicines when combined with, for instance, Calcium Dobesilate [18], Valsartan [19], and Alprostadil [20], indicating its high safety. When combined with Bailing Capsule [21] or Valsartan [22], Huangkui Capsule reduces early-stage proteinuria levels in diabetic nephropathy. Its combination with Alprostadil [23] reduces mid-stage proteinuria, while monotherapy can also assist in reducing proteinuria [24]. Monotherapy with Huangkui Capsule significantly decreases blood urea nitrogen (BUN) and serum creatinine (Scr), improving renal function.

4.2.2 Hotspot Analysis of the Combination Therapy of Huangkui Capsule and Western Medicines for Diabetic Nephropathy

In the keyword burst analysis, Bailing Capsule, liraglutide, valsartan, alprostadil, dapagliflozin, and traditional Chinese medicine preparations (TCMPs) emerged as the major co-administered drugs with Huangkui Capsule in recent years. Notably, dapagliflozin displayed the highest intensity of 2.36, followed by valsartan with 1.4, indicating that these two drug classes have been the research hotspots in the combination therapy with Huangkui Capsule. Dapagliflozin, an SGLT-2i inhibitor, not only reduces blood glucose levels but also exerts protective effects on the heart and kidneys. By inhibiting tubuloglomerular feedback, it decreases eGFR (estimated glomerular filtration rate), thereby mitigating the risk of progressive chronic kidney injury and hospitalization due to end-stage renal disease. A retrospective clinical study conducted by the Nephrology Department of Renmin Hospital of Wuhan University [29] found that the short-term efficacy (7 days after medication) of dapagliflozin manifested as reduced edema, weight loss, and an increase in Scr of less than 30% from baseline, demonstrating significant therapeutic effects. Another trial revealed that dapagliflozin effectively improved renal function and reduced urinary microalbumin. In the combination therapy of Huangkui Capsule and dapagliflozin [30], patients in the combination group received Huangkui Capsule three times daily (5 capsules each time) and dapagliflozin 10 mg once daily on an empty stomach in the morning. The dapagliflozin group and Huangkui Capsule group followed the respective dosing regimens. After 12 weeks of continuous treatment, blood glucose levels, inflammatory factors, and serum levels of cystatin C (Cys-C) and α1-microglobulin (α1-MG) were observed. The results showed that the combination group had lower levels of fasting blood glucose (FBG), 2-hour postprandial glucose (2h-PG), HbA1c, inflammatory factors (sICAM-1, HMGB1, MCP-1), Cys-C, and α1-MG compared to the dapagliflozin group and Huangkui Capsule group.

4.3 Limitations in the Research on Huangkui Capsule for Diabetic Nephropathy

4.3.1 Imbalanced Research Distribution

Current research on Huangkui Capsule for diabetic nephropathy is predominantly focused on clinical randomized controlled trials (RCTs), with relatively few basic experimental studies in this field. Among the RCTs, most studies investigate the combination therapy of Huangkui Capsule with western medicines, such as ACEI or ARB drugs in Meta-analyses [31] and the clinical value of Huangkui Capsule combined with liraglutide in treating early diabetic nephropathy [32].

4.3.2 Irregular Clinical Research

Despite the emergence of numerous clinical RCTs on Huangkui Capsule for diabetic nephropathy in recent years, existing studies suffer from issues such as inadequate rigor in design, lack of uniform observation indicators, small sample sizes, and a scarcity of high-quality RCTs. Future research could address these limitations by referring to diagnostic and treatment guidelines for diabetic nephropathy, incorporating the experience of renowned physicians, utilizing data mining to determine optimal dosages, and establishing unified observation indicators. Subsequently, conducting cross-regional, multicenter, large-scale RCTs will facilitate the development of effective treatment protocols involving Huangkui Capsule and/or combined western medicines.

5. Conclusion

In summary, research on Huangkui Capsule for diabetic nephropathy has primarily focused on clinical RCTs, yielding satisfactory therapeutic outcomes. This has promoted the clinical application of Huangkui Capsule and its compound formulations, opening up new avenues for traditional Chinese medicine in treating diabetic nephropathy. However, several deficiencies persist, including loose collaboration among research teams, limited publications from core teams, and a lack of authoritative research institutions and high-quality outcomes. The

decline in publications in this field over the past two years can be attributed to: 1) an overconcentration on clinical RCTs without standardized evaluation criteria and a shortage of authoritative research institutions and high-quality outcomes; 2) the need for further in-depth basic research to clarify the signaling pathways and targets of Huangkui Capsule in treating diabetic nephropathy, thereby supporting clinical studies. Therefore, authors and research teams in this field should strengthen collaboration, allocate resources rationally, and promote sustainable research development.

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