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## Bibliometric analysis of traditional Chinese medicine in the treatment of inflammatory bowel disease

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### KEYWORDS

bibliometric analysis;  
CiteSpace;  
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traditional Chinese  
medicine;  
VOSviewer

### Abstract

**Objective:** This study conducts a bibliometric analysis of literature on the treatment of inflammatory bowel disease (IBD) with traditional Chinese medicine (TCM) to explore its research status, hotspots, and development trends, providing ideas and references for further research. **Method:** We screened literature for treating IBD with TCM from the Web of Science Core Collection (WOSCC), and used the VOSviewer software (1.6.18) to discover cooperation among countries, institutions, authors, and information on journals, keywords, etc. We use the CiteSpace software (6.2.R2) to analyze co-citation and burst discovery of references.

**Results:** In all, 440 relevant literature papers were searched and screened from the WOSCC database. The results showed that the number of publications concerning treating IBD with TCM has shown a significant growth in the past decade. China is far ahead in terms of article output, occupying a dominant position. The institution with the most published articles is Nanjing University of Traditional Chinese Medicine. The authors who have published most of the articles are Dai Yancheng, Shi Rui, and Zhou Lian. The *Journal of Ethnopharmacology* published maximum articles in this field, while *Gastroenterology* was the most cited journal. Ungaro et al.'s article entitled "Ulcerative colitis" ([https://doi.org/10.1016/S0140-6736\(16\)32126-2](https://doi.org/10.1016/S0140-6736(16)32126-2)), published in *The Lancet* in 2017 was the most cited study. The high-frequency keywords mainly include ulcerative colitis, inflammation, NF- $\kappa$ B, expression, traditional Chinese medicine, gut microbiota, activation, mice, cells, etc.

**Conclusions:** The research heat for treating IBD with TCM has risen over the past decade, with studies focusing on three main aspects: clinical studies of TCM, basic pharmacology, and animal experimental research. The research hotspot shifted from pathogenesis, clinical study of TCM, basic pharmacology, and complementary therapies to the study of network pharmacology and the mechanism of action of TCM related to gut microbiota. Network pharmacology and gut microbiota are at the frontiers of research and turning to be the future research trends to provide new insights and ideas for further research for treating IBD with TCM.

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## Introduction

Inflammatory bowel disease (IBD) is a chronic immune-related disease, which mainly includes Crohn's disease and ulcerative colitis, with increasing incidences in recent years. This increase may be partly real, as Asia has become one of the fastest-growing regions in terms of IBD incidences with increasing work-life stress and a progressively more westernized diet; however, it may also be related to an increase in awareness and/or diagnostic resources, especially in developing countries, such as the first case discovered in Central Asia: a case of pediatric ulcerative colitis in Kazakhstan.<sup>1</sup> IBD is prevalent in the younger population, but can start at any age, and its recurrent and intractable nature can be very damaging to the health of both children and adults. The symptoms of IBD include diarrhea, abdominal pain, hematochezia, weight loss, etc.<sup>2</sup> Although the etiology of IBD is not fully understood, its pathogenesis is known to be related to irregular immune responses, gut microbiota, genetics, and environmental factors.<sup>3,4</sup> In the treatment of IBD, traditional Chinese medicine (TCM) has shown great therapeutic potential. For example, the compound *Sophora flavescens* (Kushen) had shown similar response rates as that of conventional therapies in the clinical treatment of ulcerative colitis.<sup>5</sup>

In 1969, Pritchard<sup>6</sup> was first to describe bibliometrics as a mathematical and statistical technique for examining literature, books, etc. This method, as a practical and effective literature analysis, has been widely applied in numerous scientific disciplines.<sup>7</sup> Over the past decades, more and more studies in the field of TCM therapy for IBD have been published. However, no literature has systematically assessed the published relevant literature. Bibliometrics allowed quantitative analysis of a large body of literature in a specific research area using mathematical and statistical methods to reveal numerous aspects and research trends in the field.<sup>8,9</sup> Therefore, the advantage of bibliometric analysis is that it allows scholars to understand hot topics, co-authorship, co-citation, and development situation in a certain field, laying a solid foundation for promoting the development of a certain field. Currently, CiteSpace,<sup>10</sup> VOSviewer,<sup>11</sup> and HistCite<sup>12</sup> are mainly used for scientific quantitative analysis of literature. This method has been used by numerous researchers to evaluate their respective research fields.<sup>13-15</sup>

In order to draw a scientific knowledge graph, CiteSpace and VOSviewer were utilized in this study to assess the literature pertaining to TCM treatment of IBD. This study sought to identify new hotspots and subjects while examining the evolution and development trend of research hotspots on the treatment of IBD with TCM from 2002 to 2023. This study was intended to offer new insights and ideas for further research on the treatment of IBD with TCM.

## Materials and Methods

### Data sources and retrieval strategies

All data for this study were retrieved from WOSCC (including SCI-EXPANDED) on June 6, 2023. The specific search strategy used is as follows:

#1: TS = Traditional Chinese Medicine OR TCM OR Traditional Medicine, Chinese OR Chinese Medicine, Traditional OR Medicine, Chinese Traditional OR Chinese herbal medicine OR Drugs, Chinese Herbal OR Chinese patent drugs OR classical prescriptions OR proved recipes OR decoctions OR Chinese medical formula OR (Syndrome AND TCM) OR (Syndrome Differentiation AND TCM) OR integrated traditional Chinese and Western medicine

#2: TS = Inflammatory bowel disease OR IBD OR Crohn disease OR Crohn's disease OR "ulcerative colitis" OR "Colitis, Ulcerative").

#3: #1 and #2

In all, 698 articles were obtained. Next, they were screened by the following exclusion criteria: (a) duplicate reports; (b) conference abstracts; (c) book chapters; (d) revisions, editorial material; (e) reviews and meta-analysis of literature; and (f) predominantly about other diseases. The studies were screened, checked, and confirmed by two independent researchers. Finally, 440 references were included and full record and cited references were exported in a plain text file format.

### Data analysis

We saved the extracted data file in "txt" format and named it as "download\_1-440.txt." Subsequently, we used the VOSviewer software, developed in collaboration with two young scholars, Nees Jan van Eck and Ludo Waltman, of Leiden University, the Netherlands, to visualize the published data, and to analyze countries, institutions, and authors as well as journals, keywords, etc. CiteSpace, developed by Prof. Chao-Mei Chen, was used to perform analyses, such as reference co-citation and reference citation bursts.

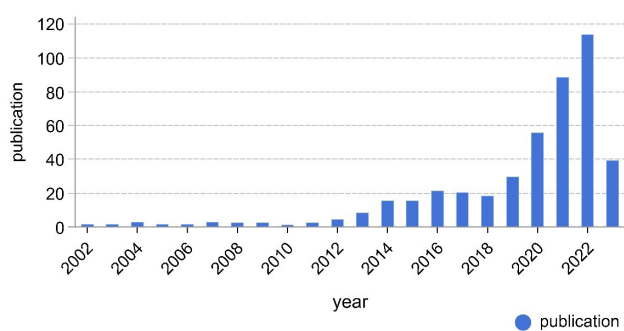
## Results

### Results of literature search

In all, 698 relevant articles were retrieved in the WOSCC database, and those not meeting the requirements were removed according to exclusion criteria and manual screening. Finally, 440 articles were included.

### Analysis of annual number of publication

As shown in [Figure 1](#), the annual publication volume in this research field was divided into three stages: (1) The embryonic stage (2002-2012): the publication volume was small; (2) slow growth stage (2013-2018): the annual publication



**Figure 1** Distribution map of annual publication volume of literature.

volume began to show slow growth; and (3) steep increased stage (after 2019): the annual publication volume showed a rapid growth trend and reached its peak in 2022, with 113 articles. It was observed that the overall number of publications in this field was rising, especially in the past decade, which has attracted more and more attention, indicating that the research heat of TCM for treating IBD was rising continuously.

### Country and institutional analysis

We carefully analyzed the screened literature using the VOSviewer software. In 20 years (2002 to 2023), 22 countries or regions and 499 institutions participated in research on treating IBD with TCM. Among these, China had the largest volume of publications (397 articles), followed by the United States (27 articles) and Japan (13 articles) (Table 1). Figure 2A shows the national cooperation network, which clearly established cooperation between 12 countries or regions, and China had cooperation with other 11 countries or regions. It could be seen that China was the most active, productive, and influential county in this field.

In addition, in terms of paper publication, Nanjing University of Traditional Chinese Medicine had the highest number of papers (38 papers), followed by Shanghai University of Traditional Chinese Medicine (36 papers), Guangzhou University of Traditional Chinese Medicine (33 papers), Beijing University of Traditional Chinese Medicine (24 papers), and Chengdu University of Traditional Chinese Medicine (20 papers) (Table 2). The cooperation between universities was also relatively strong (Figure 2B). In terms of co-cited papers, Shanghai University of Traditional Chinese Medicine had a higher frequency of citations,

**Table 1** Top five active countries/regions.

Country	Documents	Citations	Total link strength
China	397	5392	39
USA	27	617	25
Japan	13	320	3
Taiwan	8	68	0
South Korea	5	34	0

reaching 584 times, followed by China University of Pharmacy (547 times) and Nanjing University of Traditional Chinese Medicine (511 times) (Table 3). The co-citation network of these institutions is shown in Figure 2C.

### Analysis of authors

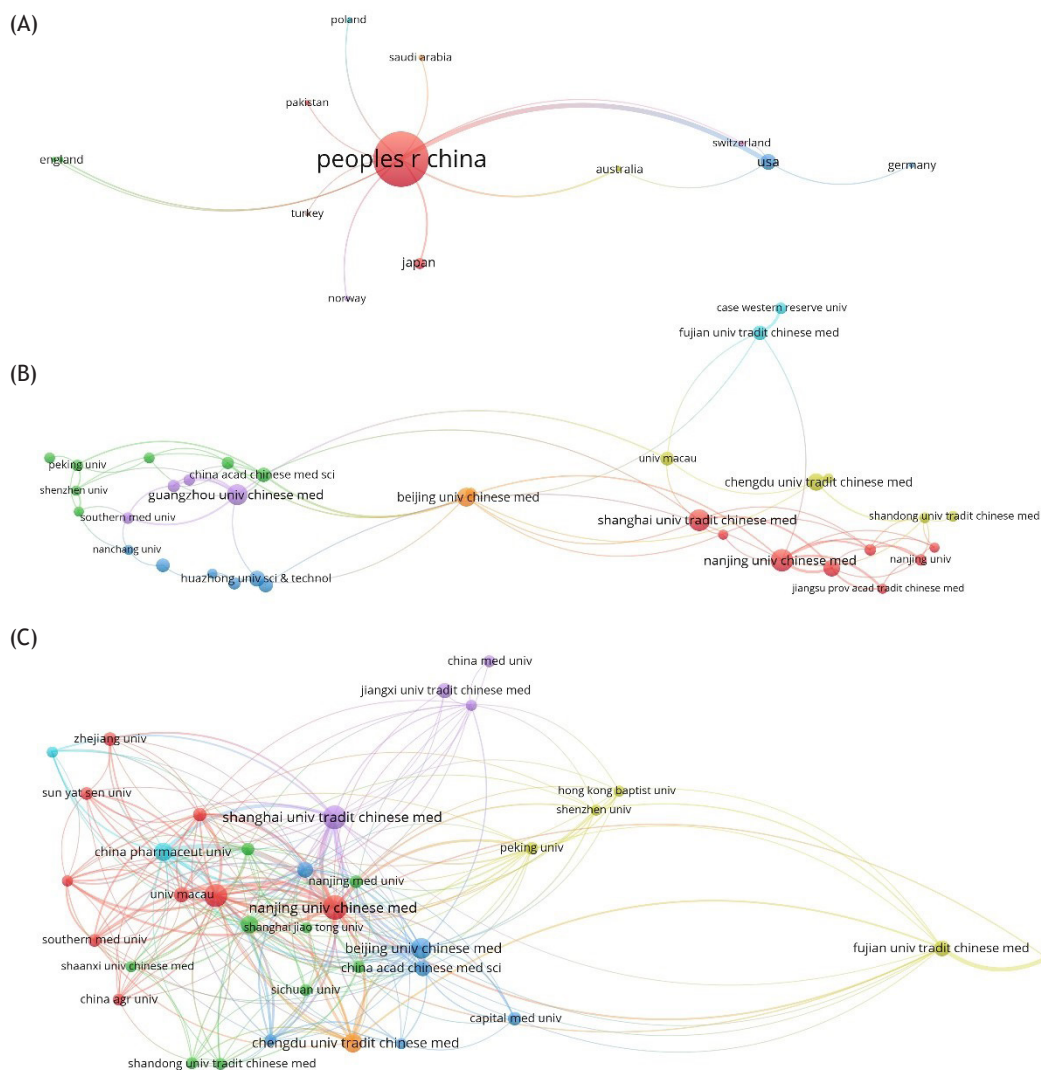
In terms of the number of published studies, Dai Yancheng, Shi Rui, and Zhou Lian were the top three authors with most of the published papers, with each of them having nine published papers in this field (Table 4). Figure 3A shows the author collaboration network diagram drawn by VOSviewer. Table 5 shows the top five authors in terms of total citations. According to the frequency of author citation, SC Ng ranked first (91 citations), followed by R. Ungaro (85 citations), MF Neurth (73 citations), I. Zhu (48 citations), and S. Wirtz (43 citations). Figure 3B shows the co-cited author network.

### Analysis of journals and co-cited journals

In all, 128 academic journals published articles on the application of TCM in the treatment of IBD, among which the *Journal of Ethnopharmacology* (66 articles, IF 2023 = 5.4) ranked first, followed by the *Evidence-Based Complementary and Alternative Medicine* (38 articles, IF 2023 = 1.8), and the third was the *Frontiers in Pharmacology* (35 articles, IF 2023 = 5.6). Table 6 shows the top five journals in terms of number of publications, and Figure 4A shows the collaboration of high-frequency journals with  $\geq 5$  publications. Meanwhile, we also analyzed the cited journals and found that *Gastroenterology*, *Journal of Ethnopharmacology*, and *Inflammatory Bowel Diseases* were the most cited journals, with 590, 559, and 441 citations, respectively (Table 7). Figure 4B demonstrates the creation of a visual network to analyze co-cited journals, where the node size was proportional to the number of citations, and *Gastroenterology* and *Journal of Ethnopharmacology* had maximum impact on the development this field.

### Analysis of co-cited references and reference citation bursts

We used CiteSpace to analyze the literature for co-citations from 2002 to 2023. As shown in Table 8, "Ulcerative colitis" was the most frequently cited reference, with 74 citations.<sup>16</sup> The second was "Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies," with 50 citations.<sup>17</sup> In addition, CiteSpace provided a burst detection feature, where we discovered reference citation bursts between 2002 and 2023 (Figure 5A) and found that the article entitled "Ulcerative colitis" by Taku et al.<sup>18</sup> in *Nature Reviews Disease Primers* had the highest citation burst value during 2022-2023, which was the strongest burst. In addition, a number of studies had experienced citation surge in recent years. While these references were further clustered, a timeline chart was created to show research process in the discipline (Figure 5B). As shown in Figure 5B,



**Figure 2.** (A) Network of country cooperation; (B) network of organizations cooperation; (C) network of co-cited organizations.

**Table 2** Top five active organizations.

Organization	Documents	Citations	Total link strength
Nanjing University of Chinese Medicine	38	511	24
Shanghai University of Traditional Chinese Medicine	36	584	8
Guangzhou University of Chinese Medicine	33	501	18
Beijing University of Chinese Medicine	24	223	14
Chengdu University of Traditional Chinese Medicine	20	77	5

the largest clustering in this study was #0 network pharmacology, followed by #1 qing-dai, #2 intestinal flora, #3 Jianqi qingchang decoctin, #4 semi-quantitative rt-cpr, #11 ayurveda, #14 permeability, #16 mitogen-activated protein kinase, and #21 costus root granules.

### Keyword analysis

Based on VOSviewer to create a keyword co-occurrence map, combined with the TOP 10 keyword list (Table 9), we

found that main keywords in the field of research on IBD treatment with TCM from 2002 to 2023 were ulcerative colitis, inflammatory bowel disease, inflammation, NF- $\kappa$ B, expression, traditional Chinese medicine, gut microbiota, activation, mice, cells, and so on. Figure 6 shows the keyword overlay time view, which combined keywords with the time factor, with different colors representing different periods of keyword appearance: blue representing earlier appearances, such as Crohn's disease, and yellow representing more recent appearances, such as gut microbiota.

Table 3 Top five organizations with most of citations.

Organization	Documents	Citations	Total link strength
Shanghai University of Traditional Chinese Medicine	36	584	113
China Pharmaceutical University	17	547	111
Nanjing University of Chinese Medicine	38	511	173
Guangzhou University of Chinese Medicine	33	501	122
China Agricultural University	6	295	18

Table 4 Top five active authors.

Author	Documents	Citations	Total link strength
Dai Yancheng	9	134	20
Shi Rui	9	120	19
Zhou Lian	9	196	7
Fan Heng	8	178	5
Chen Youqin	7	69	25

### Discussion

Traditional Chinese medicine in the treatment of IBD has developed rapidly in the last decade, and the research fervor has continued to increase, with a total of 22 countries or regions participating in this research. China is the country with the largest number of publications, and Dai Yancheng, Shi Rui, and Zhou Lian are the authors with the largest number of relevant publications. The *Journal*

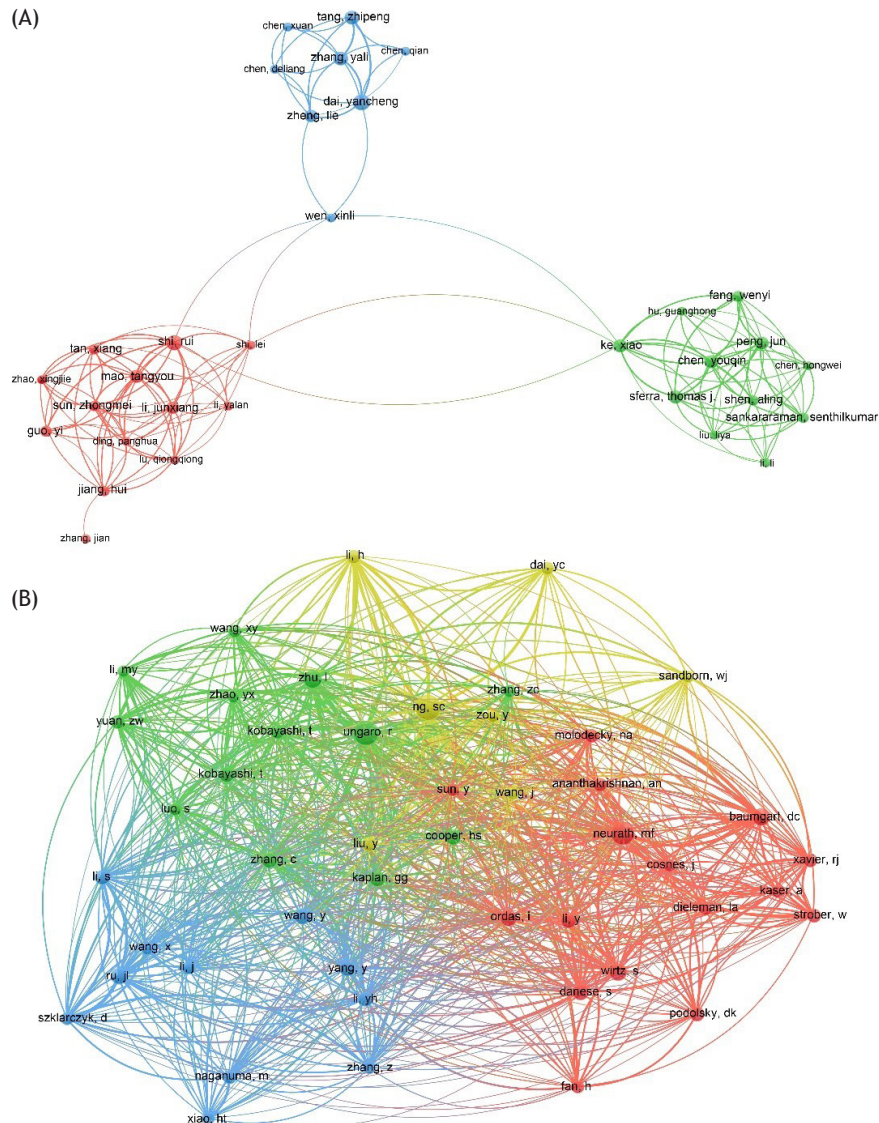


Figure 3. (A) Network of authors' cooperation; (B) network of co-cited authors.

Table 5 Top five authors with most of citations.

Author	Citations	Total link strength
SC Ng	91	416
R. Ungaro	85	379
MF Neurth	73	308
I. Zhu	48	269
S. Wirtz	43	180

of *Ethnopharmacology* and *Gastroenterology* are the two journals that had the greatest impact on the development of the field. The research mainly focused on three aspects, such as clinical studies of traditional Chinese medicine, basic pharmacology, and animal experiments. The research hotspots changed from studies on pathogenesis, clinical studies of traditional Chinese medicine, basic pharmacology, and complementary therapies to studies on network pharmacology and the mechanism of action of traditional

Table 6 Top five journals with most of published papers.

Source	Documents	Citations	Total link strength
<i>Journal of Ethnopharmacology</i>	66	1109	140
<i>Evidence-Based Complementary and Alternative Medicine</i>	38	234	101
<i>Frontiers in Pharmacology</i>	35	406	92
<i>Phytomedicine</i>	24	272	70
<i>Biomedicine &amp; Pharmacotherapy</i>	12	261	47

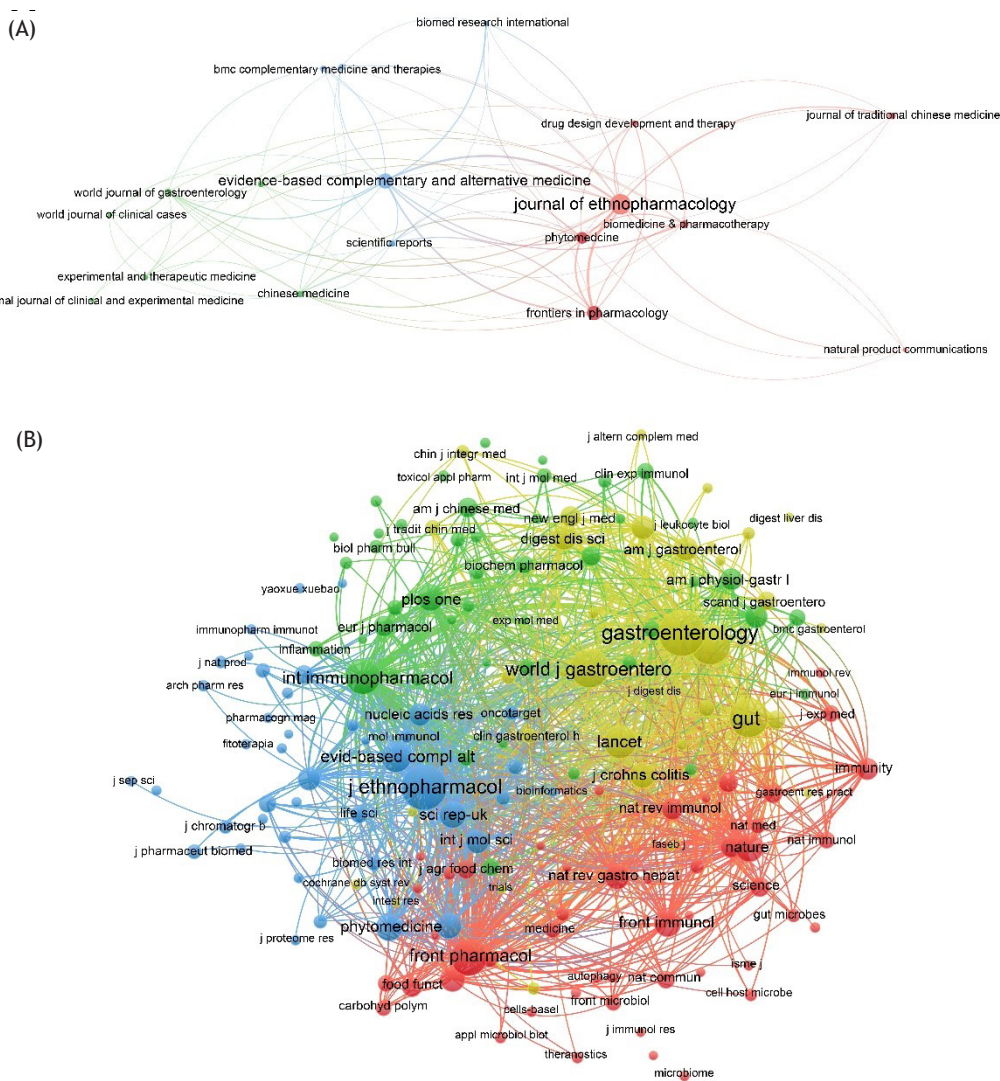


Figure 4 (A) Network of journals cooperation; (B) network of co-cited journals.

Table 7 Top five journals with most of citations.

Source	Citations	Total link strength
<i>Gastroenterology</i>	590	17,714
<i>Journal of Ethnopharmacology</i>	559	17,692
<i>Inflammatory Bowel Diseases</i>	441	14,402
<i>Gut</i>	416	13,243
<i>World Journal Of Gastroenterology</i>	406	12,743

Chinese medicines related to gut microbiota. Network pharmacology and gut microbiota are the research frontiers in this field and may become the future research trends.

Inflammatory bowel disease is a chronic inflammatory disease of the intestine whose pathogenesis is not understood completely.<sup>19</sup> Currently available treatment options mainly include pharmacological interventions, such as aminosalicylates, corticosteroids, immunomodulators, antibiotics, probiotics, biologics, small molecule drugs, etc., as well as surgical procedures.<sup>20,21</sup> Owing to the incurable

Table 8 Top five references with most of citations.

Citations count	References	DOI	Centrality
74	Ungaro et al., 2017, <i>The Lancet</i> , V389, P1756	10.1016/S0140-6736(16)32126-2	0.04
50	Ng et al., 2017, <i>The Lancet</i> , V390, P2769	10.1016/S0140-6736(17)32448-0	0.03
32	Taku et al., 2020, <i>Nat Rev Dis Primers</i> , V6, P0	10.1038/s41572-020-0205-x	0.02
20	Wirtz et al., 2017, <i>Nat Protoc</i> , V12, P1295	10.1038/nprot.2017.044	0.01
19	Zhu et al., 2019, <i>Int Immunopharmacol</i> , V68, P242	10.1016/j.intimp.2018.12.036	0.01

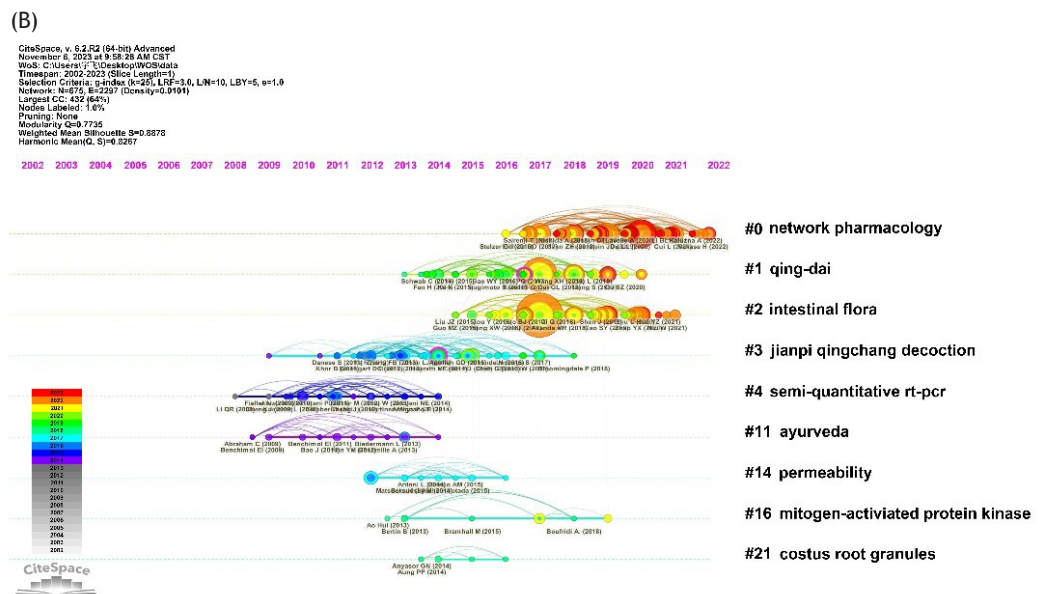
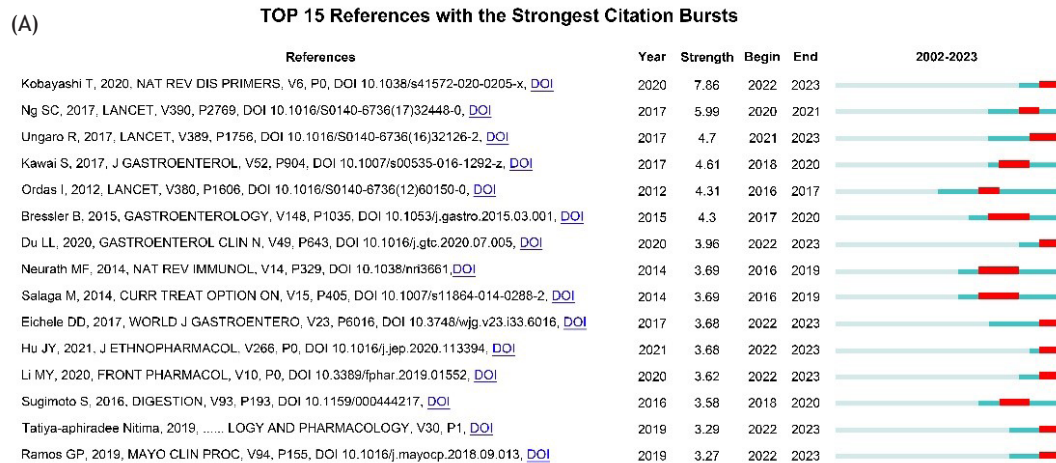


Figure 5 (A) Bursts detection of references; (B) timeline view of references.

characteristic of IBD, the long-term use of western drugs is associated with serious adverse effects, resulting in likely relapse after discontinuation of treatment, and the high cost of westernized treatment also presents a significant challenge for both doctors and patients.<sup>22</sup> On the

other hand, TCM has an important role in preventing and treating IBD that effectively alleviate symptoms, improve immunity, and curb progression of the disease.<sup>23</sup> TCM has unique advantages of having low adverse effects and stable efficacy in the overall treatment and maintenance phases of IBD. For example, the isolated rutaecarpine (RUT), a COX-2 inhibitor isolated from *Evodia rutaecarpa*, could improve dextran sodium sulfate (DSS)-induced IBD and inhibited oxidative stress.<sup>24</sup> In recent years, with increased incidences of IBD, researchers have paid greater attention to its treatment with TCM, and the pace of research has increased with the publishing of many related studies. Faced with an exponential increase in the number of papers, it is a challenge and crucial to have a comprehensive and orderly understanding of this field and maintain sensitivity to research hotspots. Compared to traditional reviews and meta-analyses, bibliometrics has the advantage of displaying research trends and identifying research hotspots.<sup>25</sup> This study has provided the first bibliometric analysis of TCM in the therapeutic field of IBD, showcasing the changes in the knowledge system over the past two decades by highlighting research hotspots and predicting the future research trends.

Table 9 Top 10 keywords.

Keyword	Occurrences	Total link strength
Ulcerative colitis	250	1368
Inflammatory bowel disease	182	1071
Inflammation	88	493
NF-κB	75	504
Expression	65	426
Traditional Chinese Medicine	65	373
Gut microbiota	64	322
Activation	62	401
Mice	53	349
Cells	51	300

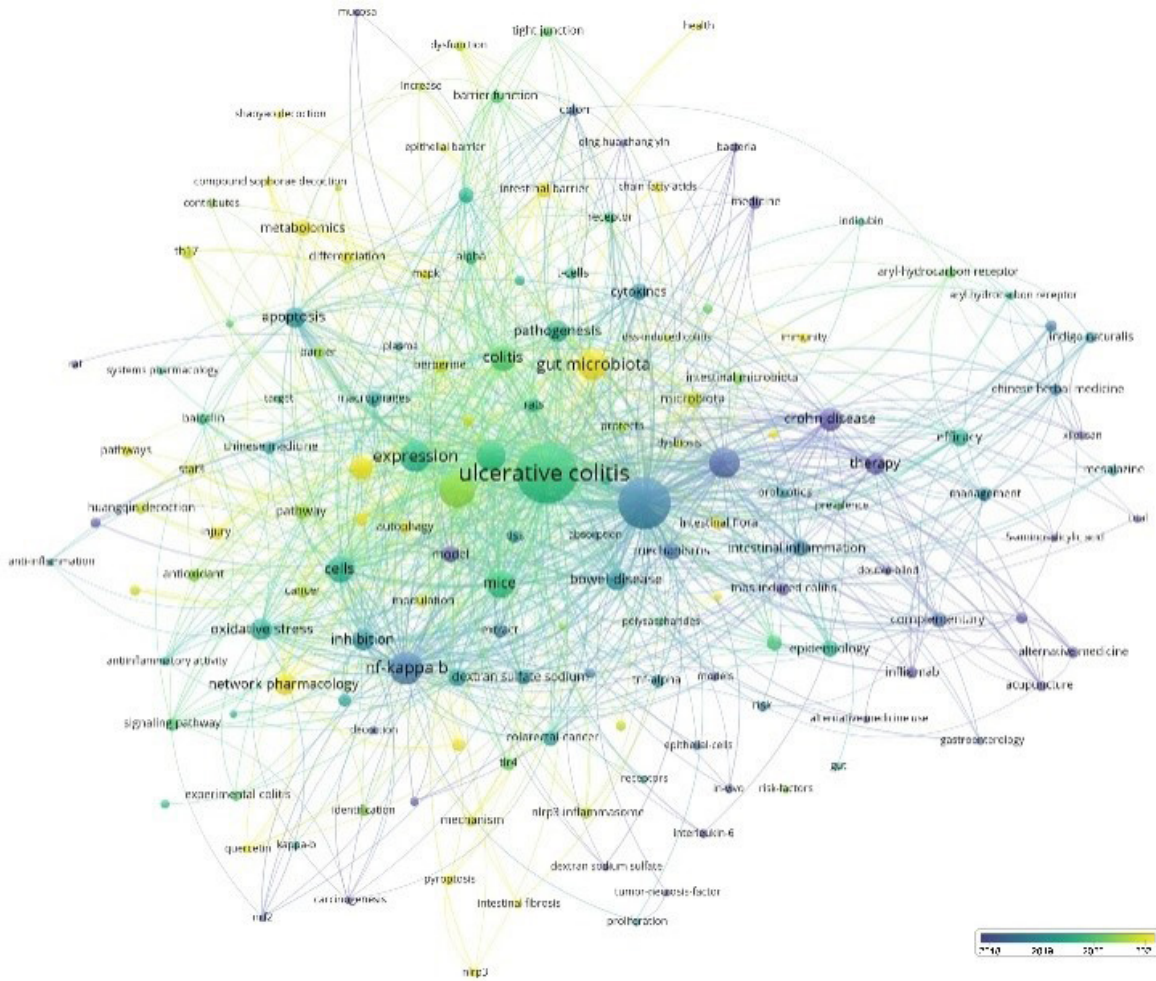


Figure 6 Overlay time view of keywords.



In this study, a bibliometric analysis of 440 articles in the WOSCC database was conducted and the results suggested that the field of TCM in treating IBD has developed rapidly over the past decade. A total of 22 countries or regions and 499 institutions have participated in the study of this subject. In the stated decade, China and the United States have achieved maximum advancements in this field of study. TCM universities in China, such as Nanjing University of Chinese Medicine, Shanghai University of Traditional Chinese Medicine etc., are the institutions that have published maximum research on TCM treatment of IBD. We also discovered cooperation between countries or regions as well as between institutions. Concerning authors, Dai Yancheng, Shi Rui, and Zhou Lian have published most of the papers; and the papers of SC Ng have been cited most frequently. Although the top three authors have contributed most of the research results to the development of this discipline, they are not cited frequently, have received limited attention, and still lack academic influence. This demonstrates that although their research has been active, its quality and depth still required enrichment. Some journals, such as *Journal of Ethnopharmacology* and *Frontiers in Pharmacology*, which focused on the research of drug and pharmacology, contributed most of papers. While top journals, such as *Gastroenterology* and *Inflammatory Bowel Diseases*, dedicated to digestive tract diseases, were the most frequently cited journals, their papers have also attracted the attention of academic community. The *Journal of Ethnopharmacology* and *Gastroenterology* have had the greatest impact on the development of this academic field.

Of note, among the various studies, Ungaro et al.'s paper, "Ulcerative colitis," published in *The Lancet* in 2017, was cited for 74 times,<sup>16</sup> was highly influential, and became an important reference of this field. In addition, CiteSpace's burst detection function detected large changes in the number of citations over specific period, and was used to identify emerging research topics in this field.<sup>26</sup>

We found that Taku et al.'s article, "Ulcerative colitis,"<sup>18</sup> in *Nature Reviews Disease Primers* had the highest citation burst value in 2022-2023, with the strongest emergence and highest impact, and was an important reference in this field. In addition, the citation surge of some studies that appeared during the last 3 years has continued to this day; these studies include "Ulcerative colitis" published in *The Lancet*, "Epidemiology and pathogenesis of ulcerative colitis," "Dextran sodium sulfate colitis murine model: an indispensable tool for advancing our understanding of inflammatory bowel diseases pathogenesis," "Qingchang Huashi (QCHS) formula attenuates DSS-induced colitis in mice by restoring gut microbiota-metabolism homeostasis and goblet cell function," "Anti-inflammatory effects of Huangqin decoction on dextran sulfate sodium-induced ulcerative colitis in mice through regulation of the gut microbiota and suppression of the Ras-PI3K-Akt-HIF-1 $\alpha$  and NF- $\kappa$ B pathways," etc. This suggested that references concerning the pathogenesis of IBD, animal experiments, and the mechanism of action of TCM were frequently cited during the past 3 years, and could be of great interest in the future. All these are important references that constitute the knowledge base of the potential research frontiers of this field.

As shown in the timeline overview in [Figure 5B](#), the clusters that appeared during 2008-2014 and later during 2015-2023 demonstrated that with the passage of time, the hotspot of research has shifted from the earlier research on pathogenesis, clinical research on TCM for treating IBD, and research on pharmacological mechanisms of action related to the regulation of inflammatory factors through signaling pathways, adjuvant therapy research in treating IBD, to network pharmacology, research on pathogenesis related to intestinal flora, and the mechanism of action of Chinese medicine.<sup>27-31</sup>

Among these clusters, #3 Jianpi Qingchang decoction and #1 Qing-dai had a relatively long time span, indicating that the clinical research on the treatment of IBD by TCM had received extensive attention. The largest cluster was #0 Network pharmacology, which indicated that researchers had a strong interest in this topic. Network pharmacology has been utilized to explore the active ingredients of Chinese herbal medicines or compounds to reveal the potential molecular mechanisms for treating IBD. For example, Chinese medicine Jiawei Jianji Tang inhibited inflammation through 15-hydroxyprostaglandin dehydrogenase, 5'AMP-activated protein kinase, interleukin (IL)-2, and macrophage colony-stimulating factor 1 (CSF-1) signaling, thereby exerting a therapeutic effect on IBD.<sup>32</sup>

Based on the strategy of network pharmacology, quercetin, a major component of Huai Hua San, was found to mediate the levels of inflammatory factors and phosphorylated c-Jun, as well as the PI3K-Akt signaling pathway, to play a potential pharmacological mechanism of anti-ulcerative colitis.<sup>33</sup> Therefore, network pharmacology has emerged as an important field of research in the treatment of IBD with herbal medicines.

The two clusters of #0 Network pharmacology and #2 Intestinal flora that emerged in recent years have continued to the present day and with unabated research could be the future research trend of this field.

Finally, the high-frequency keywords of the included literature ([Table 9](#)) were analyzed. Each category of studies was associated with specific terms, for example, the high-frequency keywords, such as "ulcerative colitis," "inflammatory bowel disease," and "traditional Chinese medicine," might be related to clinical studies, and the signaling of "gut microbiota," "inflammation," "NF- $\kappa$ B," "activation," and "expression" could be relevant to basic pharmacology research, and the terms "mice" and "cells" were related to animal experiments. It was observed that the research involving TCM treatment of IBD mainly involved the clinical research of TCM, basic pharmacology research, and animal experimental research. Combined with the keywords overlay time view ([Figure 6](#)), it was found that the nodes with large yellow color in the graph, "intestinal microbiota" and "network pharmacology," were high-frequency keywords that appeared in 2021 and could be the hotspots and the future research trends. This coincided with the research trends predicted by the previous timeline view analysis.

The bibliometric analysis showed the present status, hotspots, and research trends in the field of TCM treatment for IBD. The present study also had some shortcomings. First, we only included English articles, which could have affected the results of the bibliometric

analysis because non-English publications were not examined. Second, we only searched for publications in the WoSCC database, and the WoSCC database may not contain all relevant publications published elsewhere (e.g. PubMed), which might have resulted in some unexpected bias. Third, low citation frequency could be the result of short publication period of some recently emerged high-quality studies. Thus, citation counts did not accurately reflect the quality of a study.

## Conclusions

In order to draw a map of scientific knowledge, CiteSpace and VOSviewer were employed in this study to assess the literature concerning TCM treatment of IBD. This study sought to identify new hotspots and subjects while examining the evolution and development trend of research hotspots in TCM treatment of IBD from 2002 to 2023. It was intended that this study would provide new insights and ideas for the further research on treating IBD with TCM.

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## Competing interests

The authors declared no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

## Ethics approval

This article did not contain any experiments with humans or animals performed by any of the authors.

## Data availability

The authors declared that all data supporting the findings of this study are available in the paper and any raw data can be obtained from the corresponding author upon request.

## Author Contributions

Jing Wang, Xiaona Chen, Min Yuan designed and conducted the study. Min Yuan supervised data collection, and analyzed and interpreted the data. Jing Wang and Xiaona Chen prepared the manuscript for publication, and Min Yuan reviewed the draft of the manuscript. All authors had read and approved the final manuscript.

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