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Bibliometric analysis of intestinal microbiota in diabetic nephropathy

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Abstract. – OBJECTIVE: The purpose of this study is to use bibliometrics to explore the research overview and research hotspots.

MATERIALS AND METHODS: The relevant literature on intestinal flora and diabetic nephropathy in the Web of Science Core Collection was sorted out, and VOSviewer, CiteSpace, Scimago Graphica and other software were used to conduct data visualization analysis on the number of publications, countries, institutions, journals, authors, keywords and citations.

RESULTS: A total of 124 relevant literatures were included. From 2015 to 2022, the number of published papers increased every year. The countries, institutions and journals that published the most articles in this field are China, Isfahan University Medical Science and Frontiers in Pharmacology. Liu Bicheng and Mirlohi Maryam are the authors with the most published articles in this field. The main keywords of research in this field are obesity, inflammation, oxidative stress, indoxyl sulfate, short-chain fatty acids (SCFAs) and Chinese herbal medicine.

CONCLUSIONS: This is the first bibliometric analysis of diabetic nephropathy and gut microbiota, reporting hot spots and emerging trends. Obesity, inflammation, oxidative stress, indoxyl sulfate, SCFAs and Chinese herbal medicine are the main keywords of current research, and SCFAs and Chinese herbal medicine may be the hotspots of future research.

Key Words:
Diabetic nephropathy, Intestinal flora, Bibliometrics, CiteSpace, VOSviewer.

Abbreviations

Diabetic nephropathy (DN), the United States of America (the USA), average citations per item (ACI), the United Kingdom (the UK), impact factor (IF), G protein-coupled receptor 43 (GPR43), vascular endothelial growth factor (VEGFA), malondialdehyde (MDA), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), short-chain fatty acids (SCFAs).

Introduction

Diabetes is a metabolic disease characterized by hyperglycemia caused by insulin resistance and defective insulin secretion[1]. Epidemiology shows that the global prevalence of diabetes is increasing annually[2] and the number of people with diabetes is predicted to exceed 625 million worldwide by 2045[3]. Long-term persistent hyperglycemia can easily lead to microvascular and macrovascular lesions[4], among which diabetic nephropathy (DN) is one of the most common and serious complications of diabetes[5,6]. DN is characterized by persistent impairment of glomerular filtration and a hyperglycemic state[6], and it is the most common cause of end-stage renal disease[7,8]. Although persistent hyperglycemia is considered to be an important factor leading to the occurrence and development of DN, its specific pathogenesis is complex and has not been fully elucidated[9]. In recent years, more and more pieces of evidence[10,11] have shown that the intestinal flora is closely related to the metabolic activities of the body. Under normal circumstances, the intestinal flora that maintains a symbiotic relationship with the human body consists of 100 trillion microorganisms[12], which can regulate the secretion of substances such as insulin and glucagon[9] and

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maintain the normal metabolic activities of the body. Related studies have shown a dysbiosis of the intestinal flora in the feces of patients with DN, in which there was a significant decrease in small intestinal rose typhus and a significant increase in *Bacteroides faecalis*[13]. When the intestinal flora is in dysbiosis, abnormally proliferating strains of harmful bacteria can disrupt the intestinal mucosal barrier, leading to increased intestinal permeability and resulting in toxins from the intestine entering the kidneys through circulation[12]. These toxins activate local and systemic inflammatory responses in the kidney[12], and chronic inflammation exacerbates apoptosis and fibrosis in renal cells[14], thereby inducing the development of DN. Therefore, the dysbiosis of intestinal flora is closely related to the occurrence of DN, and the regulation of intestinal flora may be an entry point for the treatment of DN.

Bibliometrics is an emerging comprehensive method that can reveal various characteristics of a type of literature, such as countries, institutions, journals, authors, citation rates, and keywords[15,16], and is widely used to assess the scholarly impact of various types of literature and to explore recent research trends in a field[17]. Unfortunately, there are no bibliometric studies relating to DN and intestinal flora. Therefore, based on the published research on DN and intestinal flora, this study uses bibliometrics to explore the research status and latest research directions of DN and intestinal flora, aiming to provide directions for future research.

Materials and Methods

Data Sources and Search Strategy

To ensure the authenticity and availability of the data, all data for this study were sourced from the Web of Science Core Collection (WoSCC). The proposed search formula was "TS=(Gut Microbiome OR Gut Microflora OR Gut Microbiota OR Gut Flora OR Gastrointestinal Flora OR Gastrointestinal Microbiome OR Gastrointestinal Microbiota OR Gastrointestinal Microflora OR Gastrointestinal Microbial Community OR Gastrointestinal Microbial Communities OR Gastric Microbiome OR Intestinal flora OR Intestinal Microbiome OR Intestinal Microbiota OR Intestinal Microflora OR Enteric Bacteria OR Gut bacteria OR Lactobacillus OR Prebiotics OR Synbiotics OR Probiotics OR Bifidobacterium OR Lactobacillus acidophilus OR crispatus OR delbrueckii OR gasseri OR helveticus OR johnsonii OR leichmannii OR pentosus OR plantarum OR Enterobacteria OR Coliform Bacilli OR Sodalis OR Paracolobactrum OR Ewingella OR Leclercia OR Bacteroides OR fragilis OR thetaiotaomicron OR Eubacterium OR Staphylococcus OR Staphylococcus aureus OR Staphylococcus capitis OR Staphylococcus epidermidis OR Staphylococcus haemolyticus OR Staphylococcus hominis OR Staphylococcus hyicus OR Staphylococcus intermedius OR Staphylococcus lugdunensis OR Staphylococcus saprophyticus OR Achromobacter stutzeri OR Bacillus nitrogenes OR Pseudomonas perfectomarinus OR Bacterium stutzeri OR Pseudomonas perfectimarina OR Pseudomonas perfectomarina OR Achromobacter sewerinii OR Bacillus stutzeri OR Proteus OR Proteus mirabilis OR Proteus penneri OR Proteus vulgaris) AND TS=(Diabetic Nephropathies OR Nephropathies, Diabetic OR Nephropathy, Diabetic OR Diabetic Nephropathy OR Diabetic Kidney Disease OR Diabetic Kidney Diseases OR Kidney Disease, Diabetic OR Kidney Diseases, Diabetic OR Diabetic Glomerulosclerosis OR Glomerulosclerosis, Diabetic OR Intracapillary Glomerulosclerosis OR Nodular Glomerulosclerosis OR Glomerulosclerosis, Nodular OR Kimmelstiel-Wilson Syndrome OR Kimmelstiel Wilson Syndrome OR Syndrome, Kimmelstiel-Wilson OR Kimmelstiel-Wilson Disease OR Kimmelstiel Wilson Disease)". Search restrictions: language was English, type of research was article or review, and the deadline was 13 April 2023.

Data Collection and Analysis

The literature was independently screened by investigators A and B. After excluding non-English articles, non-journal articles and articles with irrelevant research topics, the rest of the included literature was exported in the formats "Plain text file" and "The delimited file". If there were any objections during the period, investigator C would make a decision.

The research data was imported into Microsoft Excel 2021 to construct a database for the bibliometric study. VOSviewer1.6.19, CiteSpace6.2.2, Pajek5.16, Scimago Graphica1.0.34 and other software were used for bibliometric analysis of the research data, including countries, institutions, authors, cited authors, journals, references, and keywords.

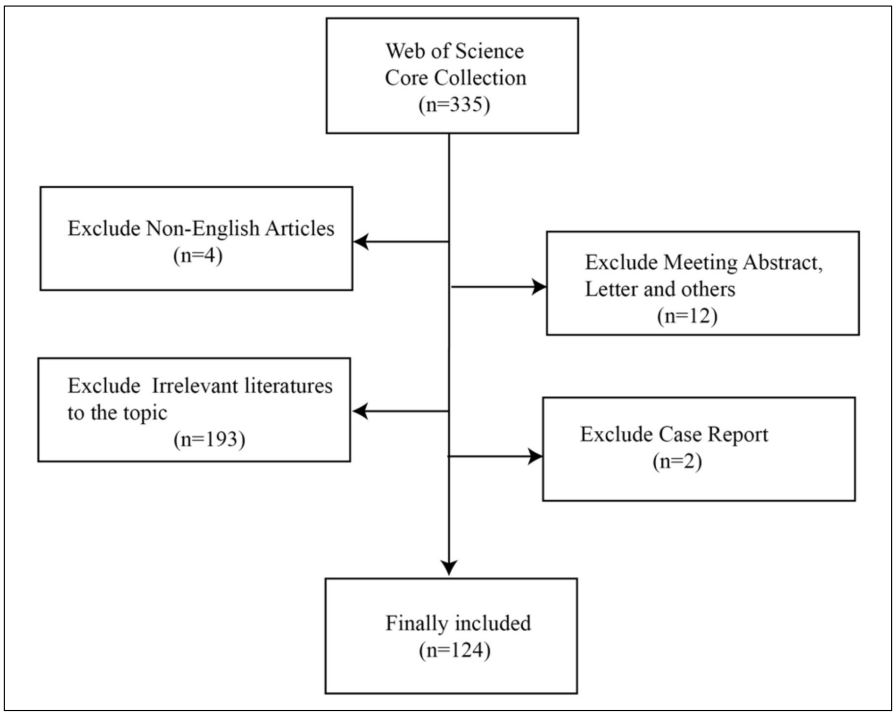


Figure 1. Flow diagram of the included literature.

Results

The Trend of Publication Outputs

As shown in the flow diagram of the included studies in Figure 1, a total of 335 literatures were collected, and 124 relevant literatures were finally included after screening. As shown in Figure 2, research on DN and intestinal flora has focused on the last decade, and the number of relevant articles published each year has grown rapidly. 80% of the literature was published after 2019, with 2.1 times more articles published in 2020 than in 2019, 1.84 times more articles published in 2022 than in 2021, and only four months of articles counted in 2023, for which no conclusions can yet be drawn.

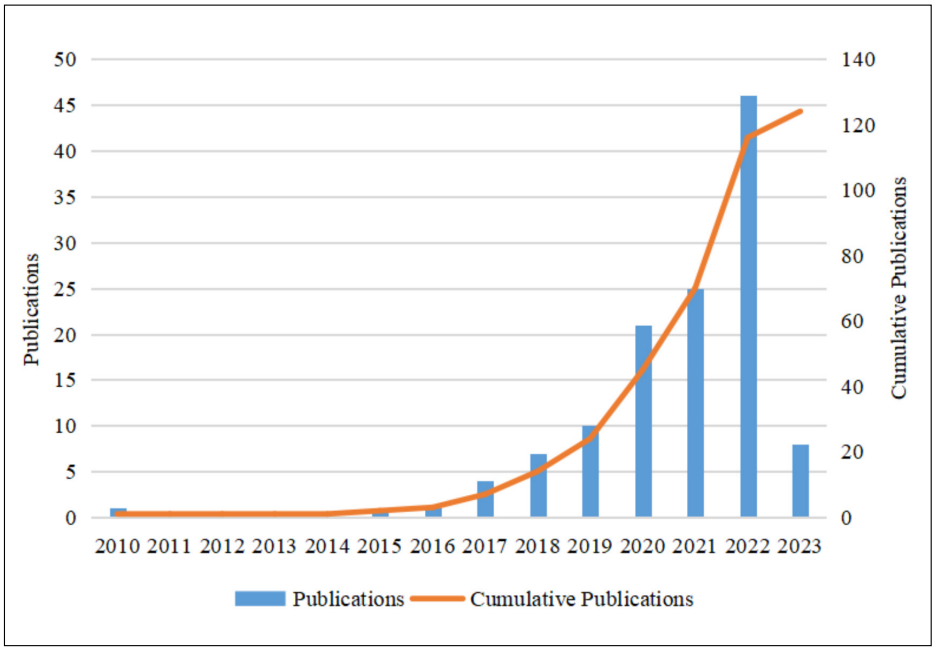


Figure 2. Trends of the annual publications related.

Table I. Top 10 productive countries.

Rank	Country	Quantity	Proportion/%	ACI	H-index	Total link strength
1	China	82	66.13%	14.83	21	14
2	Usa	9	7.26%	48.11	8	7
3	Iran	9	7.26%	21.44	7	1
4	Australia	8	6.45%	22.13	5	4
5	United kingdom	5	4.03%	26.60	5	5
6	Japan	5	4.03%	33.40	4	2
7	Romania	5	4.03%	19.20	4	1
8	South korea	3	2.42%	10.33	2	2
9	Brazil	2	1.61%	3.50	1	1
10	Denmark	2	1.61%	11.50	2	4

ACI, average citations per item.

Analysis of Countries/Regions Distribution

China was the country that most published in the field of DN and intestinal flora, accounting for 66.13% of total publications, followed by the United States of America (USA) (7.26%) and Iran (7.26%), as shown in Table I. This study used Scimago Graphica 1.0.34 to visualize the collaboration between countries. The larger the node, the more articles the country had published. The closer the node color was to red, the more articles the country had published in cooperation with other countries. The thicker the connecting line was, the closer the cooperation between the two countries was. As shown in Figure 3, China and the USA cooperate most closely in this field, followed by China and the United Kingdom (UK). H-index stands for "highly cited" and is often used to assess the influence of authors, institutions, and countries. China ranked first among the countries/regions included in the literature

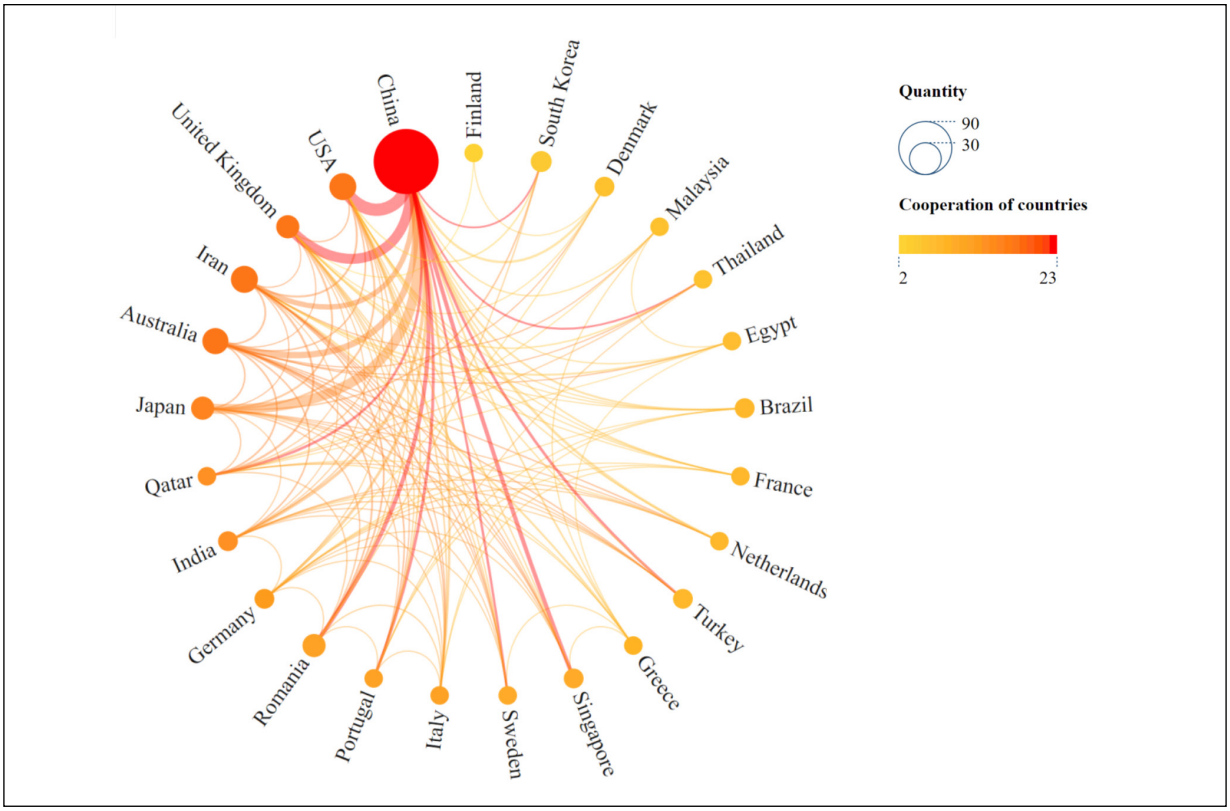


Figure 3. Scimago Graphic collaboration visualization map of country/region.

Table II. Top 10 productive institutions.

Rank	Institution	Country	Quantity	SOTC	ACI	H-index
1	Isfahan university medical science	Iran	7	145	20.71	6
2	Beijing university of chinese medicine	China	6	63	10.50	5
3	Chinese academy of sciences	China	5	58	11.60	3
4	University of london	United Kingdom	5	113	26.60	5
5	Zhengzhou university	China	5	23	4.60	2
6	China japan friendship hospital	China	4	41	10.25	3
7	Jilin university	China	4	103	25.75	3
8	Monash university	Australia	4	126	31.50	3
9	Shanghai jiao tong university	China	4	17	4.25	1
10	Southeast university china	China	4	113	28.25	4

SOTC, sum of times cited; ACI, average citations per item.

with an H-index of 21, followed by the USA and Iran. However, in terms of average citations per item (ACI), China (14.83) still has a large gap compared to developed countries such as the USA (48.11), Japan (33.40) and the UK (26.6).

Analysis of Institutions Distribution

A total of 240 institutions were involved in the included literature, among which *ISFAHAN UNIVERSITY MEDICAL SCIENCE* ranked first with 7 publications, followed by *BEIJING UNIVERSITY OF CHINESE MEDICINE* (6) and *CHINESE ACADEMY OF SCIENCES* (5). Among the top 10 institutions, 7 institutions were from China, and the remaining 3 institutions were from Iran, the UK and Australia, as shown in Table II.

The institutional co-occurrence analysis reflects the collaborative relationship between organizations. The larger the node, the higher the number of articles issued. The closer the node color was to red, the more co-occurrence there was between the organization and other organizations. The thicker the link was, the closer the collaboration between the two institutions was. As shown in Figure 4, Austin Hlth had the highest number of publications and a close partnership with Univ Melbourne.

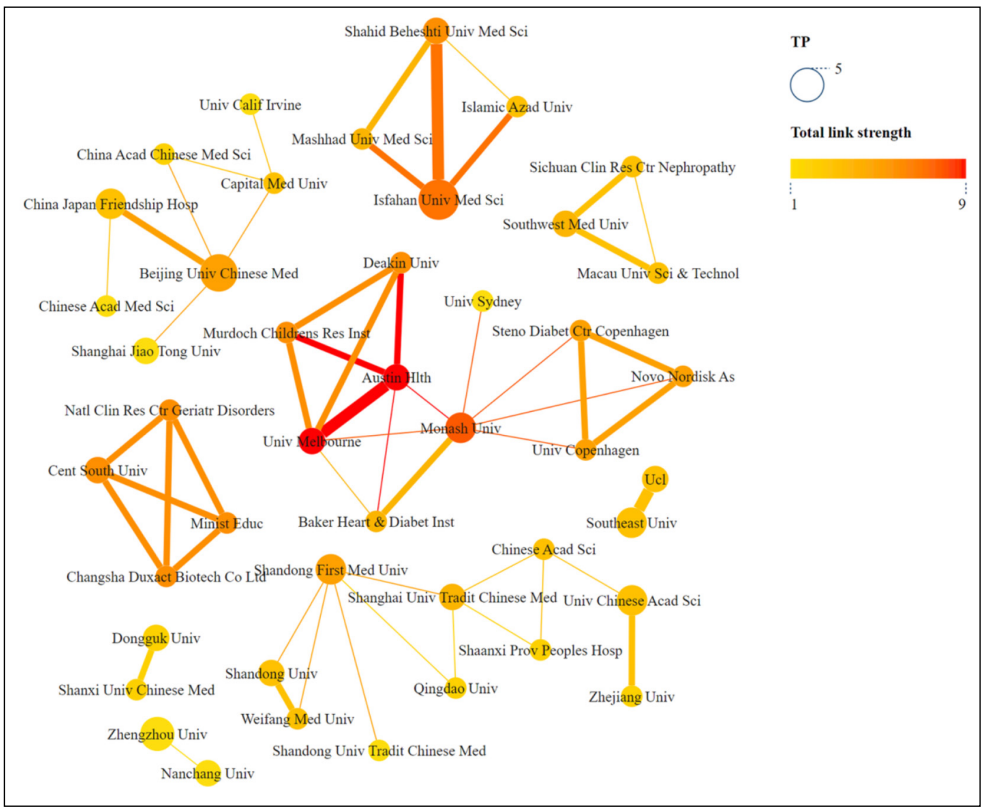


Figure 4. Scimago Graphic collaboration visualization map of institutions.

Analysis of Authors and Authors' Collaborations

A total of 842 authors were involved in the included literature, with an average of 6.79 authors per paper. 8 of the top 10 authors were from China, and the remaining two were from Canada and Iran (Table III). Liu Bicheng and Mirlohi Maryam were the most prolific authors, both with five relevant publications. Huang Wei was the author with the highest average citation rate, followed by Mirlohi Maryam, Liu Bicheng and Ruan Xiongzhong.

In the analysis of the authors' collaborative relationships, three large working groups of 10 or more people are shown in Figure 5. Among the 10 authors with the highest number of publications, Liu Bicheng, Ruan Xiongzhong, Zhang Jiaxiu and Ma Kunling collaborated closely.

Analysis of Journal Distribution

The journals that have published the most relevant publications in the field of DN and intestinal flora are listed in Table IV. The journal with the most publications was *FRONTIERS IN PHARMACOLOGY,* with 9 articles in this field, followed by *FRONTIERS IN ENDOCRINOLOGY* (6). The journal with the highest impact factor (IF) was *JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY*, with an IF of 14.978, followed by *FRONTIERS IN IMMUNOLOGY* (8.786) and *INTERNATIONAL JOURNAL OF BIOLOGICAL MACROMOLECULES* (8.025) (Table IV). In general, there are few journals with high IFs for this type of research, and there is still a lot of room for improvement. 14 of the top 20 journals in terms of the number of articles published are in Q1, 4 are in Q2 and only 2 are in Q3.

Analysis of Hotspots and Frontiers

CiteSpace was used to statistically analyze the keywords in the included literature, and the top 20 keywords with the frequency ranking were recorded in Table V. "Gut microbiota", "diabetic nephropathy" and "diabetic kidney disease", which occur more frequently, were free words for DN and intestinal flora. In addition, words such as "inflammation", "oxidative stress", "obesity" and "chain fatty acids" frequently appeared, which indicates that they are currently hot topics in the field of DN and intestinal flora.

Through the burst detection of keywords, the phased hotspots and development trends of DN and intestinal flora were reviewed and predicted. As shown in Figure 6, "probiotics" and "acidophilus" appeared earlier, with burst strengths of 1.2 and 1.26, respectively, and were topics with high early attention. "Probiotics" has been around the longest, for 8 years, followed by "acidophilus" which has been around for 6 years. "Gut microbiome" had the highest burst rate of 3.09, followed by "type 2 diabetes mellitus" with a burst rate of 2.26. In addition to the above-mentioned free words of DN and intestinal flora, "diet induced obesity" and "hemodialysis patients" were the earliest keywords that appeared, and they had the high burst, 1.5 and 1.26, respectively. This indicates that the previous studies linked the development of DN to diet and explored the dialysis treatment for DN. The burst of "indoxyl sulfate" and "cardiovascular risk" lasted for 4 years, indicating that they are research directions that researchers continue to pay attention to. The high burst of "short-chain fatty acids" in the last three years means that it has the potential to become a future research hotspot.

Table III. Top 10 authors.

Rank	Author	Country	Institution	TP	ACI	H-index
1	Liu Bicheng	China	Southeast University	5	28.25	4
2	Mirlohi Maryam	Iran	Isfahan University of Medical Sciences	5	28.50	4
3	Ma Kunling	China	Zhejiang University	4	28.25	4
4	Shang Jin	China	Zhengzhou University	4	5.50	2
5	RuanXiongzhong	China	Chongqing Medical University	4	28.25	4
6	Zhang Jiaxiu	China	Southeast University	4	27.67	3
7	Zhong Hen	China	South China Agricultural University	4	4.33	2
8	Cai Kedan	China	University of Chinese Academy of Sciences, CAS	4	4.33	2
9	Huang Wei	China	Southwest Medical University	4	50.67	3
10	Moravejolahkami Amir Reza	Iran	Isfahan University of Medical Sciences	4	10.33	2

TP, total publications; ACI, average citations per item.

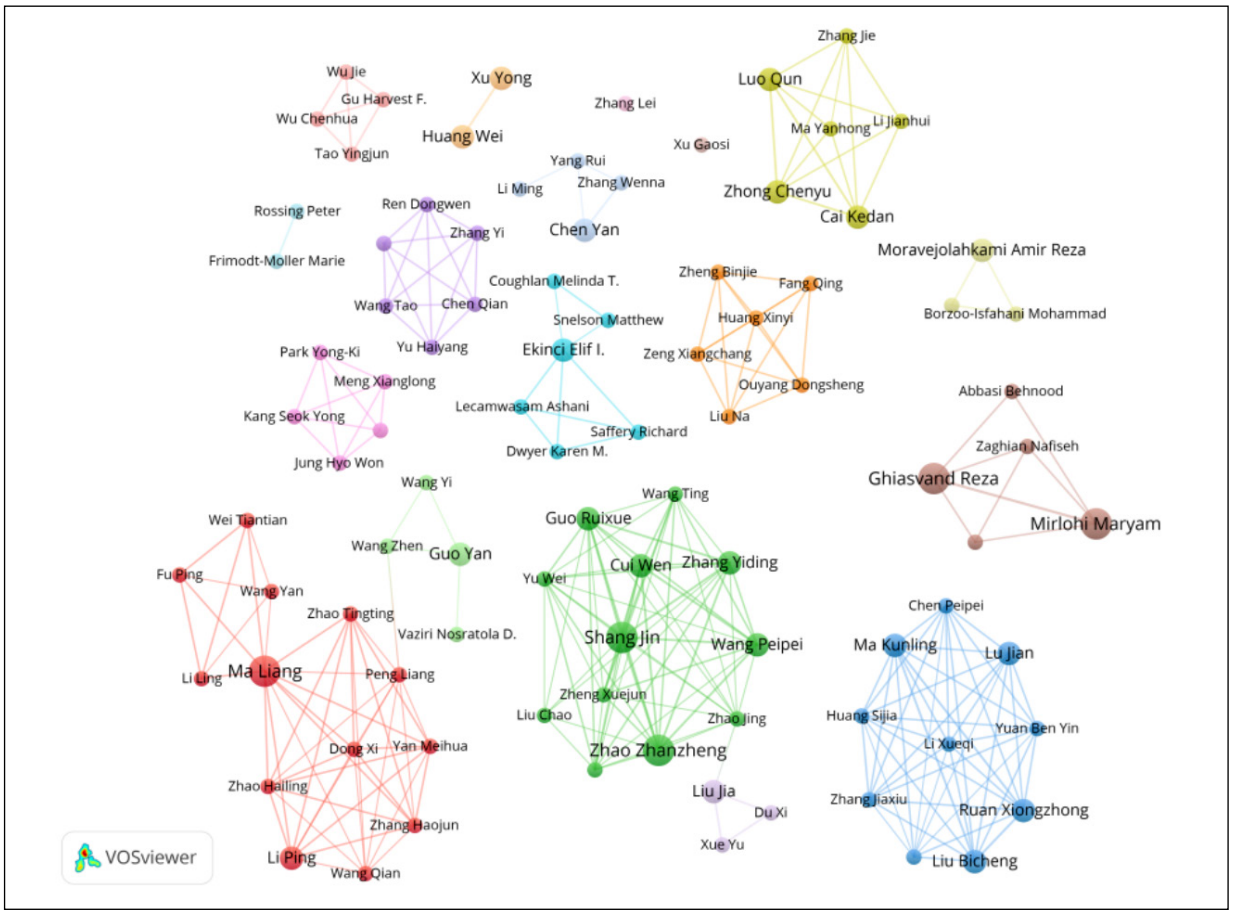


Figure 5. Analysis of author collaborations.

Table IV. Top 20 journals.

Rank	Journal	Quantity	ACI	IF (2022)	JCR
1	Frontiers in pharmacology	9	13.00	5.988	Q1
2	Frontiers in endocrinology	6	3.00	6.055	Q1
3	International journal of biological macromolecules	4	32.00	8.025	Q1
4	International journal of molecular sciences	4	9.50	6.208	Q1
5	Nutrients	4	20.75	6.706	Q1
6	Food function	3	27.33	6.317	Q1
7	Frontiers in immunology	3	3.33	8.786	Q1
8	Frontiers in microbiology	3	1.33	6.064	Q1
9	Acta diabetologica	2	31.50	4.087	Q2
10	Acta pharmacologica sinica	2	27.50	7.169	Q1
11	Best practice research clinical endocrinology metabolism	2	26.50	5.667	Q2
12	Biochimica et biophysica acta molecular basis of disease	2	52.50	6.633	Q1
13	Biomedicine pharmacotherapy	2	17.50	7.419	Q1
14	Biomedicines	2	3.50	4.757	Q2
15	Diabetes metabolic syndrome and obesity targets and therapy	2	12.00	3.249	Q3
16	Endocrine	2	13.50	3.925	Q3
17	Frontiers in nutrition	2	1.00	6.590	Q1
18	Journal of clinical laboratory analysis	2	6.50	3.124	Q2
19	Journal of the american society of nephrology	2	53.00	14.978	Q1
20	Life sciences	2	0.00	6.780	Q1

IF, Impact Factor; JCR, Journal Citation Reports

Table V. Top 20 keywords.

Rank	Keywords	Count	Centrality
1	Gut microbiota	64	0.12
2	Diabetic nephropathy	46	0.13
3	Diabetic kidney disease	37	0.1
4	Inflammation	31	0.16
5	Intestinal microbiota	23	0.18
6	Chronic kidney disease	22	0.16
7	Nephropathy	22	0.08
8	Oxidative stress	21	0.03
9	Obesity	17	0.16
10	Kidney disease	15	0.18
11	Chain fatty acids	15	0.07
12	Progression	13	0.1
13	Gut microbiome	13	0.03
14	Metabolism	9	0.04
15	Bacteria	8	0.11
16	Mice	8	0.05
17	Expression	8	0.06
18	Glucose	8	0.03
19	Disease	8	0.09
20	Health	7	0.05

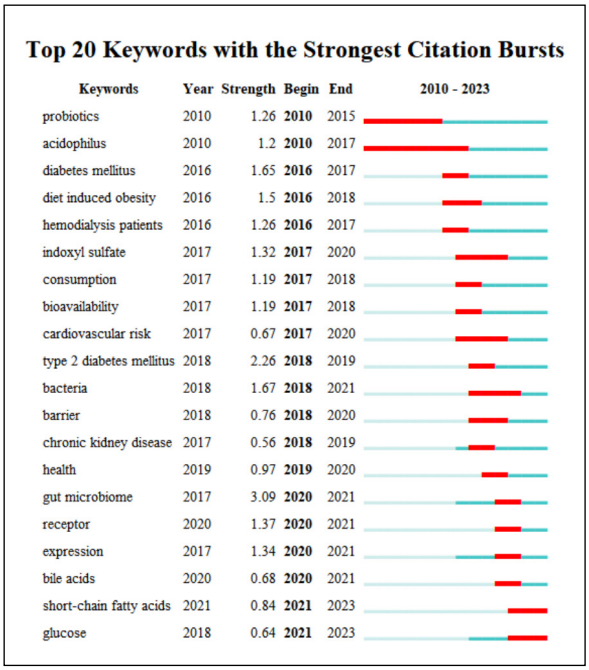


Figure 6. Keyword bursts related.

CiteSpace was used to cluster the keywords and present them in a timeline view in order to observe the basic knowledge structure and evolutionary direction of the intestinal flora in DN. A total of 13 clusters were acquired, and Figure 7 shows the clustering results of the first 10 clusters. The different colored horizontal lines with labels on the right side represent the clusters formed by the keywords. The nodes on the horizontal line represent the keywords. The position of the nodes on the horizontal line represents the year in which the literature containing the keywords first appeared, thus forming a timeline of the evolution of the keyword clusters. "#0 chronic kidney disease" is the largest keyword cluster. "#9 bacterial translocation" is the least one keyword cluster. "#5 bekhogainsam decoction" appeared first, and "#9 bacterial translocation" appeared last. With the passage of time, the nodes of "16s rdna sequencing", "microbial metabolites", "diabetic

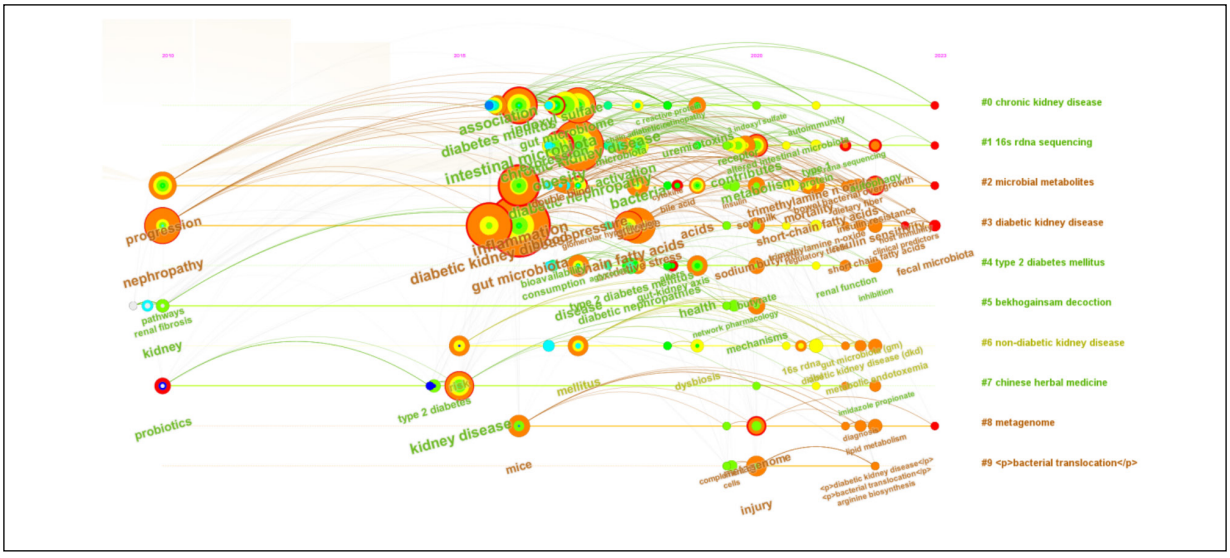


Figure 7. CiteSpace visualization timeline view of keywords clustering analysis.

kidney disease", "metagenome" and "Chinese herbal medicine" have been increasing, indicating that they may be the future hot directions in the field of DN and intestinal flora.

Analysis of Co-Cited References and Reference Burst

The most co-cited article in the total included literature is the article published by Vaziri ND with 161 citations, implying that the research associated with this article may be a research hotspot. Of the top 20 most frequently cited articles, 8 have more than 100 citations and they are high-value literature in this research area, as shown in Table VI.

The burst detection of references helps to select prominent references from numerous references in a short time and find the most influential

Table VI. Top 20 co-cited references.

Rank	Title	Journal	Author	Year	Frequency
1	Chronic kidney disease alters intestinal microbial flora	Kidney int	Vaziri ND	2013	161
2	Gut microbiome-derived phenyl sulfate contributes to a lbuminuria in diabetic kidney disease	Nat commun	Kikuchi K	2019	158
3	A metagenome-wide association study of gut microbiota in type 2 diabetes	Nature	Qin JJ	2012	151
4	Understanding the gut-kidney axis among biopsy-proven diabetic nephropathy, type 2 diabetes mellitus and healthy controls: an analysis of the gut microbiota composition	Acta diabetol	Tao SB	2019	141
5	Dietary Fiber Protects against Diabetic Nephropathy through Short-Chain Fatty Acid-Mediated Activation of G Protein-Coupled Receptors GPR43 and GPR109A	J am soc nephrol	Li YJ	2020	137
6	Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults	Plos one	Larsen N	2010	120
7	Gut Bacteria Products Prevent AKI Induced by Ischemia-Reperfusion	J am soc nephrol	Andrade-Oliveira v	2015	108
8	Gut metagenome in European women with normal, impaired and diabetic glucose control	Nature	Karlsson FH	2013	106
9	Diabetic Kidney Disease: Challenges, Progress, and Possibilities	Clin j am soc nephro	Alicic RZ	2017	98
10	Expansion of urease- and uricase-containing, indole- and p-cresol-forming and contraction of short-chain fatty acid-producing intestinal microbiota in ESRD	Am j nephrol	Wong J	2014	95
11	Diabetic gut microbiota dysbiosis as an inflammaging and immunosenescence condition that fosters progression of retinopathy and nephropathy	Bba-mol basis dis	Fernandes R	2019	94
12	Dysbiosis of intestinal microbiota mediates tubulointerstitial injury in diabetic nephropathy via the disruption of cholesterol homeostasis	Theranostics	Hu ZB	2020	89
13	Intestinal Microbiota in Type 2 Diabetes and Chronic Kidney Disease	Curr diabetes rep	Sabatino A	2017	80
14	The gut microbiome, kidney disease, and targeted interventions	J am soc nephrol	Ramezani A	2014	79
15	Short-Chain Fatty Acids Ameliorate Diabetic Nephropathy via GPR43-Mediated Inhibition of Oxidative Stress and NF- κ B Signaling	Oxid med cell longev	Huang W	2020	77
16	The potential role of the gut microbiota in modulating renal function in experimental diabetic nephropathy murine models established in same environment	Bba-mol basis dis	Li Y	2020	76
17	Probiotic supplementation in diabetic hemodialysis patients has beneficial metabolic effects	Kidney int	Soleimani A	2017	76
18	Gut microbiota dysbiosis-induced activation of the intrarenal renin-angiotensin system is involved in kidney injuries in rat diabetic nephropathy	Acta pharmacol sin	Lu CC	2020	67
19	The gut microbiota and the brain-gut-kidney axis in hypertension and chronic kidney disease	Nat rev nephrol	Yang T	2018	67
20	Alteration of the gut microbiota in Chinese population with chronic kidney disease	Sci rep-uk	Jiang SH	2017	65

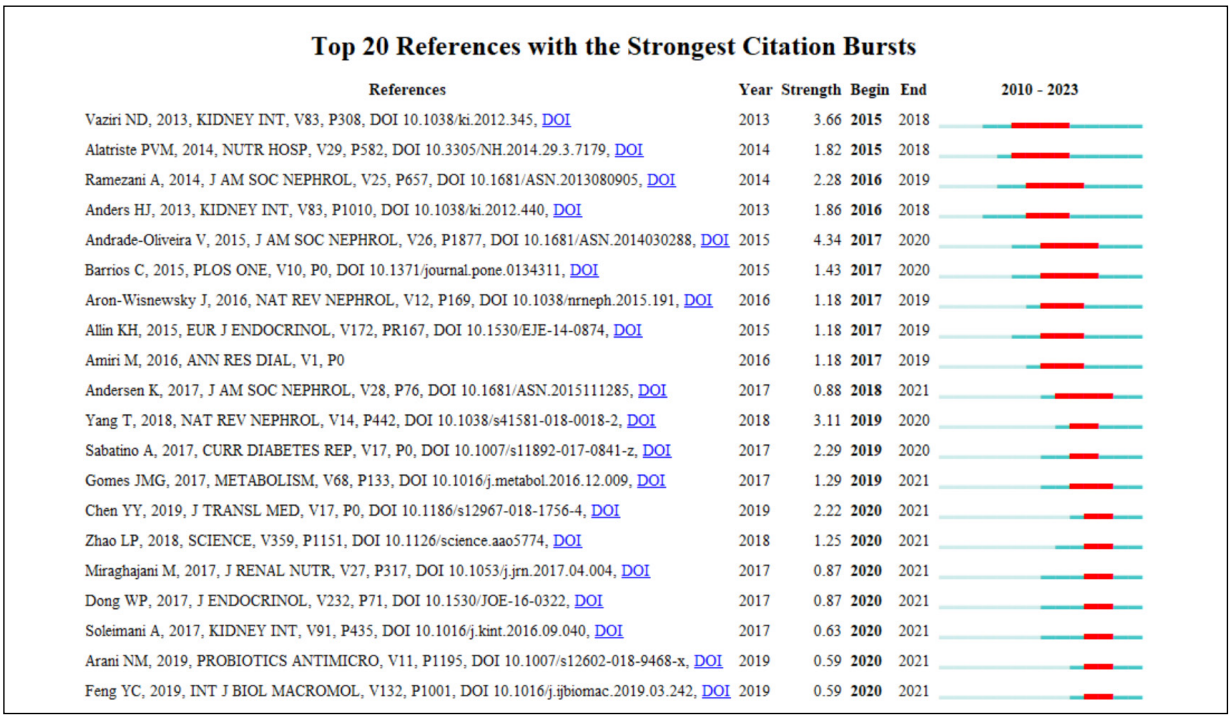
cited articles, so as to clearly discover research frontiers and trends. As shown in Figure 8, Andrade-Olveira V has the highest burst intensity, which is a bridge between two related studies and represents a current research hotspot. Vaziri ND, Alatriste PVM, Andrade-Oliveira V and Barrios C had strong bursts, all of which lasted 4 years, indicating that their studies were active for a long time. Based on the articles published in recent years, only Chen YY has higher burst intensity, while Arani NM and Feng YC both have lower burst intensity.

Discussion

General Information

There is growing evidence of a strong link between intestinal flora and DN, and the field has increasingly become a hot spot for research related to metabolic diseases. This study used bibliometrics to conduct a comprehensive and multi-angle quantitative analysis of the literature on DN and intestinal flora, with the aim of assessing the current state of research in the field and exploring the hotspots of research in the field.

Analysis of the annual number of articles shows that the research related to DN and intestinal flora is mainly concentrated in the last decade, and the number of related articles published each year is growing rapidly. This indicates that the association between DN and intestinal flora is receiving increasing attention from researchers, as shown in Figure 2. The first literature related to this field was published by Lu et al[18] in 2010 in the JOURNAL OF BIOSCIENCE AND BIOENGINEERING, which explained the effect of *lactobacillus roxellanae* GMNL-263 on renal fibrosis in diabetic rats. Previously, people have noticed that long-term intake of lactic acid bacteria is beneficial to human health, including alleviating lactose intolerance, enhancing immunity, treating diarrhea, preventing colon cancer and atherosclerosis, etc., but there are few studies related to diabetes[19,20]; until 2006, when Brugman et al[21] suggested that the composition of the intestinal flora of diabetic rats differed from that of normal rats and demonstrated that modulating the intestinal flora reduced the incidence of diabetes and delayed the onset of diabetes. Researchers began to realize that the intestinal flora might be involved in the glucose metabolism of the body and influence the course of diabetes. Since then, more and more researchers have joined in the exploration of the correlation between diabetes and its complications and



Top 20 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2010 - 2023
Vaziri ND, 2013, KIDNEY INT, V83, P308, DOI 10.1038/ki.2012.345, DOI	2013	3.66	2015	2018	
Alatriste PVM, 2014, NUTR HOSP, V29, P582, DOI 10.3305/NH.2014.29.3.7179, DOI	2014	1.82	2015	2018	
Ramezani A, 2014, J AM SOC NEPHROL, V25, P657, DOI 10.1681/ASN.2013080905, DOI	2014	2.28	2016	2019	
Anders HJ, 2013, KIDNEY INT, V83, P1010, DOI 10.1038/ki.2012.440, DOI	2013	1.86	2016	2018	
Andrade-Oliveira V, 2015, J AM SOC NEPHROL, V26, P1877, DOI 10.1681/ASN.2014030288, DOI	2015	4.34	2017	2020	
Barrios C, 2015, PLOS ONE, V10, P0, DOI 10.1371/journal.pone.0134311, DOI	2015	1.43	2017	2020	
Aron-Wisnewsky J, 2016, NAT REV NEPHROL, V12, P169, DOI 10.1038/nrneph.2015.191, DOI	2016	1.18	2017	2019	
Allin KH, 2015, EUR J ENDOCRINOL, V172, PR167, DOI 10.1530/EJE-14-0874, DOI	2015	1.18	2017	2019	
Amiri M, 2016, ANN RES DIAL, V1, P0	2016	1.18	2017	2019	
Andersen K, 2017, J AM SOC NEPHROL, V28, P76, DOI 10.1681/ASN.2015111285, DOI	2017	0.88	2018	2021	
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Sabatino A, 2017, CURR DIABETES REP, V17, P0, DOI 10.1007/s11892-017-0841-z, DOI	2017	2.29	2019	2020	
Gomes JMG, 2017, METABOLISM, V68, P133, DOI 10.1016/j.metabol.2016.12.009, DOI	2017	1.29	2019	2021	
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Zhao LP, 2018, SCIENCE, V359, P1151, DOI 10.1126/science.aao5774, DOI	2018	1.25	2020	2021	
Miraghajani M, 2017, J RENAL NUTR, V27, P317, DOI 10.1053/j.jrn.2017.04.004, DOI	2017	0.87	2020	2021	
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Arani NM, 2019, PROBIOTICS ANTIMICRO, V11, P1195, DOI 10.1007/s12602-018-9468-x, DOI	2019	0.59	2020	2021	
Feng YC, 2019, INT J BIOL MACROMOL, V132, P1001, DOI 10.1016/j.ijbiomac.2019.03.242, DOI	2019	0.59	2020	2021	

Figure 8. Top 20 references with the strongest citation bursts.

intestinal flora. In 2010, Lu et al[18] first demonstrated the role of intestinal flora in the development of DN. They found that *lactobacillus roxellanae* GMNL-263 reduced protein levels of fibrinogen activator inhibitor-1, alpha-smooth muscle actin and fibronectin in the renal cortex of rats with DN, thereby inhibiting renal fibrosis and improving the prognosis of DN. However, probably due to the fact that this study was published in a Q3 journal, it was not given sufficient attention at the time. No research related to DN and gut microbiota was published between 2011 and 2014, which means that the research in this field did not advance significantly during this period. Four years later, Firouzi et al[22] published another research study in this area in 2015, in which they found that renal function improved in patients with diabetes after 12 weeks of continuous intake of probiotics. Since then, the number of published articles on the correlation between DN and intestinal flora has shown a rapid growth trend, reaching 46 articles in 2022.

In the analysis of countries and regions, the number of publications by country partly reflects the degree of contribution to the research field. In the field of DN and intestinal flora, Chinese authors accounted for 66.13% of the publications and have contributed more to the research in this field. According to reports, there are as many as 130 million diabetic patients in China, accounting for 24.2% of the global diabetic patients, ranking first in the world[23]. This has required the Chinese government and academics to spend more time and money on research into the pathogenesis and treatment strategies for diabetes and its complications. The USA ranks second in the number of publications in this field and is also the country with the highest average number of citations in this field, which has a greater role in promoting research in this field. The data shows that the average number of citations in the USA is as high as 48.11 times, followed by Japan with 33.40 times and the UK with 26.60 times. This shows that although Chinese authors rank first in terms of the number of articles published, there is still a gap between them and developed countries such as the USA, the UK and Japan in terms of the average citation rate. Among the countries' partnerships, there is closer cooperation between China and the USA, followed by China and the UK, while there is less cooperation between other countries. In fact, most of the authors included in the literature are from the same country, which means that the cooperation between countries is not close. Therefore, international cooperation in this field still needs to be strengthened in the future to jointly promote development. Among the top 10 countries with the largest number of publications, China ranked first. But compared with developed countries such as the USA, the UK and Japan, the average citation rate of articles is lower. Therefore, it is suggested that Chinese researchers should not only focus on improving the quantity of articles but also pay more attention to improving the quality of articles.

Among the top 10 institutions, 7 institutions are from China, and the remaining 3 are from Iran, the UK and Australia. This shows that Chinese institutions have a strong interest in research in this field and are deeply exploring the inner relationship between DN and intestinal flora. Among these institutions, Iran's *ISFAHAN UNIVERSITY MEDICAL SCIENCE* has the largest number of publications and the highest total number of citations, and is the main institution promoting research in this field. In the cooperative relationship network, Isfahan University Medical Science and Shahid Beheshti University Medical Sciences cooperate most closely, and they form a cooperative group with Mashhad University Medical Science and Islamic Azad University. These four institutions are all from Iran and have no cooperation with other institutions, indicating that the cooperation of Iranian institutions in this field is mainly between domestic institutions and there is a lack of exchange with foreign institutions. In addition, Austin Health has a closer partnership with the University of Melbourne, and they form a cooperative network with five other Australian institutions and three Danish institutions. However, there is still little cooperation between institutions in the two countries, and transnational cooperation still needs to be strengthened. Notably, the presence of Chinese medicine institutions (such as the China Academy of Chinese Medical Sciences, Beijing University of Chinese Medicine, Shandong University of Traditional Chinese Medicine and Shaanxi University of Chinese Medicine) in the partnership network may be related to the recent findings of Chinese researchers that some traditional Chinese medicine can intervene in DN by modulating intestinal flora[24,25].

8 of the 10 most published authors are from China, with the remaining 2 authors from Canada and Iran. Mirlohi Maryam and Liu Bicheng are the most prolific authors in this field, and

both have a long history of research on DN and probiotics. Mirlohi Maryam is a researcher at Shahid Beheshti University of Medical Sciences, focusing on food science. With her team, they[26-28] found through clinical randomized controlled trials that, compared with conventional soy milk, supplementing probiotic soy milk can significantly improve oxidative stress factors and glomerular filtration rate in patients with DN. Liu Bicheng is the chief professor of Southeast University, and has long been committed to the research of the mechanism of renal inflammation and fibrosis. Liu et al[24] showed that diabetic rats had disturbed intestinal flora, elevated plasma acetic acid, increased proteinuria and thickened glomerular basement membrane compared to normal rats. In addition, they also found that acetate can activate G protein-coupled receptor 43 (GPR43)-mediated dysregulation of cholesterol metabolism, resulting in tubulointerstitial damage in rats with DN[29-31]. Huang Wei is a professor at the Affiliated Hospital of Southwest Medical University. His main research direction is the pathogenesis and prevention of DN. He is the most cited researcher in terms of average and total citations, with a higher citation rate than Mirlohi Maryam and Liu Bicheng, which means that Huang Wei is a significant contributor to research in the field. Huang Wei's research direction is the connection between short-chain fatty acids (SCFAs) and DN. He proposed that SCFAs can inhibit the nuclear factor-κB (NF-κB) signaling pathway by increasing the expression of GPR43 and reducing the inflammatory damage of the kidney, thereby playing a role in improving DN[32,33]. In the analysis of the cooperative relationship, we noticed that Liu Bicheng, Ruan Xiongzhong, Zhang Jiaxiu and Ma Kunling worked closely together, and these authors have accumulated valuable experience in the research of DN and intestinal flora.

The impact factor (IF) is an important reference indicator to evaluate the impact of a journal and the quality of its articles. Among the 20 most published journals, *JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY* is the most influential (Q1, IF=14.978). Founded in 1990, the journal is a high-quality journal and is the leading journal on urological and renal diseases. The journal published 2 studies related to DN and intestinal flora, with research topics including the mechanisms of progression of DN and the interventional role of dietary fiber. Linh et al[34] found that impaired mitochondrial anti-viral signal protein (MAVS) signaling in the kidney and gut was the mechanism for the progression of DN, and that disturbances in gut homeostasis may contribute to impaired MAVS signaling. Li et al[35] found that dietary fiber can prevent DN by regulating gut microbiota, enriching SCFA-producing bacteria and increasing SCFA production. *FRONTIERS IN PHARMACOLOGY* (Q2, IF=5.988), the journal with the most relevant publications, is a relevant journal in basic and clinical pharmacology, medicinal chemistry, pharmacology and toxicology, which is dedicated to the most cutting-edge research in the development of the discipline. The journal published 9 studies related to DN and intestinal flora, whose research themes focused on the regulation of intestinal flora by herbs (active compounds, extracts or formulations) through the inhibition of inflammation, oxidative stress, mitochondrial dysfunction and thus improving the prognosis of DN[9,36-38].

Hotspots and Frontiers

Based on keyword frequency analysis, timeline mapping analysis and keyword burst analysis, we obtained core keywords such as gut microbiota, diabetic nephropathy, inflammation, chronic kidney disease, oxidative stress, obesity, short-chain fatty acids, probiotics, indoxyl sulfate, barrier, bekhogainsam decoction and Chinese herbal medicine. After excluding the subject and free words for intestinal flora and DN, we obtained the following topical keywords in the field of DN and intestinal flora research: obesity, inflammation, oxidative stress, indoxyl sulfate, short-chain fatty acids and Chinese herbal medicine.

(1) Obesity: obesity is the 9th ranked keyword in the frequency analysis and is a common risk factor for many metabolic diseases. Abnormal lipid metabolism can lead to hyperlipidemia and lipid accumulation in peripheral tissues and organs[39], and the abnormal deposition of lipids can lead to local inflammation and oxidative stress, promoting the progression of kidney damage[40]. Abnormal lipid accumulation can be present in the kidney, liver, pancreas and heart of patients with DN, which is one of the important mechanisms causing its complications[41,42]. Li et al[43] showed that the ratio of *Bacteroides*/*Firmicutes* was significantly reduced in obese patients and affected the relative abundance of *Proteobacteria*, *Actinobacteria*, and *Helicobacteria*. They[43] demonstrated through microbiota transplan-

tation that obesity affects gut permeability, cytokines and vascular endothelial growth factor (VEGFA), thereby exacerbating nephropathy and retinopathy.

(2) Inflammation: inflammation is the 4th keyword in the frequency analysis. It is the keyword with the highest frequency, except the free words of DN and intestinal flora, and has a high centrality. The occurrence of complications such as DN, diabetic cardiomyopathy, diabetic retinopathy and nonalcoholic fatty liver are all related to the chronic inflammatory state of diabetic patients[44]. DN has been reported[45,46] to start with microinflammation of the kidney. The hyperglycemic state induces glomerular endothelial cell damage and promotes the expression of adhesion molecules and chemokines, which leads to macrophage infiltration into renal tissue and causes a state of renal microinflammation and metabolic dysfunction. Intestinal dysbiosis in diabetic patients leads to increased intestinal permeability and bacterial translocation, which in turn triggers an inflammatory response through toll-like receptor 4 (TLR4)-related pathways and promotes the occurrence and progression of diabetic nephropathy[12].

(3) Oxidative stress: oxidative stress is the 8th keyword in the frequency analysis. Oxidative stress plays an important role in the pathogenesis of diabetes. Abnormal oxidative degradation of glucose and protein can promote the formation of free radicals, and abnormally high levels of free radicals can cause damage to organelles and enzymes, promote lipid peroxidation, and lead to insulin resistance[47]. Oxidative stress in the kidney plays a key role in the development and progression of DN and it is the hyperglycemic state of the body that promotes the production of reactive oxygen species (ROS). Excessive ROS trigger renal fibrosis and inflammation and lead to significant tissue damage by promoting lipid peroxidation, DNA damage and protein modification or mitochondrial dysfunction[48,49]. Studies by Zhang et al[13] have shown that oxidative stress can lead to the dislocation of intestinal flora, which in turn increases the permeability of the intestinal mucosa, promotes the absorption of toxins into the blood, and eventually damages the kidneys. On the one hand, Dendrobium polyphenols can increase the content of probiotics such as *Bacteroides* and repair the intestinal barrier. On the other hand, it can reduce the content of malondialdehyde (MDA), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), increases the content of superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH), exerts anti-inflammatory and antioxidant effects, and ameliorates the kidney damage caused by inflammation and oxidative stress in diabetic mice[10].

(4) Indoxyl sulfate: indoxyl sulfate is the core keyword detected by the burst, its burst degree is 1.32, and the burst time is from 2017 to 2020. Indoxyl sulfate is one of the uremic toxins derived from dietary protein and is nephrotoxic as it promotes ROS production, causes renal inflammation and leads to tubulointerstitial damage[12]. Dysbiosis of the intestinal flora leads to elevated indoxyl sulfate and endotoxin[50], and there is a strong negative correlation between serum indoxyl sulfate levels and renal function in diabetic patients[51]. It has been shown[50] that modulation of intestinal flora significantly reduces lipopolysaccharide and indoxyl sulfate, thereby reducing inflammatory renal damage.

(5) SCFAs: SCFAs are the high-frequency keyword ranked 11th in the frequency analysis, and also the core keyword obtained from the burst detection. The burst degree of SCFAs is 0.84, and it and glucose are the only two keywords with burst duration until 2023, which may be a hot spot for future research in the field of DN and intestinal flora. SCFAs are the main products formed by the breakdown and fermentation of carbohydrates by intestinal flora[52], and the reduction of SCFAs and other intestinal flora metabolites as well as the disruption of the intestinal barrier are important mechanisms for the progression of DN[53]. Li et al[34] found that high dietary fiber feeding was effective in improving intestinal flora ecology and promoting the production of SCFAs in the intestine and feces of mice, which made the incidence of DN significantly lower than that of diabetic mice on a normal diet. In addition, studies by Huang et al[33] and Tang et al[54] have shown that supplementing exogenous SCFAs can also improve hyperglycemia in mice with DN, alleviate insulin resistance, enhance intestinal barrier function, and inhibit the progression of renal fibrosis.

(6) Chinese herbal medicine: Bekhogainsam decoction and Chinese herbal medicine are the core keywords obtained by cluster analysis,

and Bekhogainsam decoction belongs to the generalized Chinese herbal medicine, which means that Chinese herbal medicine is the hot spot and frontier of research in this field. In recent years, more and more studies[55] have confirmed that traditional Chinese medicine can interfere with DN by regulating intestinal flora, which may be related to its complex bioactive substances and chemical substances. Bekhogainsam decoction attenuates renal injury in mice with DN by modulating PI3K/ATK and mitogen-activated protein kinases (MAPK)-related protein targets, and by regulating intestinal flora[9]. Chen et al[37] summarized the currently known targets and mechanisms of Chinese herbal medicine regulating intestinal flora to intervene in DN. They pointed out that Chinese herbal medicine can regulate the composition and metabolism of gut microbiota through targets such as glucagon-like peptide (GLP), Sodium-glucose cotransporter 2 (SGLT2), sirtuin 1 (SIRT1)/AMP-activated protein kinase (AMPK), advanced glycation end products (AGE)/receptor for advanced glycation end products (RAGE), NF-κB, nuclear factor e2-related factor 2 (Nrf2), NOD-like receptor family pyrin domain containing 3 (NLRP3), Peroxisome proliferator-activated receptor-gamma co-activator-1α (PGC-1α) and PTEN-induced putative kinase 1 (PINK1)/Parkin, and improve the prognosis of DN by inhibiting inflammation, oxidative stress and reducing mitochondrial dysfunction[37]. Chinese herbal medicine covers the concepts of active compounds, herbal extracts, and herbal compounds, and the composition and effects of different herbal compounds are different, so there is a wide scope for research.

Limitations

Although we strictly followed the bibliometric research methodology, the study still has some potential limitations. First, all the data used for bibliometric analysis came from WoSCC, and only 124 articles were included, which may increase the risk of bias. Second, we excluded corrected or retracted articles, as well as those published in abstract form, which could have affected the results of the data analysis. Third, as the WoSCC is constantly updated, the number of citations and H-index of the included literature will change accordingly, which determines the inevitable time limitation of this study.

Conclusions

To our knowledge, this study is the first comprehensive and quantitative bibliometric analysis of DN and intestinal flora. Obesity, inflammation, oxidative stress, indoxyl sulfate, SCFAs and Chinese herbal medicine are hot topics in research in this field, and SCFAs and Chinese herbal medicine may be the hotspots of future research.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Availability of Data and Materials

The original data presented in this study are included in the manuscript/supplementary material. For more information, contact the corresponding author.

Ethics Approval

This study is based on published experimental research and is not currently applicable to medical ethics.

Informed Consent

Not applicable.

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Authors' Contribution

Lingwei Gao and Zheng Tian proposed ideas and concepts. Lingwei Gao wrote the first manuscript together with Xinyu Yang and Yunfeng Yu. Yunfeng Yu, Xinyu Yang and Keke Tong completed the data collection together. Xinyu Yang and Shuang Yin were responsible for the software analysis. Keke Tong and Gang Hu also participated in part of the writing. Weixiong Jian and Zheng Tian supervised and guided the whole process.

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