

Trends and frontiers in natural products for arthritis, 2000–2021

A bibliometric analysis

Junying Pan, MD^a , Haoyu Wang, MD^a, Yinghua Chen, MD^{a,*}

Abstract

Background: Arthritis has become one of the trouble diseases that upsets people. A growing number of studies have shown that natural products have great potential for the treatment of arthritis. However, few bibliometrics have been systematically studied in this area. This paper analyzes the literature data of natural products on the arthritis research, and the research hot spots and future research directions of the treatment of arthritis by natural products were explored.

Method: Through CiteSpace, VOSviewer software and Bibliometricx under the R language environment, the article and review literatures on the treatment of arthritis with natural drugs in the Web of Science core collection database were analyzed by bibliometric analysis.

Results: On December 28, 2021, a total of 2102 records were retrieved, 81.69% publications were issued in 2012 to 2021, mainly in China-dominated Asian countries, with cooperation among countries. The analysis of the number of articles published by institutions shows that the number of articles published by China Academy of Chinese Medical Sciences is up to 82. Lu, Aiping and Smolen, JS are the authors with the highest citation frequency and co-citation frequency. Keywords analysis showed that the research of natural drugs mainly focused on gene expression, anti-inflammatory and other mechanisms and signaling pathways. With the progress of science and technology and the integration of multi-disciplines, the research on natural drugs for arthritis will be more in-depth and specific.

Conclusion: In this study, literature metrology analysis was conducted on natural products in the treatment of arthritis, in order to grasp the background, trends and frontiers of the research, and predict possible research hotspots in the future. It is expected to provide some reference value and direction for future scholars in this field.

Abbreviations: H-index = Hirsch index, NF-Kappa B = nuclear factor-κB.

Keywords: arthritis, bibliometric analysis, collaborative network, citation network

1. Introduction

Arthritis generally refers to the inflammatory diseases that occur in human joints and surrounding tissues. Common clinical arthritis mainly includes the following: rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout arthritis and other diseases; At present, arthritis has become a disease afflicting many middle-aged and elderly people.^[1] In China, half of the population over 50 years old suffer from osteoarthritis, and in the population over 65 years old, 90% of women and 80% of men suffer from osteoarthritis.^[2] In severe cases, the life expectancy is shortened by about 10 to 15 years. There are already drugs for arthritis but there are some side effects, such as non-steroidal anti-inflammatory drugs short duration of hormone therapy may lead to adverse reactions to patients, such

as high blood pressure, elevated blood lipids, Gastrointestinal reaction etc.^[3–5] Therefore, looking for long side effect is low to reduce pain in patients with the best drugs to treat it is necessary.

There is growing evidence that natural products have anti-inflammatory effects in arthritis.^[6–9] In this paper, several natural products that have effects on arthritis were found through visual analysis. For example, *Tripterygium wilfordii* Hook.f.,^[10,11] turmeric,^[12,13] and *Siegesbeckia orientalis* L.^[14] are commonly used in anti-arthritis research.

It is important to note that some natural products have been all over the world were used in the treatment of patients with arthritis. For example, triptolide,^[15–17] tripterine,^[18,19] and tripterygium glycosides^[20] were extracted from *Tripterygium wilfordii* Hook.f.^[21] which was one of the commonly used drugs in arthritis,

This work was financially supported by the National Natural Science Foundation of China (grant no. 82074530), the Natural Science Foundation of Heilongjiang Province (no. ZD2021H007), and the General Research Project of Higher Education Reform in Heilongjiang Province (no. SJGY20200684).

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

This article does not contain any studies with human participants.

^a First Affiliated Hospital, Heilongjiang University of Chinese Medicine, Harbin, China.

*Correspondence: Yinghua Chen, First Affiliated Hospital, Heilongjiang University of Chinese Medicine, Harbin 150040, China (e-mail: chyh9000@163.com).

Copyright © 2022 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Pan J, Wang H, Chen Y. Trends and frontiers in natural products for arthritis, 2000–2021: A bibliometric analysis. *Medicine* 2022;101:45(e30996).

Received: 17 March 2022 / Received in final form: 1 September 2022 / Accepted: 6 September 2022

<http://dx.doi.org/10.1097/MD.0000000000030996>

effectively alleviate the patients' pain. However, it is worth noting that much of the evidence on the anti-inflammatory effects of natural products comes from preclinical studies in vitro and in vivo, and only a few natural products have been used clinically.

With the development of various scientific fields, it is particularly important to describe the development trend of a research in a scientific way, the relationship and cooperation network between countries, institutions and authors behind it, and to scientifically predict the hot spots of future research. Bibliometric analysis has been widely used to quantitatively evaluate the literature and explore the development trends in many research fields.^[22] There has been no systematic review and bibliometric analysis of studies on the treatment of arthritis by natural products. Therefore, in order to better understand the status and trends of natural products in arthritis research, the purpose of this study is to use bibliometrics to visualize references with vivid information, reveal current research trends, explore potential research hotspots, and guide researchers in the future.

2. Materials and Methods

2.1. Data collection

We query the Web of Science Core Collection online database using the following search string: TS = ("natural product*" OR "natural compound*" OR "traditional Chinese medicine*" OR "TCM*" OR "Chinese herb*" OR "phytochemical*" OR "secondary metabolite*" OR "natural medicine*") AND ("arthritis*" OR "polyarthritis*" OR "osteoarthritis*" OR "arthritis*"). The language is limited to English and only articles and reviews are selected for the period 2000 to 2021. All retrieval records were downloaded into pure text format on December 28, 2021, and imported into bibliometric tools for further analysis.

2.2. Analytical method

All records were downloaded by 2 authors independently of the Web of Science core collection, including annual number of publications, national/regional output, institution, journal, total citations, citations per paper and Hirsch index (H-Index), impact factors for journal categories and the four-area Journal Citation Report 2021. Any differences should be settled by consensus.

We used ScimagoGraphica to analyze and map the annual publication output. In addition, the current research foundation, frontier knowledge and research trend were obtained by using bibliometrics. In this study, all downloaded data were converted into

visualization software. Visual analysis of text data was carried out by using CiteSpace, Vosviewer and Bibliometricx in R language environment. These visualization tools can be used to analyze basic indicators, including co-citation analysis of countries, journals, institutions, authors and references, as well as timeline views and keywords evolution of co-cited references. CiteSpace is characterized by multiple functions and good at co-citation analysis.^[23,24] Vosviewer^[25] is easy to operate and more intuitive to export visual atlas with ScimagoGraphica. Bibliometricx can carry out keyword evolution in R language environment.

This paper as a statistical prediction does not involve ethical review issues.

3. Results

3.1. Annual publications

From the Web of Science core collection online database, by subject search of the relevant literature on natural products in joints published between January 1, 2000 and December 28, 2021, a total of 2102 article and reviews were selected. As can be seen from Figure 1A, the cumulative number of published articles from 2010 to 2021 shows a rapid growth trend, which can be divided into 2 stages: From 2010 to 2014 is stage I, during which the number of articles published tends to be stable. From 2015 to 2021 is phase II, during which the number of articles published shows explosive growth. Only 327 articles were published in 2021. Stage I published 377 English articles, and stage II published 1456 English articles, 3.86 times the number of stage I. Especially in 2015, Tu Youyou won the Nobel Prize for the discovery of artemisinin, and the research on natural products such as Traditional Chinese medicine has attracted wide attention around the world. The development of new drugs with natural compounds has accelerated the research of natural products in arthritis. Only 1185 English articles were published in 2017-2021, accounting for 57.19 % of the total. Therefore, arthritis associated with natural products has attracted more and more attention from global scholars.

3.2. Country/institution cooperation network relationships

We used VOSviewer software to conduct statistical analysis on the authors' national cooperation network. As shown in Table 1, 2102 literatures came from 92 countries or regions. Chinese authors had published 1134 related papers, accounting for 53.95% of all research papers, followed by the United States, India, South Korea, Pakistan, Australia, Italy, Germany, the United Kingdom and Brazil, all with more than 50 papers.

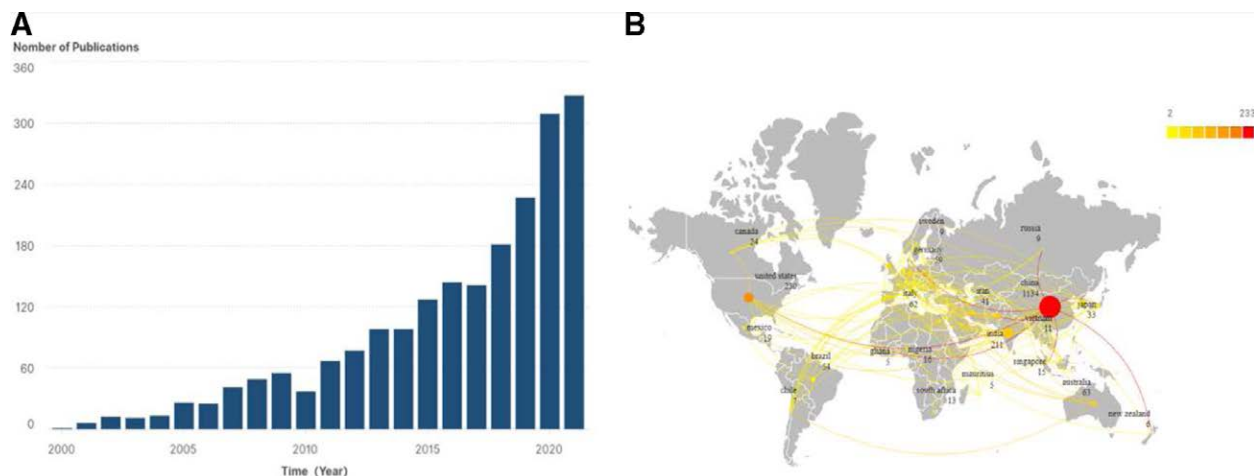


Figure 1. Trend analysis of annual publications in natural products in arthritis research. The annual worldwide publications (A). Visualization of national cooperation networks (B).

Table 1
Top 10 countries related to natural medicine in arthritis research.

Rank	Country/region	Article counts	Citations	Citations per publication	H-index	Percentage (N/2102)
1	China	1134	16,371	14.43	53	53.95
2	United States	230	11,782	51.23	49	10.94
3	India	211	4110	19.48	29	10.04
4	South Korea	101	2160	21.39	21	4.80
5	Pakistan	68	1015	14.93	18	3.24
6	Australia	63	1792	28.44	18	3.00
7	Italy	62	1737	28.02	16	2.95
8	Germany	59	3393	57.51	21	2.81
9	United Kingdom	59	3477	58.93	20	2.81
10	Brazil	54	821	15.20	11	2.57

The total number of papers published in other countries or regions was 115, accounting for about 5.48% of the research literature. This indicates that there are more studies on the association of natural products with arthritis in developed countries and rapidly developing countries.

Among the top 10 countries in terms of the number of papers published, the United Kingdom has the highest rank of citations per publication (58.93), but the frequency of cited articles (3477), and H-index (20) are lower. Although China ranked first in citation frequency (16,371) and H-index (53), it ranked lowest in citations per publication (14.43) among the 10 countries. The United States ranked high in citation frequency (11,782), H-index (49), and citations per publication (51.23) among the 10 countries.

The national cooperation network data processed by VOSviewer was exported to “gml” format, and processed by ScimagoGraphica, as shown in Figure 1B. The node size in the figure represents the number of publications, and the color from light to dark represents the strength of cooperation with other countries. China and the United States, as the largest producers, work closely together. In addition, India, South Korea and the United Kingdom are the most cooperative countries with the United States, while China mainly cooperates with Pakistan, the United Kingdom and the south Korea. As the world’s largest developing country and an ancient civilization with a history of thousands of years of traditional Chinese medicine, China is also the country with the largest number of publications from 2000 to 2021 and the highest intensity of cooperation with other countries.

Table 2 has shown the 10 most productive organizations. The leading institutions were Chinese Academy of Medical Sciences (3.90%, 82), Chinese Academy of Sciences (3.42%, 72) and

Shanghai University of Traditional Chinese Medicine (3.05%, 64 papers). All of the 10 most productive institutions are from China. The Chinese Academy of Medical Sciences has the highest H-index (22), and China Pharmaceutical University has the highest ranking among the top 10 productive universities with its citations per publication (23.08). In order to discover the potential cooperation between research institutions, we conducted a cooperative research analysis of research institutions by using CiteSpace (Fig. 2).

3.3. Authors and co-cited authors cooperative network

The authors ‘cooperation visualization map and the cited authors ‘citation visualization map can provide relevant information about influential research teams and potential partners, and help researchers establish cooperative relationships. The size of the nodes in the visualization figure represents the amount of published papers by the authors, and the connection between the authors reflects the closeness of cooperation. As shown in Figure 3A and B. Intra-State cooperation among scholars is closer than inter-State cooperation.

Table 3 shows the 10 most productive authors and co-cited in this field. The most published papers were Lu, A.P. (38 articles), Lu, C (26 articles), Moudgil, Kamal D. (20 articles), these authors have published at least 20 articles. The largest nodes were associated with the most frequently co-cited authors (Fig. 3B), including Smolen, JS (183 citations), Tao, X.L (166 citations), Wang Y (157 citations), Mcinnes, IB (145 citations), and Li, Y (141 citations).

The above results indicated that there were a large number of scholars studying natural products in the treatment of arthritis, and the main cited authors were concentrated. Further analysis of the cooperation between the above authors and the cited authors showed that the cooperation between the authors and the cited authors was close.

3.4. Reference analysis

Based on the 5 literatures with the high - cited frequency (Table 4), the most frequently cited article was Rheumatoid Arthritis: Pathological mechanisms and Modern Pharmacologic therapies (impact factors 2021, 13.567), written by Qiang Guo, has been cited 35 times. Interestingly, the top 5 co-cited papers were published after 2015, and combined with the annual number of publications, it was found that it might be related to Tu Youyou ‘s Nobel Prize for Medicine in 2015, which might partly stimulate the development of natural products associated with various diseases, and illustrate the potential of natural products for arthritis research. Two of the top 5 centrality of co-cited references were about nuclear factor- κ B (NF-kappa B), they were also published the earliest of the 5 articles.

Table 2
The top 10 productive institutions related to natural products in arthritis.

Rank	Institution	Article counts	Percentage (N/2102)	H-index	Citations per publication	Location
1	Chinese Academy of Medical Sciences	82	3.90	22	19.07	China
2	Chinese Academy of Sciences	72	3.42	20	17.76	China
3	Shanghai University of Traditional Chinese Medicine	64	3.05	17	11.16	China
4	China Pharmaceutical University	50	2.38	19	23.08	China
5	Guangzhou University of Chinese Medicine	45	2.14	8	4.31	China
6	Nanjing University Of Chinese Medicine	40	1.90	12	14.1	China
7	Zhejiang Chinese Medical University	39	1.86	8	6.13	China
8	China Medical University	35	1.66	14	12.58	China
9	Beijing University of Chinese Medicine	35	1.66	9	17.31	China
10	Hong Kong Baptist University	35	1.62	9	9.51	China

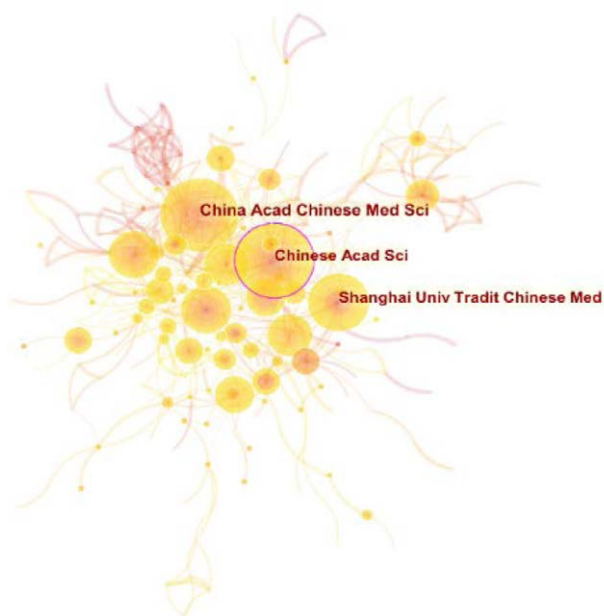


Figure 2. Citespace network visualization diagram of institutions related to natural products in arthritis research.

In addition, time co-citation analysis was performed (Fig. 4). Most of the articles were published after 2010. We found that Natural Product (Cluster #4), Meridian Therapy Diagnosis (Cluster #9) and Chinese Herbal Formula (Cluster #6) were early research hotspots. The warmer the color, the larger the nodes and the more publications. It shows that this clustering problem has been a hot topic in the study of natural products on arthritis in recent years. At the same time, cluster studies on rheumatoid arthritis (Cluster#0) and adjuvant-induced arthritis (Cluster#3) show that this clustering problem is a new hot spot and new direction in this field.

3.5. Keywords analysis

Based on CiteSpace’s analysis of the number of citations and centrality of keywords. We found that the most popular keywords were “rheumatoid arthritis,” “natural product,” “expression,” “in vitro,” “activation,” and “traditional Chinese medicine”

Table 3
The top 10 productive authors and co-cited authors related to natural products in arthritis research.

Rank	Author	Count	Rank	Co-cited author	Citation
1	Lu, A.P.	38	1	Smolen, JS	183
2	Lu, C.	26	2	Tao, X.L.	166
3	Moudgil, Kamal D.	20	3	Wang, Y.	157
4	Jiang, M.	18	4	Mcinnes, IB	145
5	Lin, N.	17	5	Li, Y.	141
6	He, X.J.	15	6	Li, S.	140
7	Li, L.	15	7	Zhang, Y.	130
8	Liu, J.	13	8	Wang, J.	120
9	Venkatesha, Shivaprasad H.	12	9	Li, J.	119
10	Xiao, C.	12	10	Zhang, L.	115

(Table 5). Through the analysis of keywords, we can find that the current research on the association of natural products with arthritis focuses on molecular mechanism.

We use CiteSpace software to detect burst keywords and identify hot spots and research frontiers over time. One of the strongest outbreaks of top 25 keyword citations is in this area, where we analyze those that have bursted since 2018 (Fig. 5A), including “hip” (with a burst strength of 3.77), “phenolic compounds” (with a burst strength of 3.73), “response” (with a burst strength of 3.58), “NLRP3 inflammasome” (with a burst strength of 4.54), “stress” (with a burst strength of 4.22). The future scholars can work from these perspectives.

By analyzing the evolution of keywords, we can see the development trend and research hotspots in a research field. We use Bibliometricx to visualize the evolution of keywords and research hotspots in R language environment, and establish the dynamic relationship of keywords evolution in different periods (Fig. 5B). In the early studies on natural products treatment of arthritis, from 2000 to 2006, the hot keywords were “expression,” “activation,” “acid,” and “inhibition.” From 2011 to 2016, hot keywords developed in a deeper, broader direction, turning to the study of “expression,” “NF-Kappa B” and other mechanisms of action. From 2017 to 2021, keywords mainly focus on “rheumatoid arthritis,” “NF-Kappa B,” “osteoarthritis,” and “extract.” The emergence of these keywords shows that the research is still advancing to a more in-depth direction, indicating that the mechanism of natural drug treatment of arthritis is more concentrated, and the research has received the attention of the majority of researchers.

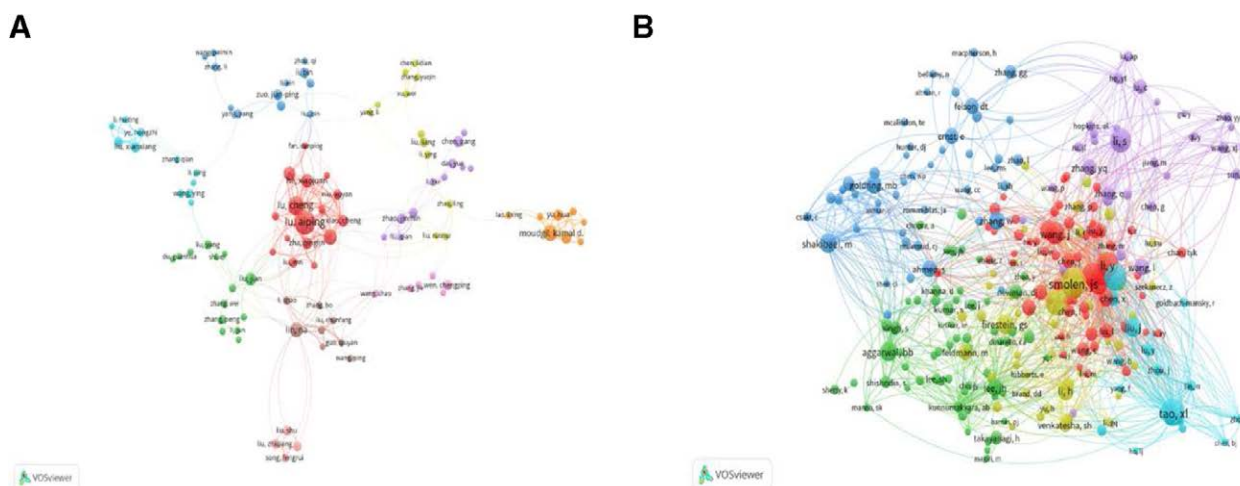


Figure 3. VOSviewer network visualization diagram of authors and co-cited authors related to natural products in arthritis research. Collaboration between authors (A). Cooperative relationship between co-cited authors (B).

Table 4
The top 5 high-cited references related to natural products in arthritis research.

Rank	Title	Journal IF	First author	Publication time	Total citations	Quartile in category
1	Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies	Bone Research (IF:13.567)	Qiang Guo,	April 2018	35	Q1
2	Rheumatoid arthritis	The Lancet (IF:79.321)	Josef S. Smolen	May 2016	26	Q1
3	Comparison of Tripterygium wilfordii Hook F with methotrexate in the treatment of active rheumatoid arthritis (TRIFRA): a randomized, controlled clinical trial	Annals of The Rheumatic Disease (IF:19.103)	Qian-wen Lv,	May 2015	25	Q1
4	Pathogenetic insights from the treatment of rheumatoid arthritis	The Lancet (IF:79.321)	Prof Iain B McInnes	June 2017	25	Q1
5	The treatment of rheumatoid arthritis using Chinese medicinal plants: From pharmacology to potential molecular mechanisms	Journal of Ethnopharmacology (IF:4.36)	Shaowa Lv	December 2015	20	Q2

As shown in Figure 5C, similar to the evolution results of keywords, the keywords “extract” are extended to 2020 with 2016 as the center. From 2012 to 2020, the extraction of natural active ingredients has attracted extensive attention of researchers. In 2020, kaempferol has been studied more and more deeply, which may be related to the rapid development of natural product extraction technology, so kaempferol may be a direction for future scholars to study the cure of arthritis.

4. Discussion

4.1. The literature distribution

This study exported 2102 articles related to natural products in arthritis research from 2000 to 2021 through the Web of Science core database. The annual publications output of this kind of literature increased steadily. From the perspective of national/regional distribution, China and the United States are the main driving forces, and have a high academic reputation in the natural products treatment of arthritis research. This is confirmed by the following characteristics: number of publications, H-index value, total number of citations and each publication citation. Although China’s publications Citations per publication is low, H-index and citations are relatively high, and the total number of publications is ranked first, indicating that China has a high impact in this area, but relatively few high-quality publications. On the other hand, more cooperation between China and the

United States and other countries can also show that China has a high influence in this field. Among the top 10 countries, India, South Korea, Pakistan, Australia and other countries have cooperated with the United States and China.

In addition, all the top 10 research institutes are from China, which shows China’s strong academic influence in this field. The Chinese Academy of Sciences is the most productive institution in the world and works closely with many other Chinese institutions, which shows that it has a high academic reputation in this field in China. In addition, China Pharmaceutical University had the highest Citations per publication and ranked third in the H-Index, indicating that it produced more high-quality publications and played a key role in promoting the development of the field.

4.2. Research basis

In the collection of 2102 articles, One of the top 5 cited literatures reviewed the active ingredients and molecular mechanism of traditional Chinese medicine with anti-arthritis effects, at the same time this article was top 5 centrality co-cited references in the field, illustrate this article for natural products research for the treatment of arthritis has good reference value, the article^[26] found: *Tripterygium wilfordii* Hook.f. monotherapy was not inferior to, and methotrexate^[27,28] + *Tripterygium wilfordii* Hook.f. was better than, methotrexate monotherapy in controlling disease activity in patients with active rheumatoid

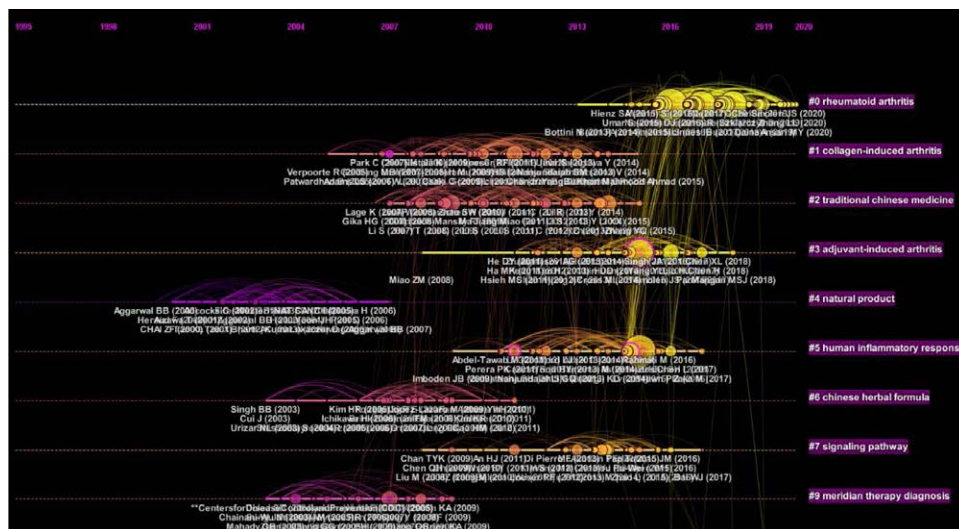
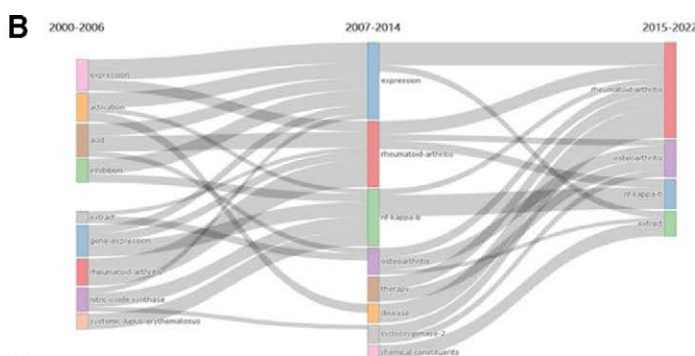
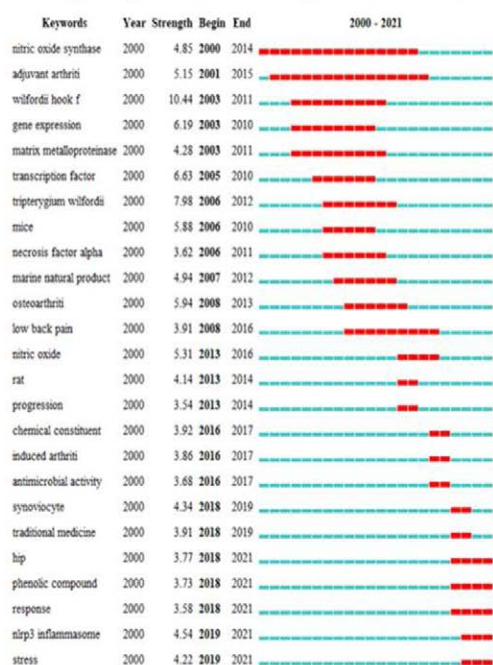
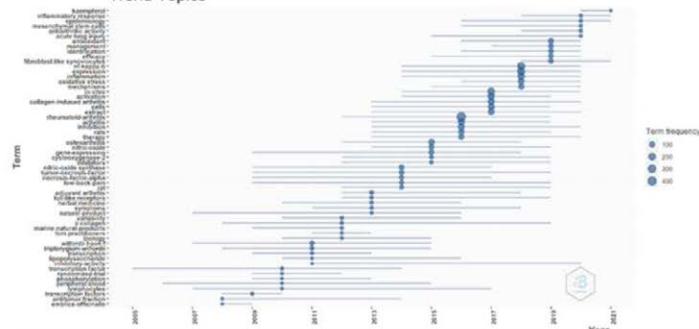


Figure 4. Timeline view of co-cited references related to natural products in arthritis research. (The cluster with warmer color and larger nodes contained more publications, indicating that this clustering issue was the hotspot in this field).

Table 5**The top 10 keywords and centrality of keywords in field of natural products in arthritis research.**

Rank	Keyword	Counts	Rank	Keyword	Centrality
1	rheumatoid arthritis	610	1	rheumatoid arthritis	0.20
2	NF-kappa B	250	2	natural product	0.11
3	expression	234	3	nitric oxide synthase	0.09
4	in vitro	225	4	In vitro	0.07
5	traditional Chinese medicine	189	5	traditional Chinese medicine	0.06
6	inflammation	188	6	acid	0.06
7	natural product	183	7	gene expression	0.06
8	extract	172	8	expression	0.05
9	activation	161	9	activation	0.05
10	collagen induced arthritis	155	10	cell	0.05

A Top 25 Keywords with the Strongest Citation Bursts**C Trend Topics****Figure 5.** CiteSpace timeline view of burst words in field of natural medicine in arthritis research (A). Bibliometrics visualization diagram of keywords evolution (B). Bibliometrics visualization diagram of topic trend (C).

arthritis. According to the high frequency cited literatures and the high school cardiac co-cited literatures, it was found that the commonly used traditional Chinese medicines for arthritis included *Tripterygium wilfordii* Hook.f., *Siegesbeckia orientalis* L., *Eucommia ulmoides* Oliv., etc.^[29]

With the development of anti-inflammatory and analgesic pharmacological studies of natural products, the anti-inflammatory or immune effects of natural products play a leading role in the treatment of rheumatoid arthritis.^[30,31] A large number of experimental studies have shown that natural products exert anti-rheumatoid arthritis effects through various mechanisms. Cytokines,^[32-34] FLS,^[35] and signal transduction pathways^[36,37] may be the inhibitory targets of natural products in the treatment of rheumatoid arthritis.^[38-42] At the same time, some basic pharmacological data of the anti-rheumatoid arthritis effect of natural products were provided for future research.

4.3. Research trends

The keywords of the literature are the core summary of the research content, and the research trend refers to the collection

and direction of the research content in a specific time and specific environment, so the analysis of keywords is very necessary. Through the visual analysis of keywords, we found that the research on the treatment of arthritis with natural products mainly focused on rheumatoid arthritis, signal pathway expression, cells and other aspects.^[43] According to the keyword evolution map, NF-kappa B^[44-48] is expected to become a research hotspot in the treatment of arthritis. However, previous studies mostly used in vitro cell experiments, and there is still a big gap between the experimental models and animal models and clinical reality. At present, there are still many unsolved mechanisms of natural products in the treatment of arthritis. With the development of global science and technology, exploring the molecular mechanism^[49,50] of natural drugs in the treatment of arthritis and modifying the structure of natural drugs to make them more suitable for clinical reference may become the focus of research.

4.4. Limitations

Some limitations should be explained in our study. On the one hand, data were only extracted from the Web of Science core

collection database, and articles published in other sources (such as PubMed and Scopus) may be omitted. On the other hand, only English articles were included in the database, which may lead to source bias.

5. Conclusion

The research potential of natural drugs in the treatment of arthritis is huge and the application prospect is broad. This paper adopts the method of literature measurement to analyze the research status of natural drugs in the treatment of arthritis, research direction and hot spots, etc. The number of articles published in this field is increasing every year, proving that people are paying more and more attention to it, by comparing h-index citations per publication and other indicators, we find that each country has its own advantages in this research field. In addition, the visualization analysis results of the author and the cited author show that the domestic cooperation intensity is much higher than the international cooperation intensity. Therefore, in order to better promote the development of this field, the cooperative relationship between countries can be strengthened. Through keyword analysis, it is speculated that the future of kaempferol treatment of arthritis may be a new starting point for the study. In short, the study of natural products in the treatment of arthritis is only started, although there are many deficiencies need to be improved, but it has great potential and needs further exploration by future scholars.

Author contributions

Conceptualization: Junying Pan, Yinghua Chen.
Formal analysis: Junying Pan.
Investigation: Junying Pan, Haoyu Wang.
Methodology: Junying Pan, Yinghua Chen.
Visualization: Junying Pan, Yinghua Chen.
Writing: Junying Pan, Yinghua Chen, Haoyu Wang.

References

- [1] Silman AJ. Epidemiology and genetics of rheumatoid arthritis. *Arthritis Res Ther.* 2002;4:1–8.
- [2] Ayesha J, G.Y M, Carolina A, et al. Incidence and progression of ankle osteoarthritis: the Johnston county osteoarthritis project. *J Seminars Arthritis Rheumatism.* 2021;51:230–5.
- [3] Kilic G, Ozgocmen S. Hand bone mass in rheumatoid arthritis: a review of the literature. *J World J Orthopedics.* 2015;6:106–16.
- [4] Guo Q, Wang Y, Xu D, et al. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. *J Bone Res.* 2018;6:107–20.
- [5] Zhao J, Chen X, Ho K-H, et al. Nanotechnology for diagnosis and therapy of rheumatoid arthritis: evolution towards theranostic approaches. *J Chin Chem Lett.* 2021;32:66–86.
- [6] Ahmed S, Pakozdi A, Koch AE. Rheumatology, regulation of interleukin-1 β -induced chemokine production and matrix metalloproteinase 2 activation by epigallocatechin-3-gallate in rheumatoid arthritis synovial fibroblasts. *Arthritis Rheumatism.* 2006;54:2393–401.
- [7] Chang SH, Choi Y, Park JA, et al. Anti-inflammatory effects of BT-201, an n-butanol extract of *Panax notoginseng*, observed in vitro and in a collagen-induced arthritis model. *Clin Nutr.* 2007;26:785–91.
- [8] Ghosh S, Banerjee S, Sil PC. The beneficial role of curcumin on inflammation; diabetes and neurodegenerative disease: a recent update. *Food Chem Toxicol.* 2015;83:111–24.
- [9] Devi KP, Malar DS, Nabavi SF, et al. Kaempferol and inflammation: from chemistry to medicine. *Pharmacol Res.* 2015;99:1–10.
- [10] Wei Yu F, Yu Ting T, Tzu Ying L et al. Triptolide prevents lipopolysaccharide-induced skeletal muscle atrophy via inhibiting NF- κ B/TNF- α and regulating protein synthesis/degradation pathway. *Br J Pharmacol.* 2021;178:2998–3016.
- [11] Wang L, Gong L, Zhang X, et al. Tripterygium wilfordii Hook F. in the treatment of synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: a clinical trial. *J Clin Rheumatol.* 2021;40:2427–38.
- [12] Wenli D, Wenqiang Y, Xi L, et al. Effectiveness of curcuma longa extract versus placebo for the treatment of knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *J Phytother Res.* 2021;35:5921–35.
- [13] Shubha S, Nazer H, Kirti N, et al. Bioavailable turmeric extract for knee osteoarthritis: a randomized, non-inferiority trial versus paracetamol. *J Trials.* 2021;22:1–11.
- [14] Huh J-E, Baek Y-H, Lee J-D, et al. Therapeutic effect of *Siegesbeckia pubescens* on cartilage protection in a rabbit collagenase-induced model of osteoarthritis. *J Pharmacol Sci.* 2019;107:317–28.
- [15] Jianting W, Jian L, Xin W, et al. Triptolide promotes the apoptosis and attenuates the inflammation of fibroblast-like synoviocytes in rheumatoid arthritis by down-regulating lncRNA ENST00000619282. *J Phytother Res.* 2021;35:4334–46.
- [16] Binghua G, Feng Q, Yonghua L, et al. Triptolide laden reduced graphene oxide transdermal hydrogel to manage knee arthritis: in vitro and in vivo studies. *J Biomaterials Sci.* 2021;32:1288–1300.
- [17] Qing Q, Qian L, Hongwen Z, et al. Triptolide analogue LLDT-8 ameliorates psoriasis-like dermatitis in BALB/c mice via suppressing the IL-36 α signaling pathway. *J Pharmacol Res.* 2021;169:105678.
- [18] Wang Y. Tripterygium monosodium urate crystal-induced gouty arthritis by altering macrophage polarization via the miR-449a/NLRP3 axis. *J Inflammation Res.* 2021;70:323–41.
- [19] Li X, Wei W, Zhao Z, Lv S. Tripterygium up-regulates miR-223 to alleviate lipopolysaccharide-induced damage in murine chondrogenic ATDC5 cells. *Int J Immunopathol Pharmacol.* 2019;33:2058738418824521.
- [20] Yang J, Li TX, Wang XY, et al. [Systematic reviews of effects of tripterygium glycosides tablets on pro-inflammatory factors in rheumatoid arthritis]. *J Zhongguo Zhong Yao Za Zhi.* 2020;45:764–74.
- [21] Li JM, Jiang Q, Tang XP, et al. [Study advances in regulation effect of Tripterygium wilfordii and its extracts on innate immune system in rheumatoid arthritis cases]. *J Zhongguo Zhong Yao Za Zhi.* 2019;44:3384–90.
- [22] Chen C. Searching for intellectual turning points: Progressive knowledge domain visualization. *Proc Natl Acad Sci USA.* 2004;101(suppl 1):5303–10.
- [23] Chen C. Technology, CiteSpace II: detecting and visualizing emerging trends and transient patterns in scientific literature. *J Am Soc Inf Sci Technol.* 2006;57:359–77.
- [24] Chen C, Ibekwe-SanJuan F, Hou J. The structure and dynamics of cocitation clusters: a multiple-perspective cocitation analysis. *J Am Soc Inf Sci Technol.* 2010;61:1386–409.
- [25] Yu Y, Li Y, Zhang Z, et al. A bibliometric analysis using VOSviewer of publications on COVID-19. *J Annal Translational Med.* 2020;8:816.
- [26] Lv QW, Zhang W, Shi Q, et al. Comparison of Tripterygium wilfordii Hook F with methotrexate in the treatment of active rheumatoid arthritis (TRIFRA): a randomised, controlled clinical trial. *Ann Rheum Dis.* 2015;74:1078–86.
- [27] Shi YL, Bai JP, Wang WP. Ion-channels in human sperm membrane and contraceptive mechanisms of male antifertility compounds derived from Chinese traditional medicine. *Acta Pharmacol Sin.* 2003;24:22–30.
- [28] Zhen QS, Ye X, Wei ZJ. Recent progress in research on Tripterygium: a male antifertility plant. *Contraception.* 1995;51:121–9.
- [29] Liu S-T, Yu H, Hou A-J, et al. A review of the pharmacology, application, ethnopharmacology, phytochemistry, quality control, processing, toxicology, and pharmacokinetics of *Paridis Rhizoma*. *World J Traditional Chin Med.* 2022;8:21.
- [30] Lü S, Wang Q, Li G, et al. The treatment of rheumatoid arthritis using Chinese medicinal plants: from pharmacology to potential molecular mechanisms. *J Ethnopharmacol.* 2015;176:177–206.
- [31] McInnes IB, Schett G. Pathogenetic insights from the treatment of rheumatoid arthritis. *The Lancet.* 2017;389:2328–37.
- [32] Cheng HL, Guo J. Research progress on the balance of Th1/Th2 cytokines and rheumatoid arthritis. *Jilin Med J.* 2006;03:334–6.
- [33] Choi EM, Lee YS. Luteolin suppresses IL-1 β -induced cytokines and MMPs production via p38 MAPK, JNK, NF- κ B and AP-1 activation in human synovial sarcoma cell line, SW982. *Food Chem Toxicol.* 2010;48:2607–11.
- [34] Song CY, Zeng X, Wang Y, et al. Sophocarpine attenuates toll-like receptor 4 in steatotic hepatocytes to suppress pro-inflammatory cytokines synthesis. *J Gastroenterol Hepatol.* 2015;30:405–12.
- [35] Huang H, Xiao Y, Lin H, et al. Increased phosphorylation of ezrin/radixin/moesin proteins contributes to proliferation of rheumatoid fibroblast-like synoviocytes. *Rheumatology.* 2011;50:1045–53.
- [36] Vaddi K, Luchi M. JAK inhibition for the treatment of rheumatoid arthritis: a new era in oral DMARD therapy. *Expert Opin Investig Drugs.* 2012;21:961–73.

- [37] Xu H, He Y, Yang X, et al. Anti-malarial agent artesunate inhibits TNF- α -induced production of proinflammatory cytokines via inhibition of NF- κ B and PI3 kinase/Akt signal pathway in human rheumatoid arthritis fibroblast-like synoviocytes. *Rheumatology*. 2007;46:920–6.
- [38] Wang QH, Li Y, Dou DY, et al. Nicotinamide mononucleotide-elicited NAMPT signaling activation aggravated adjuvant-induced arthritis in rats by affecting peripheral immune cells differentiation. *J Int Immunopharmacol*. 2021;98:107856.
- [39] Hecquet S, Totoson P, et al. Intestinal permeability in spondyloarthritis and rheumatoid arthritis: a systematic review of the literature. *J Seminars Arthritis Rheumatism*. 2021;51:712–8.
- [40] Jun Y, Yanping H, Meimei L, et al. [N-acetylcysteine inhibits the proliferation of hydrogen peroxide treated fibroblast-like synoviocytes in rats with adjuvant arthritis (AA) via blocking Nrf2/Keap1 pathway]. *J Xi bao yu fen zi mian yi xue za zhi*. 2021;37:687–92.
- [41] Pei H, Sen DZ, Shuang Z, et al. The effects of miR-26b-5p on fibroblast-like synovial cells in rheumatoid arthritis (RA-FLS) via targeting EZH2. *J Tissue Cell*. 2021;72:101591.
- [42] Li DW, Wang XT, Mu BC, et al. Effects of hydroxysafflor yellow A on rats with collagen-induced arthritis. *J Biochem Biophys Res Commun*. 2021;570:26–34.
- [43] Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet (London, England)*. 2016;388:2023–38.
- [44] Klein B. Positioning NK- κ B in multiple myeloma. *Blood*. 2010;115:3422–4.
- [45] Luo H, Vong CT, Tan D, et al. Panax notoginseng Saponins modulate the inflammatory response and improve IBD-like symptoms via TLR/NF- κ B and MAPK signaling pathways. *Am J Chin Med*. 2021;49:925–39.
- [46] Proteins - Transcription Factors. Findings from Wuhan University Has Provided New Data on Transcription Factors (Conjugated Linoleic Acid Attenuates 2,4-dinitrofluorobenzene-induced Atopic Dermatitis In Mice Through Dual Inhibition of Cox-2/5-lox and Tlr4/nf-kappa B Signaling). *J Chem Chem*. 2020;81:108379.
- [47] Ma R, Chen Q, Li H, et al. Extract of *Oenothera biennis* L. stem inhibits LPS-induced inflammation by regulating MAPK and NF- κ B signaling pathways. *Pak J Pharm Sci*. 2020;33:1473–81.
- [48] Tan S, Liu H, Wang Y, et al. The molecular mechanisms associated with the effects of propofol in a rat model of pain due to inflammation following injection with complete Freund's adjuvant. *J Med Sci Monitor*. 2019;25:10190.
- [49] Honma M, Hayashi K. Psoriasis: recent progress in molecular-targeted therapies. *J Dermatol*. 2021;2746:761–77.
- [50] Yan BZ, Luo D, Li JC, et al. Molecular mechanism of Wutou Decoction in the treatment of osteoarthritis: a bioinformatics and molecular docking study. *Ann Palliat Med*. 2021;10:7706–20.