

# *Visual Analysis of TCM Treatment of Rheumatoid Arthritis Based on CiteSpace*

Cheng Hao<sup>1,a</sup>, Zhang Libo<sup>1,b</sup>, Jiang Xiaofan<sup>2,c,\*</sup>

<sup>1</sup>The First Clinical College of Medicine, Shaanxi University of Chinese Medicine, Xi'anyang, China

<sup>2</sup>Department of Traditional Chinese Medicine, Shaanxi Provincial People's Hospital, Xi'an, 710068, China

<sup>a</sup>1034093945@qq.com, <sup>b</sup>2502337200@qq.com, <sup>c</sup>jiangxf7906@163.com

\*Corresponding author

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**Abstract:** In order to better promote the research and development in the field of traditional Chinese medicine treatment of rheumatoid arthritis, this paper takes CNKI, WANFANG DATA and VIP DATABASES as data sources, and searches the related research literatures on traditional Chinese medicine treatment of rheumatoid arthritis collected from January 1, 2013 to April 30, 2023, and uses CiteSpace 6. 2. R2 analysis software to make a visual analysis of the published articles, authors, research institutions and keywords. The results show that there is little cross-regional cooperation in the treatment of rheumatoid arthritis by traditional Chinese medicine, and the future research focus will be on the study of cytokines and immune microenvironment in the treatment of rheumatoid arthritis and the prevention and treatment of complications by external treatment methods such as traditional Chinese medicine and acupuncture and acupoint application.

## 1. Introduction

Rheumatoid Arthritis (RA) is a chronic systemic autoimmune disease characterized by excessive release of inflammatory mediators and persistent synovitis, mainly involving joints and their surrounding tissues<sup>[1]</sup>. The global incidence of RA is about 0. 5%-1%, and that of China is about 0. 42%, with a total number of patients reaching 5 million<sup>[2]</sup>. Disability is a high probability event that patients with long-term RA will encounter, which is often called "immortal cancer" and affects their physical and mental health and quality of life. At present, the commonly used therapeutic drugs in western medicine include nonsteroidal anti-inflammatory drugs (NSAIDs), Glucocorticoid (GC), traditional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biological disease-modifying anti-rheumatic drugs (bDMARDs). The treatment of these drugs can control or even completely relieve the condition of most RA patients, but at the same time, patients may still face infection, hepatorenal toxicity, bone marrow suppression, gonadal suppression, tuberculosis.

Tumors and other adverse reactions<sup>[3]</sup>. The research shows that the combination of western medicine and traditional Chinese medicine can not only improve the clinical efficacy of RA, but

also reduce the adverse reactions caused by western medicine<sup>[4]</sup>. Traditional Chinese medicine pays attention to the holistic view of "from local to whole, from outside to inside" and the dialectical principle of "exterior-interior cold and heat deficiency and excess and yin and yang" in treating RA. Treatment methods can be divided into internal treatment method and external treatment method. The internal treatment method of traditional Chinese medicine includes oral Chinese medicine compound, single Chinese medicine preparation and Chinese patent medicine, while the external treatment method includes acupuncture, massage, acupoint application of traditional Chinese medicine, fumigation of traditional Chinese medicine and functional exercise.

CiteSpace is an information visualization software developed by using Java language. Based on Co-citation analysis theory (Co-citation) and path Finder algorithm, Citespace measures the documents (collections) in specific fields to find out the critical path and knowledge inflection point of the evolution of disciplines, and draws a series of visual maps to form the analysis of the potential dynamic mechanism of discipline evolution and the detection of the frontier of discipline development<sup>[5]</sup>. In this paper, CiteSpace 6. 2. R2 software is used to visually draw and analyze the knowledge map of the literature related to RA treatment in traditional Chinese medicine, such as publishing trends, authors, research institutions, keywords, etc., and analyze the current research status, research hotspots and future development trends in this field, in order to provide a clearer research direction for future research and promote the development of this field.

## **2. Materials and Methods**

### **2.1 Data Source**

CNKI, WANFANG DATA and VIP DATABASES are used as data sources for advanced retrieval. Search keywords: (Chinese medicine AND RA) OR (Wang Bi) OR (Moxibustion AND RA) or (Apply Externally AND RA). Retrieval period: January 1, 2013 to April 30, 2023. Search language: Chinese. Search literature categories: traditional Chinese medicine, traditional Chinese medicine, integrated traditional Chinese and western medicine.

### **2.2 Inclusion and Exclusion Criteria**

The researchers included the literature on internal and external treatment of RA with TCM in the research scope, and excluded the relatively worthless literature, such as repeated literature, conferences, master's and doctoral papers and articles entitled arthritis, synovitis and rheumatism.

### **2.3 Data Processing**

The researcher imported the retrieved documents into NoteExpress 3. 8 software, and used duplicate checking function to eliminate duplicate documents. Then, according to the inclusion and exclusion criteria, the topics and abstracts of the literature were independently screened, and the documents with objections were discussed and decided with the other two researchers. Finally, the sorted documents are exported in Refworks format, and the exported documents are converted and analyzed by CiteSpace 6. 2. R2 software.

## **3. Results**

### **3.1 Analysis on the Trend of Document Publishing**

A total of 3013 core journal articles were retrieved, and the remaining 1691 articles were

screened according to the admission criteria. During 2013-2021, the number of literatures on RA treated by traditional Chinese medicine showed a rapid growth trend, reaching the peak in 2021, reaching 199 articles; In 2022, the number of documents issued dropped slightly, but it remained at a high level. From the overall publishing trend, it shows that this field has been in the research hotspot stage; In 2023, only four months' relevant literature was counted, and the data was incomplete, so it was not included in the analysis for the time being. See Figure 1 for details.

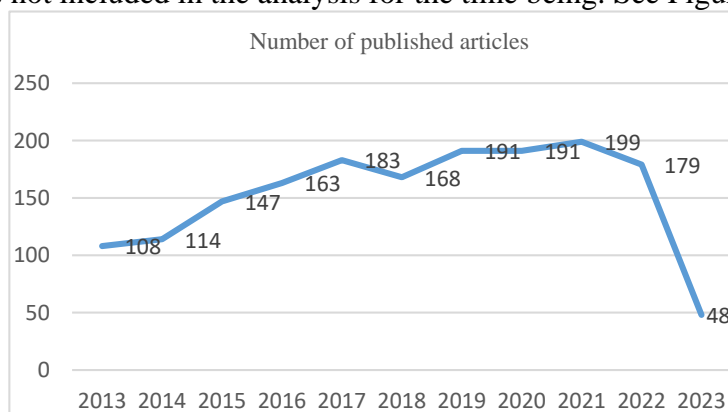


Figure 1: Annual distribution map of published documents

### 3.2 Author Co-occurrence Map Analysis

The author analyzed the documents included in the standard, and obtained 470 nodes and 882 connections, with a network density of 0.008. It shows that a total of 470 authors have entered the co-occurrence analysis map of RA authors in TCM treatment, the number of connections indicates the number of cooperation between authors, the network density reflects the degree of cooperation between authors, and the cooperation between authors in this field is scattered, as shown in Figure 2. According to Price law  $N = \sqrt{0.749n_{max}}$  ( $n_{max}$  is the number of articles published by the most prolific authors), the threshold value of core authors is calculated to be  $N=12$ , and those with more than 12 articles are core authors, [6] there are 19 core authors who have published more than 12 articles. See Table 1 for details. The size of the nodes and names in Figure 2 represent the author's activity in this field. The larger the nodes and names, the higher the activity. The author with the highest activity is Liu Jian, followed by Jiang Quan, Ma Wukai, Yao Xueming, Liu Wei, Lin Changsong and others. However, the thickness of the connection line between authors represents the closeness between them, and the thicker the connection line, the higher the closeness. According to the strength value of the connection line, no particularly close cooperative relationship was found. The depth of the connection color represents the time of cooperation. The lighter the connection color represents the earlier the cooperation time, and the darker the color represents the closer the cooperation time is to the present. The earlier the cooperation time is, the Zhou Haiyan team and Liu Jian team, and the closer the time is, the Jiang Quan team.

The relationship between most core authors revolves around the clinical application of tripterygium wilfordii in the treatment of RA, [7] to some extent, it affirmed the application value of tripterygium wilfordii in the treatment of RA patients. Because the composition of tripterygium wilfordii is complex, the effective dose is similar to the toxic dose. [8] It is easy to cause toxicity of multiple systems, such as reproductive system and blood system. Therefore, under the premise of ensuring the curative effect of tripterygium wilfordii on RA, the researchers conducted research for the purpose of safe application of tripterygium wilfordii. For example, Linna et al. [9] studied the dose and toxicity of tripterygium wilfordii polyglycoside tablets and tripterygium wilfordii tablets in the treatment of RA; Zhang Yi and others studied the safety, toxicity reduction and synergy of

traditional Chinese medicine combined with tripterygium wilfordii in the treatment of RA. [10]

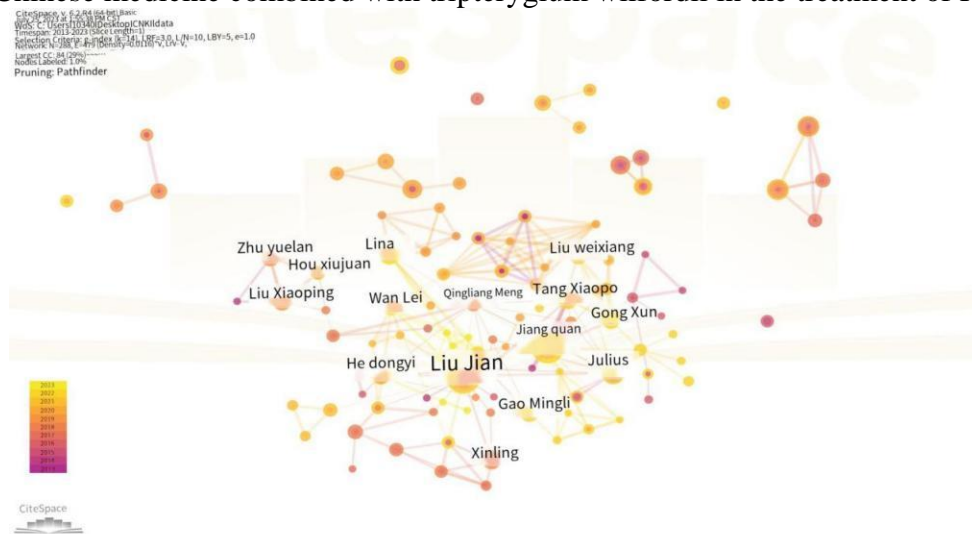


Figure 2: Author's co-occurrence map

Table 1: Number of Papers Published by Core Authors (Top 19)

Serial Number	Author	Quantity of documents issued
1	Liu Jian (First Affiliated Hospital of Anhui University of Chinese Medicine)	49
2	Jiang Quan (Guang 'anmen Hospital, China Academy of Chinese Medicine)	46
3	Ma Wukai (Guizhou University of Traditional Chinese Medicine)	24
4	Yao Xueming (Guizhou University of Chinese Medicine)	22
5	Liu Wei (First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine)	22
6	Lin Changsong (First Affiliated Hospital of Guangzhou University of Chinese Medicine)	21
7	Tang Xiaopo (Guang 'anmen Hospital, China Academy of Chinese Medicine)	20
8	Zhu Yuelan (Oriental Hospital, Beijing University of Chinese Medicine)	19
9	Linna (Institute of Chinese Materia Medical China Academy of Chinese Medical Sciences)	18
10	Zhou Haiyan (Chengdu University of Traditional Chinese Medicine)	17
11	Du Xiaozheng (Gansu University of Chinese Medicine)	16
12	Liu Xuguang (Chengdu University of Traditional Chinese Medicine)	16
13	He Dongyi (Shanghai University of Traditional Chinese Medicine)	16
14	Xinling (First Affiliated Hospital of Anhui University of Chinese Medicine)	15
15	Wan Lei (First Affiliated Hospital of Anhui University of Chinese Medicine)	14
16	Liu Xiaoping (Oriental Hospital of Beijing University of Chinese Medical Sciences)	13
17	Gong Xun (Guang 'anmen Hospital, China Academy of Chinese Medicine)	13
18	Gao Mingli (Affiliated Hospital of Liaoning University of Traditional Chinese Medicine)	12
19	Wenjianing (First Affiliated Hospital of Anhui University of Chinese Medicine)	12

### 3.3 Analysis of High-profile Research Institutions and Their Cooperation Maps

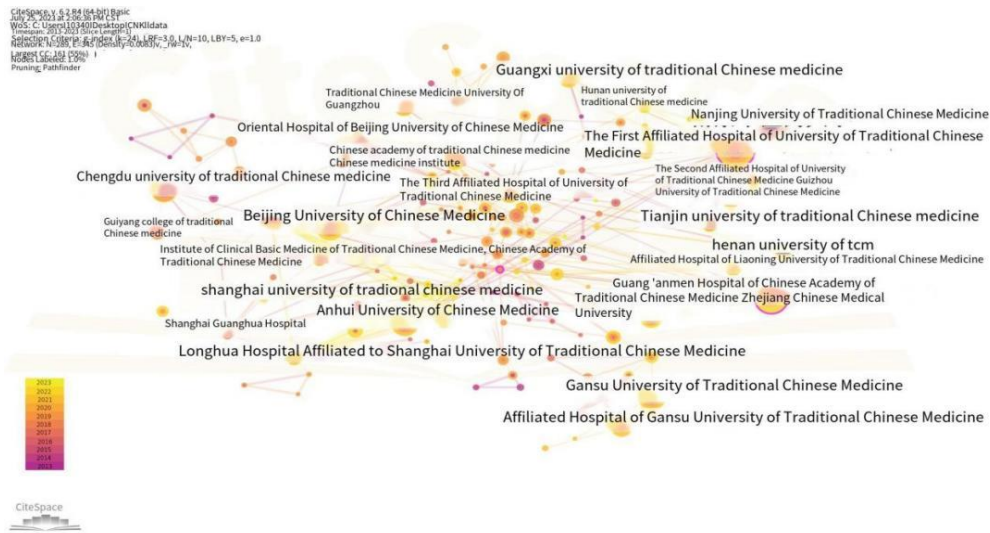


Figure 3: Knowledge Map of Institutional Cooperation

Table 2: Research institutions with high publication volume (top 19 publications)

Serial Number	Organization	Quantity of documents issued	Centrality
1	The First Affiliated Hospital of University of Traditional Chinese Medicine	76	0.14
2	Guang 'anmen Hospital, China Academy of Chinese Medical Sciences	60	0.17
3	Anhui University of Chinese Medicine	45	0.03
4	Chengdu university of Traditional Chinese medicine	42	0.06
5	Beijing University of Chinese Medicine	42	0.07
6	Gansu University of Chinese Medicine	38	0.01
7	Nanjing University of Chinese Medicine	31	0.05
8	Oriental Hospital of Beijing University of Chinese Medicine	28	0.04
9	Guangzhou University Of Chinese Medicine	28	0.05
10	Zhejiang chinese medical university	24	0.02
11	Affiliated Hospital of Gansu University of Chinese Medicine	23	0.01
12	China Academy of Chinese Medical Sciences	22	0.08
13	Guangxi university of Chinese medicine	20	0.01
14	Henan university of Chinese Medicine	20	0.02
15	The Third Affiliated Hospital of University of Traditional Chinese Medicine	20	0.07
16	Tianjin university of Traditional Chinese medicine	17	0.02
17	Guizhou University of Traditional Chinese Medicine	15	0.01
18	Affiliated Hospital of Liaoning University of Traditional Chinese Medicine	15	0
19	LongHua Hospital Shanghai University of Traditional Chinese Medicine	14	0.05

The analysis shows that the top 19 research institutions are the First Affiliated Hospital of





external treatment of traditional Chinese medicine, quickly relieve the symptoms of swelling and pain, and be easy to operate, so external treatment is easier to be favored and selected by patients than internal treatment, and has good compliance; Among them, acupuncture is the most commonly used treatment method in external treatment of traditional Chinese medicine.

Table 3: Key Frequency and Centrality Statistics (Top 20 Frequencies)

Serial Number	Keyword	Frequency	Centrality
1	Acupuncture and Moxibustion	200	0.12
2	Rheumatoid	127	0.29
3	Clinical efficacy	116	0.16
4	Moxibustion method	98	0.18
5	Wang Bi	92	0.16
6	Traditional Chinese Medicine	92	0.22
7	Amethopterin	66	0.07
8	Summarize	60	0.14
9	Research Progress	45	0.10
10	Inflammation	40	0.10
11	External Application of Traditional Chinese Medicine	38	0.12
12	Traditional Chinese Medicine Fumigation	34	0.08
13	Chinese Traditional Treatment	33	0.15
14	Mechanism of Action	25	0.04
15	Active Stage	22	0.08
16	Traditional Chinese Medicine Syndrome	22	0.04
17	Famous Doctor Experience	21	0.06
18	Traditional Chinese Medicine Syndrome Types	20	0.02
19	Etiology and Pathogenesis	19	0.03
20	Rat	18	0.03

### 3.4.2 Keyword Clustering

After keyword clustering, 11 clustering labels were obtained, among which the clustering module value was 0.5596 ( $> 0.3$ ), indicating that the clustering structure was significant. The average contour value of clustering is 0.816 ( $> 0.7$ ), which indicates that the clustering results are highly reliable.<sup>[11]</sup> The cluster analysis map is shown in Figure 5. Each color block represents a cluster label. The higher the cluster ranking, the larger the scale of the cluster, that is, the more nodes are included in the cluster. Cluster # 0 is the largest, mainly for applying network pharmacology to traditional Chinese medicine compound to explain the action mechanism of traditional Chinese medicine in treating RA, and to discover the effective substances/active compositions of traditional Chinese medicine, so as to provide new ideas for the discovery and research of new drugs. Keyword clustering can be divided into three categories: action mechanism (# 0; # 1), research type (# 8; # 9; # 10) and clinical (# 2; # 3; # 4; # 5; # 6; # 7).

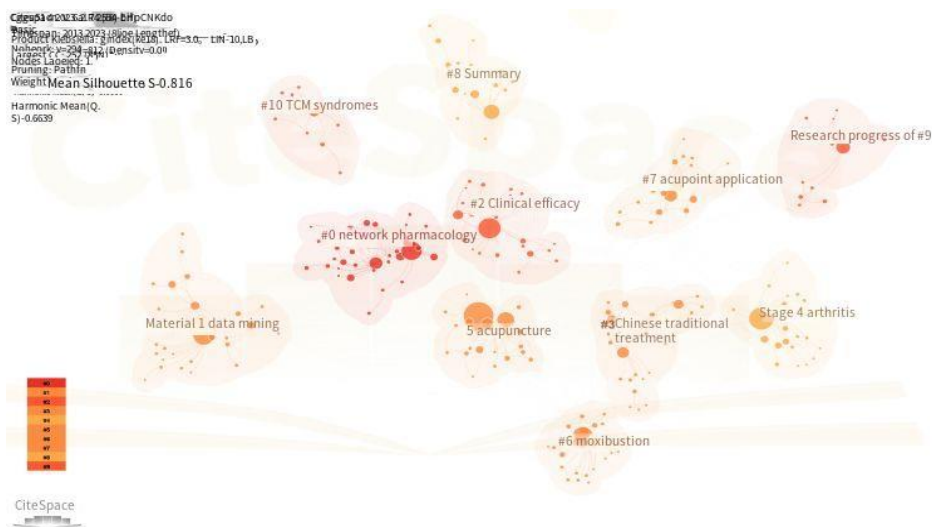


Figure 5: Keyword clustering map

### 3.4.3 Keywords Time Line Chart

In CiteSpace 6. 2. R2 software, we can find the research focus of this field in different time periods by drawing the time line diagram of keywords, in which the X axis represents the time line, from left to right, from far to near, and the Y axis represents the cluster number and keywords, as shown in Figure 6. It can be found that the time span of clustering #2 "Clinical Efficacy", #3 "TCM Treatment", #6 "Moxibustion" and #10 "TCM Syndrome" is the widest. From 2013 to 2015, the treatment of RA by traditional Chinese medicine is in the development stage, and the research content is relatively broad. The hot spots of the treatment of RA by traditional Chinese medicine mainly focus on etiology and pathogenesis, syndrome differentiation, experience of famous doctors and the law of medication, as well as the clinical efficacy and mechanism of external treatment of traditional Chinese medicine such as external application of traditional Chinese medicine, acupuncture and moxibustion combined with methotrexate or oral administration of traditional Chinese medicine. From 2015 to 2020, with the rise of data mining and molecular docking technology, the research content is more refined, and the research focus is mainly on the correlation between cold-dampness syndrome or damp-heat syndrome and bone destruction and inflammatory factors in RA patients. On this basis, Chinese patent medicines such as tripterygium wilfordii preparation, Xinfeng capsule and Wangbi tablet, as well as external treatments of traditional Chinese medicine such as hot-patching acupuncture, electroacupuncture, warming acupuncture and acupoint injection have been widely used and developed. From 2020 to now, the research focus of traditional Chinese medicine in treating RA has shifted from the previous mechanism of reducing serum inflammatory factors to the regulation of cytokines and immune microenvironment and other signal pathways. Therefore, it is considered that external treatment of traditional Chinese medicine, treatment based on syndrome differentiation and signal pathway may still be the main research directions in this field.



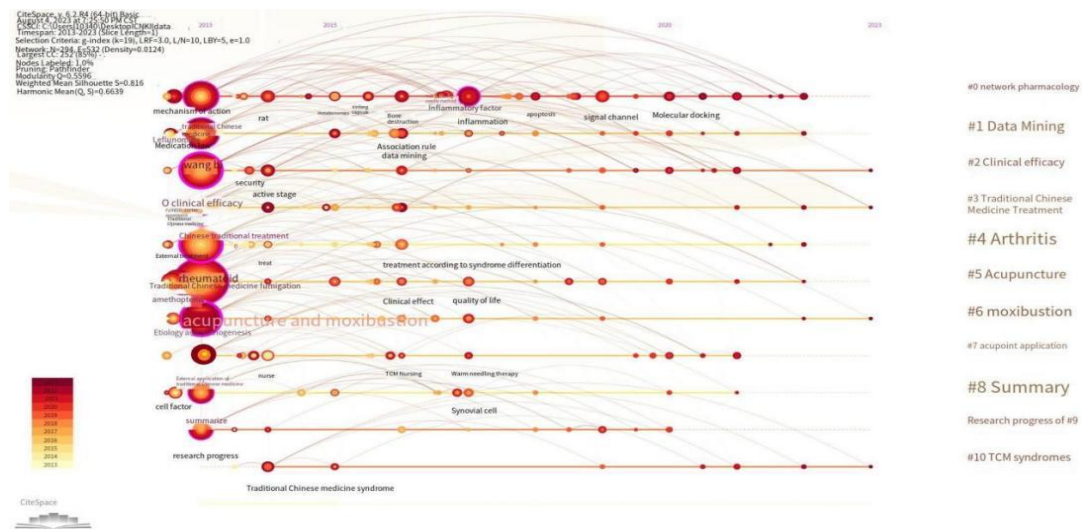


Figure 6: Keyword Time Line Diagram

### 3.4.4 Keyword Emergence

#### Top 15 Keywords with the Strongest Citation Bursts

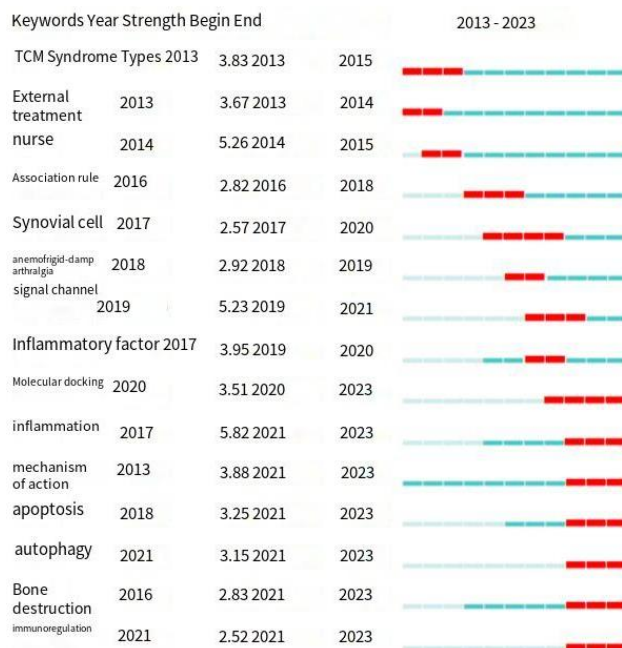


Figure 7: Keyword Emergence Map

The keyword pop-up diagram can show the past and present research hotspots in this field, and predict the future development trend of this field through analysis, as shown in Figure 7. TCM syndrome types, external treatment and TCM nursing emerged earlier, and received extensive attention during 2013-2015, which indicated that the application of external treatment of TCM in the treatment of RA under the guidance of the theory of syndrome differentiation and treatment was effective, and it was a relatively early research hotspot in this field. Subsequently, the researchers focused on the correlation between wind-cold-dampness arthralgia syndrome and inflammatory factors and synovial cells in RA patients, as well as the correlation rules and signal pathways of

traditional Chinese medicine in treating RA wind-cold-dampness arthralgia syndrome. Molecular docking, inflammation, Mechanism of action, apoptosis, autophagy, bone destruction and immunomodulation are the key words that have continued since the emergence, indicating that these key words are highly active in this field at present. It can be seen that research hotspots may be the focus of future research.

#### 4. Discuss

This paper analyzes 1691 literatures on RA treated by TCM in recent 10 years, and summarizes the current research status, hot spots and future development trends in this field. The results show that the literature on the treatment of RA by traditional Chinese medicine shows an overall upward trend, and more and more researchers affirm the role and value of traditional Chinese medicine in the treatment of RA. Geographically speaking, research institutions in Beijing, Anhui, Chengdu and other regions have strong scientific research capabilities and great influence, which belong to the main research positions of traditional Chinese medicine treatment of RA, but there is less cooperation between provinces and cities, and the research has certain regionality. As far as researchers are concerned, Liu Jian's team has the highest number of papers. The main research direction is to study the mechanism of tripterygium wilfordii preparation and its compound preparation in treating RA and the effects of various signal pathways on RA inflammation and oxidative stress through experiments. [12, 13, 14]

Tripterygium wilfordii is the most studied Chinese medicine and Chinese medicine monomer in the treatment of RA, and acupuncture and acupoint application are the most studied external treatments for RA. Tripterygium wilfordii and its extract can strongly inhibit the proliferation of T and B lymphocytes. By down-regulating the expression of cyclooxygenase (COX)-2 gene, it can inhibit prostaglandin E2, matrix metalloproteinases and so on, and play a role in regulating immunity, relieving inflammation and pain, and protecting cartilage. [15] However, the effective dose of tripterygium wilfordii is similar to the toxic dose, which is easy to cause many adverse reactions. The existing instructions of traditional Chinese medicines and preparations related to tripterygium wilfordii are too simple and extensive as clinical guidance, which leads to the difficulty for clinicians to individually grasp the indications and dosage of patients, resulting in different curative effects and side effects. Therefore, researchers have carried out a series of studies on the "Reducing toxicity and increasing efficiency" of Tripterygium wilfordii in the treatment of RA, and the specific methods are summarized as follows: ① Different processing methods are used to attenuate toxicity and synergize, such as making medicine juice<sup>[16]</sup>, Microwave stewing<sup>[17]</sup>; ② Reducing toxicity and increasing efficiency through compatibility of traditional Chinese medicines, such as Xinfeng capsule and compound tripterygium wilfordii decoction; ③ Through the structural modification of the effective components of tripterygium wilfordii, the toxicity is reduced and the efficiency is enhanced, such as tripterygium wilfordii Shu;<sup>[18]</sup> ④ By changing the route of administration, tripterygium wilfordii preparation or tripterygium wilfordii compound preparation is externally applied to reduce toxicity and increase efficiency. Such as tripterygium ointment<sup>[19]</sup>, Tripterygium wilfordii compound coating agent<sup>[20]</sup>. Because the processing method requires higher pharmaceutical process, the quality of the processed drugs is not uniform, which is difficult for clinicians to grasp; The compatibility of traditional Chinese medicine compound is limited by the TCM theory and experience of clinicians; The structural modification method has strict requirements on science and technology; Therefore, the external application of tripterygium wilfordii has become the simplest and most commonly used choice. Compared with oral administration, the traditional external preparation of Tripterygium wilfordii has obvious analgesic effect, and at the same time, it greatly reduces the gastrointestinal irritation and hepatorenal toxicity

caused by oral administration of *Tripterygium wilfordii*. However, due to the outdated preparation technology, there are generally some shortcomings such as slow absorption, low bioavailability, short-lasting drug effect and skin irritation. The microneedles made of hydrogel can painlessly pierce the stratum corneum barrier, form micron-sized pores, and can be dissolved harmlessly, and distribute their payload into the tissue fluid around skin cells and enter the blood. [21, 22] The drug enters the skin from the pore, so the permeability and bioavailability are greatly improved, and the nerves and blood vessels in the dermis are not damaged at the same time, and the skin in the administration area heals quickly. [23, 24] Therefore, it has high research value and development potential to prepare sustained-release tripterygium wilfordii hydrogel microneedles by carrying effective components of tripterygium wilfordii on hydrogel microneedles.

The focus of traditional Chinese medicine in treating RA has changed from early TCM syndromes and famous doctors' experience to the study of clinical efficacy. At present, the research focus is on the specific mechanism of traditional Chinese medicine compound in treating RA and preventing and treating complications. [25, 26, 27] The focus of external treatment of RA in traditional Chinese medicine has gradually shifted from the early clinical application and curative effect observation of external treatment methods such as acupuncture and acupoint application to the study of the mechanism of treatment of RA. [28, 29, 30] The focus of experimental research has gradually shifted from serology and pathology to the study of signal pathways such as cytokines and immune microenvironment. [31, 32]

In recent years, there have been more and more researches on the treatment of RA with traditional Chinese medicine. With the continuous updating and development of science and technology and research methods, the research content has become more refined, but there are some shortcomings in general. The research cooperation is mostly confined to local medical colleges and their affiliated hospitals, and there is less cross-regional and cross-school cooperation, so researchers have not formed a close cooperative relationship. The future development direction should focus on the cooperation and exchanges between multi-schools, multi-regions and multi-institutions to better promote it. The purpose of traditional Chinese medicine in treating RA is not only to relieve and improve symptoms, but to cure diseases. The future development direction of traditional Chinese medicine is not to cure diseases, but to prevent diseases. Sun Simiao, a drug king, once said in *Qian Jin Fang* that "The first-class doctor cured the disease before it happened; Inferior doctors have to wait for the disease to happen and even be very critical before treating it", and clearly put forward the three-level prevention and treatment thought of medicine. In this study, only the Chinese core literature was extracted and analyzed, but the English literature was not included, and the results obtained based on different cutting methods were not the same, so there may be some bias and errors in the results, which cannot present the whole research picture of RA in traditional Chinese medicine to a certain extent. Later research should seek more accurate retrieval and research methods to improve the results.

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