ISSN 2618-1584 Vol. 5, Issue 7: 34-47, DOI: 10.25236/FMSR.2023.050706

Visualization Analysis of Research Hotspots and Trends in the Treatment of Diabetic Retinopathy with Traditional Chinese Medicine

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Abstract: *This paper aims to make a systematic visualization analysis on literature relating to the treatment of diabetic retinopathy (DR) with Traditional Chinese Medicine (TCM), and explore the research hotspots and frontier trends in this field, thus providing references for future research. All literature relating to this field, which were published between the time when the databases were released and August 29th 2022, was retrieved from databases such as China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database(VIP), Wanfang Database and Web of Science Core Collection (WOSCC).Citespace software was used for visualization analyses on co-occurrence, clustering and citation burst of the keywords of papers published, and the category, authors, institutions, keywords of the papers as well as the research hotspots in the field. A total of 507 Chinese articles and 765 English papers in this field were obtained. Through analysis, it was found that there were 24 core authors in Chinese articles and only one in English articles. Chengdu University of Traditional Chinese Medicine and Nanjing University of Traditional Chinese Medicine each published 12 Chinese papers in the field, the most Chinese papers that an institution had ever published, while Chinese Academy of Medical Sciences published 22 English papers, the most English papers an institution had ever published. The co-occurrence analyses for keywords showed that 362 keywords were captured from Chinese articles, which included "traditional Chinese medicine" "review" and "deficiency of both Qi and Yin", etc. And a total of 583 keywords were captured from English articles, which focused on "oxidative stress" "medicinal plant" and "cell", etc. By clustering the keywords, seven clustering labels were formed using keywords identified from Chinese articles, including "#0 diabetic retinopathy" "#1 traditional Chinese medicine" and "#2 laser photocoagulation". And nine clustering tags were formed using keywords from English articles, including "# 0 diabetes mellitus", "# 1 diabetes retina" and "# 2 antioxidant activity". The citation burst analysis of keywords from Chinese papers showed that Chinese herbal drug was the keywords with the longest duration of research focus, and together with laser photocoagulation, constituted the topics in the earliest research of the field. While in English paper analysis, glycemic control was a topic with the longest research duration, and constituent was the subject in the earliest research of the field. Conclusions are as follows, the number of literature in the field of TCM treatment for DR has increased year on year. However, cooperation and interactions between researchers and research institutions didn't look promising over the years, which apparently should be enhanced. Clinical treatments for DR and their mechanism has been the hotspots in this research field, with mechanism research, drug therapies and DR mortality as the trending research directions.*

Keywords: *Traditional Chinese medicine (TCM); Diabetes; Retinopathy; CiteSpace; Visualization analysis*

1. Introduction

Diabetic Retinopathy (DR) is the most important manifestation of diabetic microangiopathy. It is a kind of fundus disease resulted from particular changes that seriously harms patient's vision and is one of the serious complications of diabetes. Epidemiological investigation shows that the global prevalence rate of DR is 22.27%, and some experts predict that by 2045, the burden brought by DR will still be heavy in the world[1] . The symptoms are latent in the early stage of the disease, which often fails to attract the attention of diabetic patients. When the symptoms turn to be blatant, the best treatment period is already passed, leading to serious vision damage and even permanent blindness.

Metabolic disorder control, anti-vascular endothelial growth factor (anti-VEGF), laser and vitrectomy

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[2] are the approaches generally adopted by western countries for DR treatment, which might result disadvantages of vitreous hemorrhage and other many complications [3]. Diabetes Branch of Chinese Medicine Association [4] summarized the clinical experience and academic research of doctors nowadays and concluded that the main cause of DR in patients was deficiency of both qi and yin, which extended to weakness of liver and kidney, and eventually growing into yin and yang deficiency. In addition, blood stasis, depression and phlegm are important factors in the pathogenesis. However, physician have different understandings of DR pathogenesis, they thus normally employ different treatments. These treatments can characterized into special prescription therapy for a certain disease, syndrome differentiation treatment and combined treatment. An growing number of studies show that TCM has good curative effect and little adverse reactions in DR treatment under the guidance of "syndrome differentiation and treatment" and "disease prevention" theories, and can reduce the economic burden of patients as well as obtain satisfactory long-term benefits, which enable DR patients more open to TCM therapy. TCM has become an important part in terms of DR prevention and treatment [5][6]. With continuous development of medical science and technology and the deepening understanding of DR, literature in TCM for DR treatment has been growing rapidly. Therefore, it is of great significance to visually analyze the research on DR treatment with TCM. Therefore, with China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database(VIP), Wanfang Database and Web of Science Core Collection (WOSCC) as data sources and the help of Citespace software, a research tool for visualization analysis, this paper analyzed the amount of articles published, the cooperation and interaction between authors and between institutions, and papers with high citations, and co-occurrence, clustering and citation burst of key words, with a purpose to explore the hotspots and frontier trends in this field and provide references for future research.

2. Data and methods

2.1. Data sources

CNKI, VIP , WOSCCand Wanfang were used to obtain Chinese papers, which became available since the foundation of the databases to August 29, 2022. Literature retrieval process was carried out professionally. Taking CNKI as an example, the professional formulas used for retrieval were: Subject% = Chinese Medicine + Chinese Herbal Medicine + Chinese Patent Medicine + Prescription + Formula + Animal Medicine + Mineral Medicine + Herb Medicine Therapy + Plant Medicine + Extract, or Title% = Chinese Medicine + Chinese Herbal Medicine + Chinese Patent Medicine + Formula + Animal + Mineral Medicine + Biotherapy + Herb Medicine + Extract. And topic% = diabetic retinopathy + type 2 diabetic retinopathy + DR+aggravated retinopathy + proliferative retinopathy, or title% = diabetic retinopathy + type 2 diabetic retinopathy + DR + proliferative retinopathy + proliferative retinopathy.

2.2. Inclusion criteria

(1)Papers were included if they were relevant to the treatment of DR with TCM.(2)their contents included animal experiments, clinical research, clinical experience summary, literature review etc; they were about specific application of TCM treatment (such as acupuncture and Chinese medicinal herb preparations etc.). (3)Their contents, such as titles, authors, keywords and sources, were complete.

2.3. Exclusion criteria

(1)Papers were excluded if they were conference notice, news, solicited papers, master or PhD paper and others irrelevant to the field. (2)They were published in more than one journal; and they focused on other diseases, such as stroke or Parkinson's disease.

2.4. Data collection and conversion

Papers were checked and screened to get rid of repeated ones by EndNote X7 software. If institutions that the papers attached to were the same but only in different levels, these institutions were listed in the same category. The synonyms were merged. Original papers were opened in the Notepad++ software to supplement the missing information, if there was any. The papers downloaded from CNKI, VIP, Wanfang and WOSCC databases were stored as Refworks format, and converted into Data format that was recognizable with the use of the Import/Export function in CiteSpace (6.1.R3) software.

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2.5. Data analysis

Citespace is a software developed by Professor Chen Meichao using Java language for visualization analyses of academic papers and data digging [7]. It is capable of transforming a large amount of literature data into visualized knowledge maps for hotspots exploration in a certain field through data analysis, so that people can straightforwardly identify information hidden in the data and correlations that are hard to distinguish among the data[8].

The time span was set as since the foundation of the databases to August 29th 2022 using CiteSpace, with an interval of one year. Then, threshold values were set. The network map was simplified through choosing the cut and connect mode of Pathfinder's to underpin important features. The cut mode was defaulted. If the initial visualization result is confusing, the cut mode can be set as the value of Pathfinder to again simplify the network and highlight its important feature. The final map was presented by means of Cluster View-static and Show Merged Network visualizations. Keywords from different years were sorted separately according to their frequencies and centrality, which straightforwardly showed the status and frontier findings of the research on DR treatment with TCM. Finally, through the co-occurrence, clustering and citation burst analysis of keywords, the hotspots and trends in the field were explroed and presented intuitively.

3. Results

3.1. Literature retrieval and screening

After searching literature on DR treatment with TCM in CNKI, VIP and Wanfang databases published since the establishment of the database, a total of 803 Chinese papers were retrieved, but only 507 were remained after manual screening and exclusion of conference notices, news, solicited papers, master's and doctoral theses and other papers irrelevant to the subject. After searching literature on DR treatment with TCM in WOSCC database published since its foundation, as many as 765 English academic papers were retrieved, all of which met the eligibility of the study.

3.2. The number of papers published

Figure 1 shows the amount of articles published in the field. A total of 803 Chinese papers were published over the past years. The publication number was used to calculate the annual growth ratio of the papers, and it was found that since the establishment of the databases to the year of 2004, only a small amount of papers were published each year with slow growth. However, as researchers became increasingly interested in DR treatment with TCM, the number of articles published in this field has entered a stage of rapid growth from the years of 2004 to 2011, with an average of 22 articles published each year, and the highest publication number reached 39 in 2011; however, this research field seemed to have encountered its bottleneck between 2011 and 2014,, for the number of articles published during this period showed a downward trend, in spite of the fact that the publication number still remained at a high level; from 2014 to 2020, the number of papers published in this field showed a steady growth, with a publication growth and increased heat in the research field year on year, and an average annual publication of 27 papers.

A total of 765 English articles were published in the field, and the annual publication could be divided into four stages: stage one is between 2000 and 2005, during which period papers published in the field was still in short; stage two is between 2006 and 2010, when paper publication in the field showed a steady growth, and the publication numbers increased faster than before; stage three is between 2011 and 2014, during which period violent fluctuation in the number of papers published in the field was observed, as well as a sharp increase from 2011 to 2013 and a turning point in 2013, when a significant reduction was marked; stage four is between 2014 and 2020, a period with some fluctuations observed. More specifically, even though the overall number of papers published in the field had risen, there were some ups and downs. Due to the fact that some of the papers submitted between 2021 and 2022 haven't been published in journals yet, so there is a great chance of miscalculation in terms of the number of papers published during this period, we therefore dropped the analysis on the publication numbers of this period for the time being.

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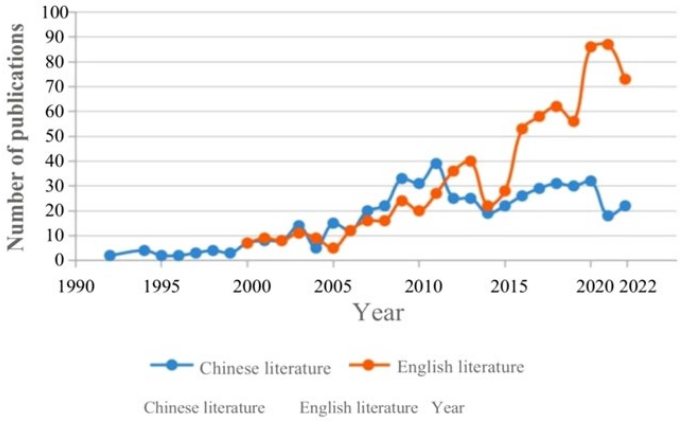
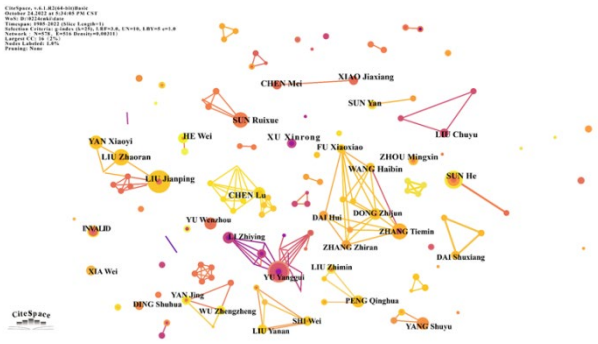


Figure 1: The number of Chinese and English literature on DR treatment with TCM published each year.

3.3. Cooperation between authors

The 507 Chinese articles included a total of 1223 authors, among whom PENG Qinghua from Hunan University of Traditional Chinese Medicine, YANG Shuyu from Xiamen Hospital of Traditional Chinese Medicine, YU Yanggui from the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, ZHANG Tiemin and WANG Haibin from the Affiliated Hospital of Chengde Medical College each had published 7 articles in the field, the most publication of all. According to Price's law, any author who has published as many as four papers is deemed as core authors. The cooperation between authors was visualized in Figure 2A. However, cooperation in the field is scattered on a whole, and a comprehensive cooperation network between authors hasn't been formed yet. Even though authors who have published many papers have established stable cooperation, such as the close cooperation between YU Yanggui's team from the First Affiliated Hospital of Guangzhou University of Chinese Medicine and ZHANG Tiemin's team from the Affiliated Hospital of Chengde Medical College. Some of the authors formed pairwise cooperation to work on the field. As shown in Figure 2A, there are also scattered independent nodes, suggesting some researchers conduct their study independently without stable and large-scale cooperation with other researchers in the field.

There were 610 authors captured from the 765 English papers, a relatively small number. Of the 610 authors, TONG Xiaolin (4 articles), Rahmani Rami (3 articles), Han Jing(3 articles) and Wang Wei (3 articles) ranked top in terms of the number of papers published in the field. According to Price's law, any author who has published no less than 4 papers is considered as core authors. So, only one core author was identified in the study, which was TONG Xiaolin of Guang'anmen Hospital of Chinese Academy of Traditional Chinese Medicine. TONG Xiaolin's team primarily focused on investigation of DR treatment with TCM via conducting animal experiments and clinical trials[9][10]. The cooperation between authors was visualized in Figure 2-B.



(A)

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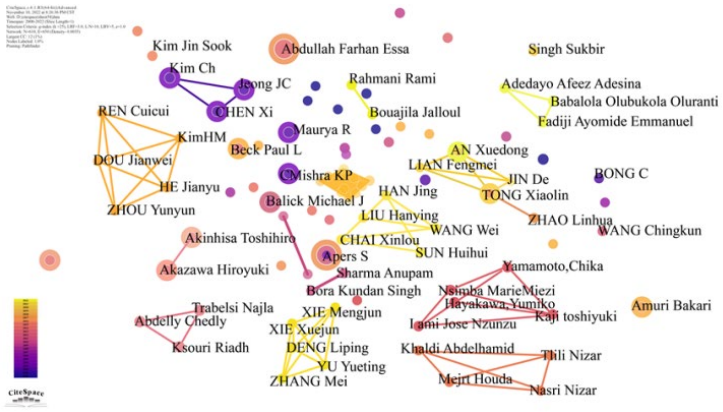

(B)

Figure 2: Cooperation between the authors.

A, cooperation between authors who had published Chinese articles. B, cooperation between authors who had published English articles. Each node in the Figure represents a core author. Cooperation between different authors is represented by different colors. The larger the nodes are, the more papers the authors had published. The lines between authors represent their cooperative relationship.

3.4. Cooperation between institutions

Scientific research institutions play a vital role in creating innovation in the scientific research world. By analyzing papers from different scientific research institutions, we can understand the distribution of research resources in the field of DR treatment with TCM, as shown in Figure 3. In Chinese articles, a total of 368 institutions were captured from the 507 articles for visualization analysis. As shown in Table 1, out of 368 institutions, 6 have published over 10 articles, and 24 institutions have published over 5 papers.Figure 2, these institutions are all core ones with the most papers published in the field and closest cooperation with other institutions. For example, Nanjing University of Traditional Chinese Medicine has a close cooperation with Shandong University of Traditional Chinese Medicine. And Hunan University of Traditional Chinese Medicine cooperated closely with Guangxi College of Traditional Chinese Medicine as well as the First Affiliated Hospital of Hunan University of Traditional Chinese Medicine, suggesting these institutions are authoritative in the research field. Apart from the 6 dominant institutions mentioned above, research resources are evenly distributed in the remaining universities and hospitals, with less scientific research cooperation observed between different institutions.

In English articles, a total of 519 institutions were found to be involved in the 765 papers through visualization analysis. As shown in Table 2, there are 3 institutions with no less than 10 articles published and 6 institutions with no less than 5 articles. Figure 3 shows that institutions with high paper outputs engage in close cooperation with other institutions. For example, the close cooperative relationship between China Acad Chinese Med Sci and China Med Univ and Beijing Univ Chinese Med, and several other institutions. Chengdu Univ Tradit Chinese Med also has formed close cooperation with institutions such as China Acad Chinese Med Sci, Hospital of Chengdu University of Traditional Chinese Medicine, and Chinese Academy of Sciences. Therefore, it is concluded that institutions with high paper productions is normally in a close and table cooperative relationship with other institutions, and even form a cooperative network along with several other institutions.

Table 1: Institutions with over 10 Chinese articles published on DR treatment with TCM.

Ranking	institution	Number of documents issued
1	Chengdu University of Traditional Chinese Medicine	12
2	Nanjing University of Chinese Medicine	12
3	Hunan University of Chinese Medicine	11
4	Beijing University of Chinese Medicine	11
5	Department of Ophthalmology, Affiliated Hospital of Chengde Medical College	10
6	The First Hospital of Hunan University of Chinese Medicine	10

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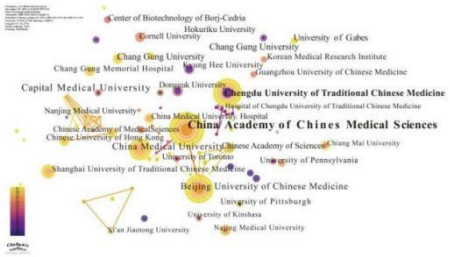
Table 2: Institutions with over 5 English articles published on DR treatment with TCM.

Ranking	institution	Number of documents issued
1	China Academy of Chinese Medical Sciences	22
2	Beijing University of Chinese Medicine	15
3	Chengdu University of Traditional Chinese Medicine	13
4	Capital Medical University	7
5	Shanghai University of Traditional Chinese Medicine	7
6	China Medical University Hospital	6

(A)



(B)

Figure 3: Visualization analysis of cooperation between diagram of mechanism cooperation.

A. Cooperation between institutions with Chinese article publication. B. Cooperation between institutions with English article publication. Each node represents an institution. The larger the node and words are, the more papers the institutions had published. Each line represents cooperation between institutions.

3.5. Keyword co-occurrence analysis

Keyword co-occurrence analysis was carried out by Citespace software based on the content of literature, which was realized through extracting keywords from articles and analyzing the ones with high frequency to find research hotspots in this field. In this study. Keywords were extracted from both English and Chinese papers for co-occurrence analysis, as shown in Figure 4. A total of 351 nodes were drawn, with 587 lines and 362 keywords captured. After getting rid of meaningless keywords, merging abbreviations and synonyms, such as TCM therapy and TCM treatment, the top 30 keywords in the field were obtained and shown in Table 4. According to Figure 3 and Table 3, the research focus in this field is mainly concentrated in two aspects: (i) clinical treatment of DR; (ii) mechanism research. In English articles, a total of 583 nodes were drawn for co-occurrence analysis, with 1514 lines and 583 keywords captured. After getting rid of meaningless keywords, merging abbreviations and synonyms, the top 30 keywords in the papers on DR treatment with TCM were obtained and shown in Table 3. According to Figure 3 and Table 4, these papers mainly focus on clinical treatment research and mechanism research centering on topics such as oxidative stress, medicinal plant, cell and endocrine growth factor. It is suggested by these papers after keyword co-occurrence analysis that researchers have mastered a

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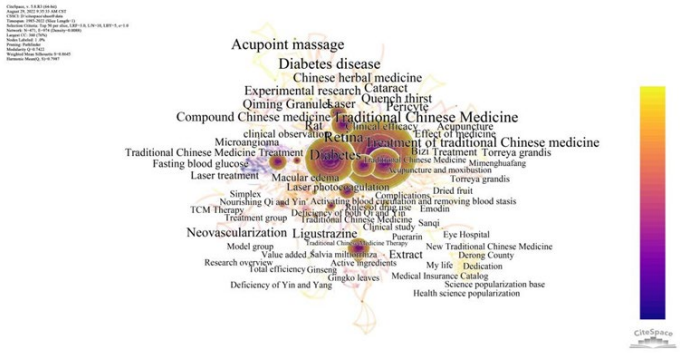
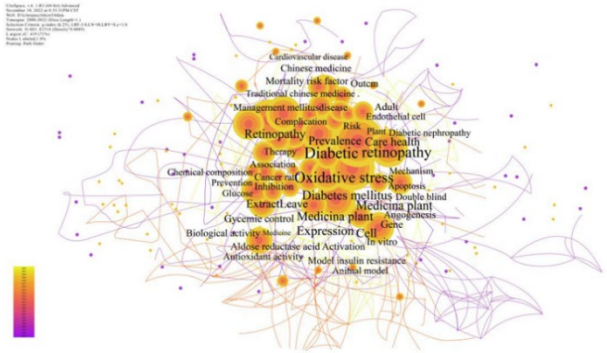
relatively systematic understanding and cognition of DR treatment.



(A)



(B)

Figure 4: Keyword co-occurrence diagram of DR treatment with TCM.

A. Co-occurrence analysis of keywords from Chinese papers. B. Co-occurrence analysis of keywords from English papers. In the graph, each node represent a keyword. With larger the node and words are, suggesting higher-frequency the keywords have. Lines represent connections between keywords, with same color suggesting close connection of some certain keywords. The outermost circle of a node represents the intermediate centrality of the node, and its thickness is represented by the thickness of the ring frame, with thicker boundary suggesting stronger intermediate centrality and higher importance the node represents in the graph.

Table 3: Top 30 keywords from Chinese papers on DR treatment with TCM

Serial number	Keywords	Count	Serial number	Keywords	Count	Serial number	Keywords	Count
1	Traditional Chinese medicine	78	11	Clinical observation	8	21	Deficiency of Qi and Yin	6
2	Diabetes	50	12	Chinese medicine	8	22	Compound Chinese Medicine	6
3	Overview	39	13	Law of medication	8	23	Clinical effect	5
4	Traditional Chinese medicine therapy	27	14	Treatment group	7	24	Microangioma	5
5	Traditional Chinese Medicine	27	15	Rat	7	25	Curative effect	5
6	Chinese medicine treatment	23	16	Macular edema	7	26	Proprietary Chinese Medicine	5
7	Laser photocoagulation	16	17	Clinical research	7	27	Diabetes ophthalmopathy	5
8	Laser	16	18	Lontophoresis	7	28	TCM Treatment	5
9	Promoting blood circulation and removing blood stasis	11	19	Retina	7	29	Traditional Chinese medicine combination	5
10	Chinese herbal medicine	9	20	Laser therapy	6	30	Pericyte	4

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Table 4: Top 30 keywords from English papers on DR treatment with TCM

Serial number	Keywords	Count	Serial number	Keywords	Count	Serial number	Keywords	Count
1	Diabetic retinopathy	73	11	Expression	21	21	Glycemic control	13
2	Oxidative stress	46	12	In vitro	22	22	Mortality	13
3	Medicinal plant	34	13	Mellitus	23	23	Inhibition	13
4	Diabetes mellitus	33	14	Therapy	24	24	Mechanism	12
5	Extract	32	15	Activation	25	25	Model	12
6	Complication	32	16	Cell	26	26	Endothelial growth factor	11
7	Risk	26	17	Management	27	27	Apoptosis	11
8	Prevalence	26	18	Antioxidant activity	28	28	Outcm	11
9	Traditional chinese medicine	25	19	Care	29	29	Health	11
10	Disease	25	20	Association	30	30	Rat	11

3.6 Keyword clustering analysis

Based on the keyword co-occurrence network, we clustered the keywords about DR treatment with TCM for further analysis[11]. The clustering analysis of keywords is a process of classifying scattered information according to different degrees using certain calculation methods, which is helpful to understand the framework of this research field. CiteSpace software was used to visualize Chinese articles for analysis. Figure 5 shows seven clustered keywords: #0 diabetic retinopathy, #1 traditional Chinese medicine, #2 laser photocoagulation, #3 non-proliferative diabetic retinopathy, #4 proliferative diabetic retinopathy, #5 traditional Chinese medicine and #6 emodin. In order to analyze the figure more intuitively, the clusters were reorganized, as shown in Table 5. The network modularity and contour value show that the map can well reflect the research hotspots in this field[12].

The network modularity = 0.7422 (> 0.3) shows that the keywords were effectively clustered. The contour value = 0.8645 indicates that the clustering result is convincing. According to Figure 5 and Table 5, the 7 keyword clusters can be categorized into 4 aspects: (i) research direction. There are two research directions: TCM treatment for non-proliferative DR and proliferative DR, demonstrating how TCM and western medicine are combined for DR treatment with TCM, and that a systematic and profound situation has been formed in the field. (ii) research on treatment ideas and mechanism. The main keywords are TCM treatment, laser photocoagulation, hemorheology, interleukin -6 and extract; (iii) clinical research progress. The clustered keywords mainly include experimental research, experimental test, clinical efficacy and systematic evaluation. Excluding the keywords that are inseparable with the research field studies, such as TCM and DR, the remaining ones are laser photocoagulation and emodin, which are the research hotspots from Chinese articles in this field.

English articles, were visualized for analysis using CiteSpace software, with a total of 9 clusters formed: #0 Mortality, #1 Type 2 diabetes melitus, #2 Antioxidant activity, # 3 diabetes retinopathy, #4 Neuroprotection and #. 5 bone rearrangement, # 6 sparse cells, # 6 sparse cells, #7 Differentiation and # 8 astronomical iv. A keyword co-occurrence knowledge map was obtained, as shown in Figure 5. The clustering results were reorganized, as shown in Table 5. The network modularity is 0.652 5 (> 0.3), which shows that the keywords were effectively clustered. The contour value = 0.8498,suggesting the clustering result is credible. According to Figure 5 and Table 6, the 9 keyword clusters can be categorized into 2 aspects: (i) clinical treatment. For example, a multi-center clinical trials on DR targeted treatment with TCM led Tong Xiaolin of Guang 'anmen Hospital and China Academy of Chinese Medical Sciences[13][14]; (ii)pathogenesis. For instance, research on therapeutic significance of TCM in preventing DR by regulating antioxidant activity and genetic pathway led by Rahmani, Rami of Research Unit of Valorisation of Actives Biomolecules, Higher Institute of Applied Biology Medenine and University of Gabes.

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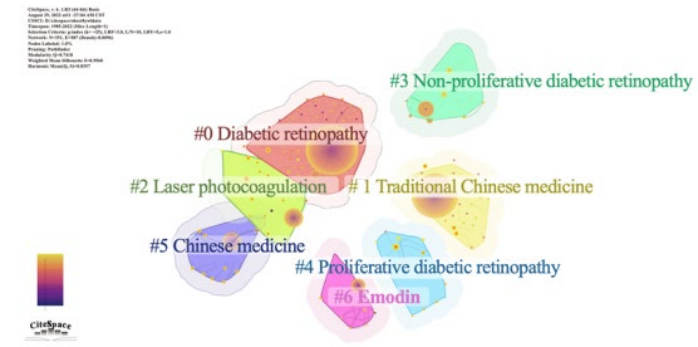

(A)

(B)

Figure 5: Keyword clustering analysis of TCM for DR treatment.

A, clustering analysis of keywords in Chinese articles. B, clustering analysis of keywords in English articles. Each color represents a keyword cluster.

Table 5: Clustering details of keywords from Chinese papers

Cluster ID	Size	Sihouette	Mean(y)	Topic	LLR
0	77	1	2013	Diabetic retinopathy	Chinese medicine iontophoresis (1.86); Endothelin(et) (1.86); Mimeng flower decoction (1.86)
1	34	0.937	2015	Traditional Chinese medicine	Experimental research (0.47); Clinical trials (0.47); Icam-1 (0.47); Shiqing drink (0.47); Severe type npdr (0.47)
2	20	0.939	2013	Laser photocoagulation	Herbal granule (0.14); Tonifying Qi (0.14); Qi yin supplementing therapy (0.14)
3	20	0.972	2016	Non proliferative diabetic retinopathy	Chinese patent medicine (0.16); Interleukin-6 (0.16); Iontophoresis of TCM (0.16)
4	18	0.94	2017	Proliferative diabetic retinopathy	Fundus fluorescein angiography (0.09); Integration of Traditional Chinese and western medicine (0.09); Yuanqi Quyu Prescription (0.09)
5	16	0.987	2012	Chinese medicine	Tang hong (0.08); Diabetic peripheral neuropathy (0.08); Production place (0.08)
6	14	0.975	2015	Emodin	Compound Danshen dropping pill (0.16); Notoginseng (0.16)

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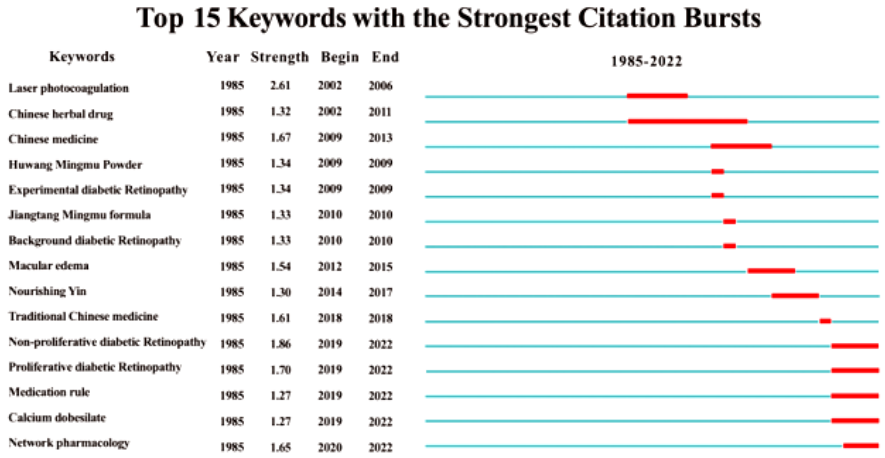
Table 6: Clustering details of keywords from Chinese papers

Cluster ID	Size	Silhouette	Mean (y)	Topic	Label (LLR)
0	46	0.844	2013	Diabetes mellitus	Cross-sectional study (187.41, 1.0E-4)
1	34	0.796	2013	Diabetic retinopathy	Sodium-glucose cotransporter inhibitor prescription (93.3, 1.0E-4)
2	34	0.837	2014	Antioxidant activity	Antioxidant activity (291.32, 1.0E-4)
3	26	0.8	2012	Diabetic retinopathy	Diabetic retinopathy (319, 1.0E-4)
4	23	0.818	2012	Microvascular complication	Cell death (114.88, 1.0E-4)
5	22	0.864	2008	Drynariae rhizoma	Drynariae rhizoma (181.91, 1.0E-4)
6	22	0.914	2008	Diabetic retinopathy	Monocyte-derived dendritic cell (101.83, 1.0E-4)
7	22	0.882	2011	Diabetic complication	Hg-induced cell injury (95.11, 1.0E-4)
8	19	0.86	2008	Diabetic retinopathy	Adult-onset diabete (88.2, 1.0E-4)

3.7. Citation burst analysis

The citation burst degree of keywords can reflect the citation change rate of papers that the keywords are in, which demonstrates the hottest research topics at a certain stage and is helpful to understand the research trend in this field. In this study, the keywords of Chinese articles and English articles in this field are analyzed to find the research hotspots in this field at different stages, as shown in Figure 6. In Chinese articles, it can be seen that Chinese herbal drug is a hot topic with the longest research duration in this field. It is a topic that has been studied at the earliest stage, so is laser photocoagulation. Since then, the hot topics turned into Huwang mingmu powder and Experimental DR in 2009. In 2010, the research hotspots were Jiangtangmingmu formula and mack ground iabetic retina. Macular edema was a research hotspot from 2012 to 2015, which was a physical sign closely related to vision. Optical coherence tomography shows that subretinal effusion in macular area can cause retinal thickening. Nourishing yin is a hot research topic from 2014 to 2017. The basic pathogenesis of DR is deficiency of both qi and yin, so nourishing yin should be treated according to syndrome differentiation. It was concluded via analyzing citation burst of keywords from English papers that diabetic control was a hot topic with the longest research duration, and constituent was a topic studied at the earliest stage. DR is a keyword with the highest citation burst, with a Strength value of 8.55 and the initial bursting time in 2020. Secondly, TCM, in-vitro and risk once became research hotspots, with strength value all greater than 4. However, their heat lasted less than 2 years.



(A) The top 15 most cited keywords in Chinese articles.

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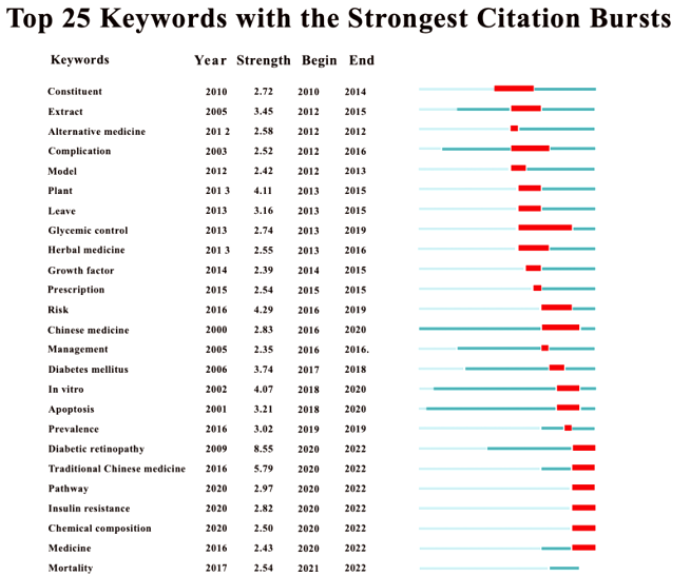

(B) The 25 most cited keywords in English articles.

Figure 6: Keywords citation burst analysis chart.

4. Discussion

DR is an important microangiopathy of diabetes and one of the main causes of blindness[15]. With the rapid growth of the prevalence of DM, the incidence of DR is also increasing year by year. How to effectively prevent and treat DR has attracted attention of scientific researchers. TCM has unique advantages and certain clinical effects for DR treatment. In this study, with the help of Citespace software, the literature on DR treatment with TCM in CNKI, VIP, Wanfang and WOSCC databases were analyzed, and the number of literature, cooperation between authors and institutions, research hotspots and trends in the field were identified through knowledge maps, which helped to understand the status of research on DR treatment with TCM more clearly and provide references for subsequent research, diagnosis and treatment.

4.1. Literature data

In terms of the number of papers published int he field, an overall increase was observed in the publications year on year. So, it is expected that the publication of literature in the field will remain rising in the next few years. It is worth noting that the research in this field published in English articles started late, but the overall growth rate far exceeds that in Chinese articles, which also shows this field has been attracting an increasing amount of attention of international communities. As for the authors, there are 1,223 authors identified from Chinese articles, including 24 core authors, accounting for less than 2% of the total number of authors who had published articles in the field; and there are 610 authors captured from English articles, including one core author, accounting for less than 0.2% of the total number of authors studied here. Both results indicate that core authors are still insufficient in the field, and there is still much room for improvement in terms of research quality and influences in this field. In terms of cooperation between authors and between institutions, cooperation only took place between authors in the same institution. For example, the team led by Zhang Tiemin from Chengde Medical College has close cooperation with Dong Zhijun and Wang Haibin, also from the College, whose publication volumes in the field all ranked top, probably because cooperation with the same institution benefits more from contacting, communicating and working with other researchers. However, there were also cooperation between institutions. For example, the teams led by Liu Zhaolan from Beijing University of Chinese Medicine and by Chen Lu of the Affiliated Hospital of Guizhou University of Chinese Medicine have close cooperation. The two are both core authors. But the cooperation in the research field is not colse on the whole. So, strengthening communication and cooperation between authors and institutions is conducive to academic development and progress in the field, and there is still much room left for progress. Nanjing University of Chinese Medicine, which has the largest number of Chinese articles published, has close cooperation with many other institutions. Although there is no core author int the

ISSN 2618-1584 Vol. 5, Issue 7: 34-47, DOI: 10.25236/FMSR.2023.050706

institution at present, this institution has still produced the highest number of articles int the field. This also shows from another perspective that institutions are enhancing cooperation with other institutions is an extremely good approach for one institution to make academic progress in the field. According to results from analyzing English articles, the cooperation between authors and between different institutions is relatively close.

4.2. Research hotspots

There are two main research hotspots in the treatment of DR with TCM, one is the clinical treatment research and the other is mechanism research.

4.2.1. Clinical treatment of DR

From TCM perspective, DR is classified as "diabetic eye disease", which originates from long-suffering of diabetes.The basic pathogenesis of diabetes is Yin deficiency with internal heat and viscera deficiency.Suffering from DR for a long time further leads to worsened qi deficiency and blood stasis, which enters the eye channels. As eye channels are numerous, thin and deeply placed, making it an easy target of blood stasis. Blood stasis in turn blocks blood circulation and nutrition in the eyes, resulting in microangiomas.As a consequence of microangiomas, blood flow does not follow meridians, and even ooze from the veins, likely resulting in retinal exudation, bleeding or falling off, which is manifested as blurred vision or blindness.Therefore, promoting blood circulation and removing blood stasis is an important method for DR treatment in TCM [16]. Syndrome differentiation and treatment, a basic principle in TCM to understand and treat diseases, is also essential in DR treatment Good clinical effects have been achieved in DR treatment with TCM.

Based on the theory of syndrome differentiation and treatment in TCM, progress has been made in the research on the treatment of DR with TCM. To be specific: (1) From the perspective of clinical research, Qiming Granules (including Huangqi (Astragali Radix), Gegen(Puerariae Radix), Shudihuang(Rehmannia Glutinosa), Gouqizi(Lycium chinense Mill), Juemingzi(Catsia tora Linn), Puhuang (Pollen Typhae), Chongweizi(Fructus Leonuri) and Shuizhi(Leech)) were proved to be effective in benefiting qi and nourishing yin, via studying 1224 DR patients who had received TCM treatment [17]. (2) From the perspective of academic research, in recent years, the establishment of a syndrome differentiation system in ophthalmology by Professor Peng Qinghua, and the implementation of a systematic digital diagnosis and treatment model have jointly made tremendous contribution to scientific research int he field as well as the clinical diagnosis and treatment[18].

4.2.2. Studies on themechanism of TCM for DR treatment

According to keyword co-occurrence and clustering analyses, the exploration of immune regulation such as antioxidant activity and target gene analysis in this field is a hot topic at present, and the research on the mechanism of TCM for DR treatment has made great achievements, which has further promoted the clinical treatment of DR.

Firstly, from the perspective of clinical trials, MA et al.[19]studied a control group in which patients with early DR were given epalrestat and the observation group in which patients received additional Yinxingdamo injection that could promote blood circulation and remove blood stasis, and observed the effects of the treaments on inflammatory factors and oxidative stress. It was found that epalrestat combined with Yinxingdamo injection can alleviate the oxidative stress reaction and relieve inflammation in patients with early DR. Moreover, this combined treatment can help improve patient's vision defect, which is worthtaking. (2) From the perspective of pharmacological research, a study designed a group of rats receiving Danhuang Mingmu Tang that has nourishing Yin and alleviating diuresis effects, whose histopathological examinations results showed mild retinal edema and fundus vascular damage, low expressions of VEGF expressions and high expressions of PEDF protein keveks, suggesting Danhuang Mingmu Tang could effectively reduce the expression of VEGF and PEDF via inhibiting a large amount of production of cAMP and cGMP in serum, so as to prevent microvessels from being further damaged to repair the injuries in retinal tissue after laser photocoagulation on DR rats[20]. Some bioactive chemical compounds of Danhuang Mingmu Tang have been identified, such as catalpol in Dihuang(Rehmannia glutinosa), paeonol in Mudanpi(Cortex Moutan), and polysaccharide in Baimaogen(Rhizoma Imperatae). Pharmacological research shows that the compounds in the above herbs have obvious anti-diabetes, anti-oxidation and anti-inflammatory effects.

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4.3. Research trends

Through the keyword citation burst analysis, combined with research hotspots, it is concluded that the development trend of this field lies in the mechanism research, therapeutic drugs and the mortality rate of DR. The trend analysis was finished in combination with analyzing high-frequency keywords.

(1) Mechanism study. Research on the mechanism of treating DR with TCM mainly includes network pharmacology, insulin resistance etc., and exploration on the pathogenesis and treatment. All these stages represent the potential possibility of terminating disease progress. PITALE et al[21]. found that the main regulator of insulin signal transduction and glucose metabolism in retina is TRIB3, which was induced in DR patients, leading to the over-expression of HIF1a, GFAP, VEGF, GLUT1 and EGFR. In addition, HIF1a also regulates the expression of GLUT1 and control glucose absorption in retina together with TRIB3. ZHOU et al.[22]predicted the active components and targets of Mingmu Dihuang Pill through network pharmacology, among which 203 targets intersected with the therapeutic targets of DR. It mainly includes PIK3RA, TP53, SRC, JUN, HRAS, AKT1, VEGFA, EGFR, ESR1 and PI3KCA. It is determined that the signal pathways of AGE-RAGE, PI3K-AKT and Rap1 are the main ones for Mingmu Dihuang Pill to participate in the DR treatment. TONADE et al[23] found that nerve cells (photoreceptors) and adjacent retinal pigment epithelium (RPE) in the retina play an important role in the progress of DR, and both of them will affect the retinal vascular changes in the early stage of retinopathy. Studying and exploring the pathogenesis and treatment mechanism of DR is helpful to provide theoretical basis for academic research and clinical treatment of this disease, which has important scientific significance.

(2) Therapeutic drugs. Due to the limitations of traditional surgical treatment[24], in recent years, drugs with less side effects and longer curative effects for the treatment of DR have been developed, including drugs for targeted therapy, mesenchymal stem cell injection, SGLT2 inhibitors etc. AI et al. [25]conducted animal experiments on Xiao Bopi(XBP) with the efficacy of clearing away heat and toxic materials, and showed that XBP effectively improved the glucose tolerance and insulin sensitivity of DR mice, while markedly thickened the retinal of DR mice. XBP alleviates angiogenesis and apoptosis by inhibiting HIF-1α/VEGF/DLL-4/Notch-1 pathway, which is a new clue for the potential mechanism of XBP in treating DR patients.

5. Conclusion

The number of papers on DR treatment with TCM increases year by year, but the cooperation between researchers and institutions is still unsatisfactory. So cooperation between them should be strengthened to promote the further development of this research field. The hotspots in this field is the clinical treatments of DR and their mechanisms. The main trend in the research field is mechanism exploration, drug treatment, mortality and so on. We should make full use of the advantages of TCM based on syndrome differentiation and multi-target treatment for DR, so as to delay the disease's progress and alleviate patients' pain. Meanwhile, mechanisms in DR treatment with TCM should be explored in scientific research to provide scientific evidences and theoretical basis in the field. It is hoped that this paper can provide information about the treatment of DR with TCM for clinicians and researchers, and broaden research ideas to some extent.

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