



## Visual analysis of research hotspots and trends in the treatment of immune thrombocytopenia with traditional Chinese medicine

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### ARTICLE INFO

#### Article history

Received 25 July 2022

Accepted 22 August 2022

Available online 25 September 2022

#### Keywords

Immune thrombocytopenia

Traditional Chinese medicine (TCM)

Bibliometrics

Visual analysis

CiteSpace

VOSviewer

Carrot2

Research hotspot

### ABSTRACT

**Objective** Through bibliometrics and visual analysis of the related studies on traditional Chinese medicine (TCM) treatment of immune thrombocytopenia (ITP), this study aims to sort out the overall research progress, hotspots, and trends in this field, and provide reference for further research in ITP.

**Methods** The articles on ITP treated by TCM were retrieved from China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal Database (VIP), Web of Science Core Collection (WOSCC), and PubMed. The retrieval time was from the establishment of the databases to July 31, 2022. VOSviewer, CiteSpace, Carrot2, and Note-Express were used for data analysis of the articles in terms of their quantities, types, and journals, and for visualization of research hotspots, authors, institutions, and keywords.

**Results** 1 493 Chinese articles and 40 English articles were included. The articles in Chinese mainly focus on clinical trial research and clinical experience summary, while the English articles mainly focus on clinical trial research and animal research. The Chinese articles were published in 317 Chinese journals, while English articles were published in 29 English journals. Research hotspots include the clinical syndrome differentiation of ITP, the therapeutic effect of TCM compounds on ITP, and the mechanism of ITP treatment. Keyword analysis shows that there are many research achievements in integrated traditional Chinese and western medicine treatment, clinical research, famous doctors' experience, TCM treatment, cellular immunity, and humoral immunity. The authors with the most articles in Chinese and English are Professor CHEN Xinyi and Professor MA Rou, respectively, and the research institutions with the most articles are Dongzhimen Hospital of Beijing University of Chinese Medicine and Xiyuan Hospital of China Academy of Chinese Medical Sciences. Chinese herbs often used to treat ITP clinically include Xianhecao (*Agrimoniae Herba*), Nvzhenzi (*Ligustri Lucidi Fructus*), Mohanlian (*Ecliptae Herba*), Zhongjiefeng (*Sarcandrae Herba*), etc., and the prescription usually used to treat ITP include Guipi Decoction (归脾汤), Xijiao Dihuang Decoction (犀角地黄汤), Bazhen Decoction (八珍汤), Erzhi Pill (二至丸), and Xiaochaihu Decoction (小柴胡汤). The main development trends toward retrospective study, TCM treatment mechanism, and data mining.

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Peer review under the responsibility of Hunan University of Chinese Medicine.

DOI: 10.1016/j.dcmcd.2022.10.009

**Citation:** GAO Y, WU ZH, WU M, et al. Visual analysis of research hotspots and trends in the treatment of immune thrombocytopenia with traditional Chinese medicine. Digital Chinese Medicine, 2022, 5(3): 326–339.

**Conclusion** The research on TCM treatment of ITP has progressed steadily, but in-depth studies and close cooperation between research institutions are necessary for the modernization of TCM in treating ITP.

## 1 Introduction

Immune thrombocytopenia (ITP) is a hemorrhagic autoimmune disorder characterized by mucosal hemorrhage, visceral hemorrhage, and peripheral thrombocytopenia. The incidence of ITP is about (2 – 5.5)/100 000 people per year, and it is mainly treated with dexamethasone clinically [1, 2]. According to the theory of traditional Chinese medicine (TCM) [3], ITP can be classified as “asthenia” “rash” “blood syndrome” “purpura”, etc. The etiology of ITP is complex, and the pathogenesis is not clear, and it is urgent to explore appropriate treatment. In recent years, a growing number of studies have confirmed that TCM has achieved remarkable results in the treatment of ITP [4–6], and then it is important to use a scientific and objective method to help researchers to find the research hotspots and develop trends in a large number of literatures.

CiteSpace is a kind of information visualization software developed with Java [7]. VOSviewer is a type of software developed by Nees Jan van Eck and Ludo Waltman of Leiden University in the Netherlands, which is based on Java environment for knowledge map visualization and bibliometrics analysis [8]. Carrot2 is an open-source clustering tool based on search results [9]. This study intends to measure and visually analyze the articles published in China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal Database (VIP), Web of Science Core Collection (WOSCC), and PubMed from the establishment of the databases to July 31, 2022, so as to find the research hotspots and trends of TCM treatment of ITP, and provide new ideas for TCM treatment of ITP.

## 2 Data and methods

### 2.1 Data sources

The Chinese articles were sorted out from CNKI, Wanfang, and VIP databases. The retrieval time was from the establishment of the databases to July 31, 2022, and the retrieval scope was journals. Taking CNKI as an example, “topic = immune thrombocytopenic purpura” OR “topic = immune thrombocytopenic” OR “topic = idiopathic thrombocytopenic purpura” OR “topic = ITP” was used as the searching formula and TCM was selected as the retrieval subject.

English articles were sorted out from WOSCC and PubMed, and the retrieval time was from the establishment of the databases to July 31, 2022. Taking WOSCC as an example, “TS = (immune thrombocytopenia OR ITP OR idiopathic thrombocytopenia)” AND “TS = (traditional Chinese medicine OR Chinese material medicine OR decision OR power OR prescription on Chinese medicine)” was used as a searching formula, and the literature type was limited to articles and reviews.

### 2.2 Literature screening criteria

**2.2.1 Inclusion criteria** (i) Literature related to TCM treatment of ITP. (ii) Literature types including clinical trial research, animal research, clinical experience summary, literature research, review, etc. (iii) Application of TCM treatment (TCM preparations, single Chinese herb, acupuncture, etc.). (iv) Articles with complete bibliographic information (including title, author, keywords, and sources).

**2.2.2 Exclusion criteria** (i) Conference papers, newspapers, patents, achievements, etc. (ii) Repeated publications. (iii) Articles including discussion on other diseases, such as diabetes, hypertension, and hepatitis B.

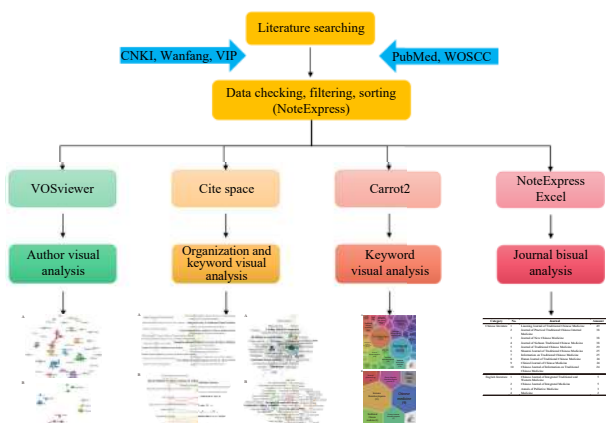
### 2.3 Data collection and conversion

The documents were exported in the format of NoteExpress, and duplicate checking and screening were carried out using NoteExpress (3.6.0.9220). The subordinate institutions of the same institution in the screened literature data are filed under the first-level institution. For example, “Department of Hematology, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine Affiliated to Shanghai University of Traditional Chinese Medicine” was identified as “Yueyang Hospital of Integrated Traditional Chinese and Western Medicine Affiliated to Shanghai University of Traditional Chinese Medicine”, and “Postgraduate Department of Henan University of Traditional Chinese Medicine” was identified as “Henan University of Traditional Chinese Medicine”. Synonyms are also grouped together: “immune thrombocytopenic purpura” “idiopathic thrombocytopenic purpura”, and “primary immune thrombocytopenic purpura” are determined as “immune thrombocytopenia”. Afterwards, the documents were exported as “download\_\*.txt” and

“carrot2.xml” files, respectively. English documents were exported from WOSCC in tab format as “download\_\*.txt” files. Finally, the format of the retrieved documents is converted by the built-in Data Import/Export function of CiteSpace.

## 2.4 Data analysis

VOSviewer 1.6.18 and Carrot2 (<https://search.carrot2.org/>) were used to analyze core author cooperation and keywords, respectively, and then CiteSpace (5.8.R3 and 6.1.R2) was used to visualize the keywords, authors, and organization of the converted data files. The time span in Time Slicing was set from the establishment of the databases to July 31, 2022, for Chinese and English articles, and the slicing frequency was one year per slice. The co-occurrence analysis of Node Types selects keywords and institutions, respectively. The pruning mode is set to the default value. If the initial results of visualization are messy, the pruning mode can be set to path finder to simplify the network and highlight its important structural features, or to minimum spanning tree to make the operation simple and the results fast. Carry out co-occurrence analysis, cluster analysis, and emergent analysis on the included data, generate and adjust the knowledge map, and form visual analysis. The workflow of this study is shown in Figure 1.



**Figure 1** Visualization process of TCM treatment of ITP

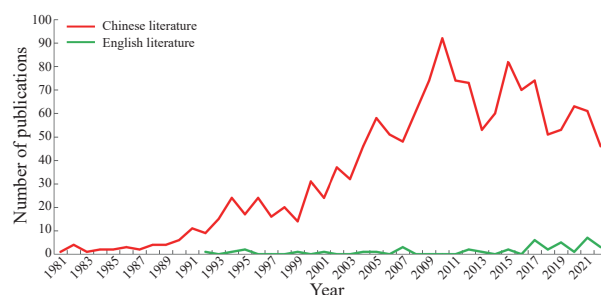
## 3 Results

### 3.1 Literature retrieval and screening results

2 262 Chinese articles (891 from CNKI, 860 from Wanfang, and 511 from VIP) and 137 English articles (71 from WOS CC and 66 from PubMed) were retrieved. After duplicate checking and screening, 1 493 Chinese articles and 40 English articles were obtained.

### 3.2 Annual publication of literature

Analysis of the annual publishing trend of TCM treatment of ITP revealed an upward overall trend (Figure 2). The total number of published Chinese articles is 1 493, with an average annual number of 36. In 1981, the first article on TCM treatment of ITP was published, and the maximum annual number of published articles (92) was reached in 2010. The development in annual publication volume can be divided into three stages: (i) the year from 1981 to 1990 marks the initial stage in which the annual publication volume was less than 10; (ii) the year from 1991 to 2003 indicates a slow growth stage with small increases in the number of published articles; (iii) the year from 2004 to 2022 is a fluctuation period, in which the number of articles published dropped sharply in 2013 and 2018. The total number of published English articles is 40, with the first related article appearing in 1992 and a peak of seven articles published in 2021, but as a whole, the articles published in English were rather few. The classification of Chinese and English articles is shown in Table 1. The Chinese articles are mainly based on clinical trial research and clinical experience summary, while the English ones focus on clinical trial research and animal research.



**Figure 2** Annual publication volume of TCM treatment of ITP

**Table 1** Classification of Chinese and English articles on TCM treatment of ITP

Literature type	Chinese articles	English articles
Clinical experience summary	432	4
Animal research	136	17
Clinical trial research	756	12
Review	130	3
Others	39	4

### 3.3 Analysis of published journal types

Analysis with NoteExpress (3.6.0.9220) showed that the Chinese articles were published in 317 Chinese journals. There are 45 journals publishing more than 10 articles, and the top 10 Chinese journals of publication volume are shown in Table 2. The English articles have been published in 29 journals, among which four journals have published more than or equal to two articles (Table 2).

**Table 2** The top 10 Chinese journals and top four English journals on TCM treatment of ITP

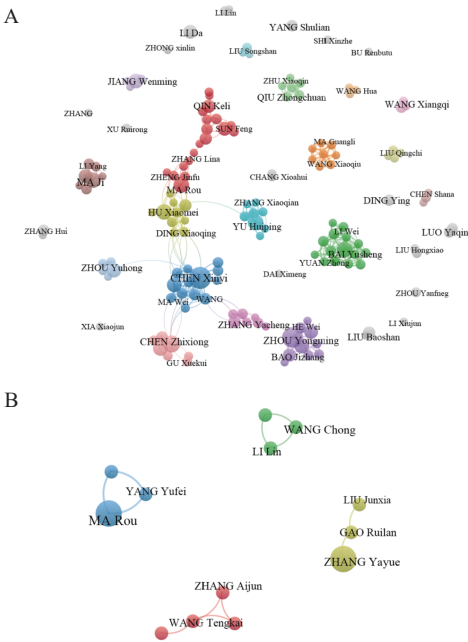
Category	No.	Journal	n
Chinese article	1	Liaoning Journal of Traditional Chinese Medicine	49
	2	Journal of Practical Traditional Chinese Internal Medicine	38
	3	Journal of New Chinese Medicine	38
	4	Journal of Sichuan of Traditional Chinese Medicine	38
	5	Journal of Traditional Chinese Medicine	29
	6	Shaanxi Journal of Traditional Chinese Medicine	25
	7	Information on Traditional Chinese Medicine	25
	8	Hunan Journal of Traditional Chinese Medicine	24
	9	Clinical Journal of Chinese Medicine	24
	10	Chinese Journal of Information on Traditional Chinese Medicine	24
English article	1	Chinese Journal of Integrated Traditional and Western Medicine	5
	2	Chinese Journal of Integrated Medicine	5
	3	Annals of Palliative Medicine	3
	4	Medicine	2

3.4 Visual analysis of author cooperation

A total of 2 672 authors from Chinese articles were obtained by visual analysis, and the top 10 authors are shown in Table 3. According to Price’s Law ( $M_p=0.749*\sqrt{N_{pmax}}$ , the number of articles published by core authors  $> M_p$ ),  $M_p=4.56$  is determined. Thus, the authors with a number of articles  $\geq 5$  are regarded as core authors. There are 161 Chinese core authors, and seven relatively stable cooperation teams represented by CHEN Xinyi, ZHOU Yongming, BAI Yusheng, HU Xiaomei, MA Rou, CHEN Zhixiong, and YU Huiping (Figure 3). Among them, the largest team is represented by CHEN Xinyi [10, 11], whose researches focus on treating ITP from the spleen, Jianpi Yiqi Shexue Formula (健脾益气摄血方), and animal research. The team represented by ZHOU Yongming [12-14] mainly focuses on ITP treatment based on the theory of Qi and fire in spleen and kidney, Shengxueling (生血灵), the theory of opposition and submission, immune cells and so on. The main research contents of the team represented by BAI Yusheng [15-17] contain different syndrome types of ITP and hormone therapy response, bone marrow cytological characteristics of ITP, and immune cell expression. The team represented by DING Xiaoqing and HU Xiaomei [18-20] mainly studies Yiqi Shexue Formula (益气摄血方), peripheral blood miRNAs, and anti-platelet integrin- $\beta$  3-antibody. The team represented by MA Rou [21, 22] focuses on the theory of strengthening Yang and the treatment of ITP with Yiqi Tongyang

**Table 3** The top 10 authors in Chinese and English articles on TCM treatment of ITP

No.	Chinese article		No.	English article	
	Author	n		Author	n
1	CHEN Xinyi	37	1	MA Rou	4
2	ZHOU Yongming	32	2	GAO Ruilan	4
3	CHEN Zhixiong	23	3	ZHANG Yayue	4
4	HU Xiaomei	19	4	ZHOU Aixiang	2
5	BAI Yusheng	19	5	WANG Teng kai	2
6	MA Ji	19	6	HOU Ming	2
7	YU Huiping	19	7	LI Lin	2
8	MA Rou	18	8	WANG Chong	2
9	ZHOU Yuhong	17	9	YANG Yufei	2
10	ZHU Wenwei	16	10	ZHANG Aijun	2



**Figure 3** Visual map of author cooperation in TCM treatment of ITP

A, cooperation of authors in Chinese articles. B, cooperation of authors in English articles. The visual map of author cooperation only lists the core authors with cooperative links, and each node in the map represents a core author. The larger the node, the more papers published by the author. The line represents the cooperative relationship among authors, and the cooperative relationship among different authors is represented by different colors.

Formula (益气通阳方). The research content of the team represented by CHEN Zhixiong [23, 24] mainly focuses on treating ITP from the liver and spleen, and the mechanism of Jianpi Shexue Formula (健脾摄血方). The research team represented by YU Huiping [25-27] focuses on clinical research, “cocktail” treatment [consisting of self-made Xi-anshao Dangui Decoction (仙芍丹归汤), low-dose methylprednisolone tablets, spleen aminopeptide, compound rutin tablets, multidimensional tablets], and ITP in



Children. A total of 201 authors from English articles were obtained by visualization, and  $M_p = 1.50$ . Therefore, the number of articles  $\geq 2$  was designated as the criterion for core authors, and there were 13 core authors in English articles, along with four relatively stable cooperative teams represented by MA Rou, LI Lin, GAO Ruilan, and ZHANG Aijun [28-31], whose studies mainly focus on TCM therapies, pathogenesis, Shengxueling, and Qingdai (*Indigo Naturalis*).

3.5 Visual analysis of cooperation between research institutions

A total of 632 nodes and 242 connections were obtained in the cooperation map of institutions in Chinese articles with 666 institutions included. Most of the research institutions were universities of TCM and their affiliated hospitals. Table 4 lists the top 10 institutions with the most publications. Among them, Dongzhimen Hospital of Beijing University of Chinese Medicine (54 articles) published the most articles, followed by Shanghai University of Traditional Chinese Medicine (38 articles) and Xiyuan Hospital of China Academy of Chinese Medical Sciences (28 articles). It can be seen from Figure 4 that Dongzhimen Hospital of Beijing University of Chinese Medicine, Xiyuan Hospital of China Academy of Chinese Medical Sciences, and First Affiliated Hospital, Heilongjiang University of Chinese Medicine have close cooperation. The results show there are more studies carried out on TCM treatment of ITP in northern regions than in the south, and although there are many institutions working in this field, the cooperation between them is inadequate – international cooperation in particular. A total of 55 nodes and 54 connections were obtained in the cooperation map of institutions in English articles with 55 institutions included. Except for Xiyuan Hospital of China Academy of Chinese Medical Sciences, which contributed three articles, each institution has published one article. Among them, the collaborations between Lianjiang People's Hospital and Sun Yat-sen University, between Xiyuan Hospital of China Academy of Chinese Medical Sciences and Oriental Hospital of Beijing University of Chinese Medicine, and between Southern University and Tianjin University of Traditional Chinese Medicine were relatively close, but generally speaking, the inter-institutional cooperation represented by the English articles was insufficient.

3.6 Visual analysis of keywords

**3.6.1 Keyword co-occurrence analysis** A total of 546 nodes and 1 178 lines were formed by keyword visual analysis (Figure 5). After extraction of keywords with centrality  $\geq 0.01$ , they were classified, and a total of seven classifications were obtained (Table 5). The clinical

Table 4 The top 10 institutions with most Chinese articles on TCM treatment of ITP

No.	Institution (Chinese articles)	n
1	Dongzhimen Hospital of Beijing University of Chinese Medicine	54
2	Shanghai University of Traditional Chinese Medicine	38
3	Xiyuan Hospital of China Academy of Chinese Medical Sciences	28
4	Henan University of Chinese Medicine	26
5	Liaoning University of Traditional Chinese Medicine	25
6	First Affiliated Hospital, Heilongjiang University of Chinese Medicine	24
7	Tianjin University of Traditional Chinese Medicine	24
8	Beijing University of Chinese Medicine	22
9	Nanjing University of Chinese Medicine	21
10	Affiliated Hospital of Shandong University of Traditional Chinese Medicine	21

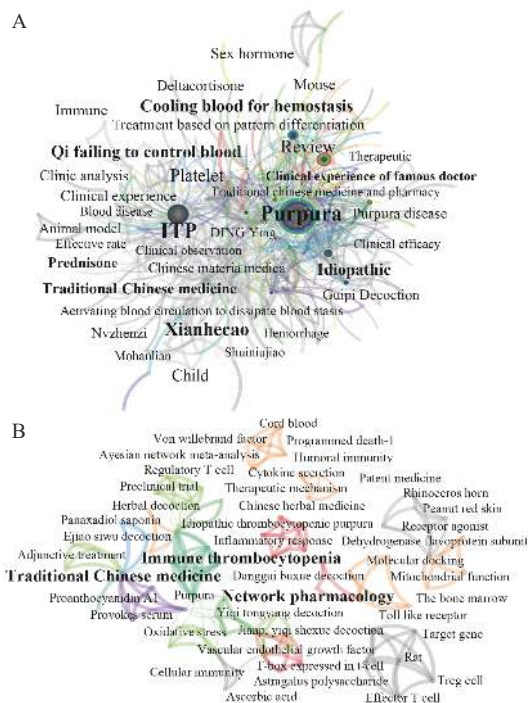


Figure 4 Visual map of inter-institutional cooperation in TCM treatment of ITP

A, cooperation between institutions in Chinese articles. B, cooperation between institutions in English articles. The visual map of inter-institutional cooperation only lists the institutions with cooperative links, and each node in the map represents an institution. The larger the node and text, the more papers published by the institution, and the line represents the cooperative relationship between the institutions.

manifestations of ITP include purpura, bleeding, etc. Under the guidance of syndrome differentiation and treatment, the common syndrome types are Qi failing to control the blood, and kidney deficiency. The academic thought of treatment is to remove heat from blood to stop bleeding, clear the heat to cool the blood, activate blood circulation and remove blood stasis, treat from spleen

and liver, and strengthen spleen and kidney. Xianhecao (Agrimoniae Herba), Nvzhenzi (Ligustri Lucidi Fructus), Zhongjiefeng (Sarcandrae Herba), Huangqi (Astragalus Propinquus), Guipi Decoction (归脾汤), Erzhi Pill (二至丸), Purpura Granule (紫癜颗粒), Shengxueling (生血灵), Ziqian Capsule (紫茜胶囊), Shengban Decoction (升板汤), Bazhen Decoction (八珍汤), Xiaochaihu Decoction (小柴胡汤), and Shengxue Powder (生血散) are commonly used single Chinese herbs and therapeutic prescriptions. The commonly used drugs in western medicine are prednisone. The main research types are clinical experience summary, review, clinical research, data mining, experimental research, etc. Children and animal models are the most common research subjects. The mechanism of action focuses on platelets, immune function, megakaryocytes, NK cells, CD86, bone marrow, cytokines, etc. There are 119 nodes and 269 lines in the visual analysis of keywords in English articles. Combined with Table 6, the keywords with centrality  $\geq 0.01$  in the English articles are ITP, TCM, network pharmacology, panaxadiol saponin, and receptor agonist.



**Figure 5** Keyword co-occurrence map for TCM treatment of ITP

A, co-occurrence analysis of Chinese keywords. B, co-occurrence analysis of English keywords. In the keyword co-occurrence map, nodes with connections between keywords are selected so that each node in the map represents a keyword. The larger the node and text, the greater the frequency of the keyword; the line represents the connection between keywords, and the same color represents the close connection of a certain type of keywords; the outermost ring of the node represents the intermediary centrality of the node, whose thickness is represented by the thickness of the ring frame; the thicker the ring border, the stronger the intermediary centrality of the node, and the higher the importance of the node in the visual map.

**3.6.2 Keyword cluster analysis** A keyword clustering diagram (Figure 6) was formed by using the log-likelihood ratio (LLR) algorithm. Q value (Chinese) = 0.6288, Q value (English) = 0.8146 (Q value > 0.3), S value (Chinese) = 0.7249, and S value (English) = 0.8216 show that the divided community structure is significant, and the clustering is efficient and convincing. A total of 11 representative clusters are formed for the Chinese articles, while four representative clusters are formed for the English articles (Figure 6).

Carrot2 keyword cluster selects the largest categories that can be displayed (occurrence frequency  $\geq 5$  for Chinese keywords and occurrence frequency  $\geq 3$  for English keywords). The key research hotspots with high frequency were extracted by Carrot2 software (Figure 7). After removing the keywords such as ITP and TCM treatment, which are integral to the topic, the keywords such as integrated traditional Chinese and western medicine therapy, clinical observation, Xijiao Dihuang Decoction (犀角地黄汤), hormone, cellular immunity (regulatory T cells), and platelet-related antibodies are determined as the research hotspots in this field in the Chinese articles. In English articles, network pharmacology, mouse model and clinical study are the research hotspots in this field.

The timeline view in the control panel is used to form a timeline map with time as the horizontal axis and clustering as the vertical axis (Figure 8), focusing on sketching the relationship between clusters and the historical span of documents in a certain cluster. In the Chinese articles before the year of 2000, the research hotspots of TCM treatment of ITP were clinical trials and pathogenesis research, but after the year of 2000, animal research, acupuncture and massage, and mechanism research gradually emerged. Before the year of 2016, the English articles mainly focused on clinical trials. After the year of 2016, the rise of molecular researches such as target genes and molecular docking, and network pharmacology gradually turned the research direction to the research of therapeutic mechanism. Figure 8 revealed that the majority of the research hotspots lie in the following aspects: (i) clinical syndrome differentiation of ITP, (ii) study on the therapeutic effect of TCM prescriptions on ITP, (iii) study on the therapeutic mechanism of ITP.

**3.6.3 Keyword burst** Burst detection in the control panel was used to obtain a list of bursting keywords (Figure 9). There are 17 bursting words, among which “clinical efficacy” and “clinical experience” are the strongest bursting words. The burst of clinical curative effect, cytokines, children, blood syndrome, and famous doctor's experience continues to this day, which shows that they are the recent research hotspots and trends in TCM treatment of ITP. There are five bursting words in English articles, which are network pharmacology, Chinese medicine, immune thrombocytopenia, immune thrombocytopenic purpura, and TCM.

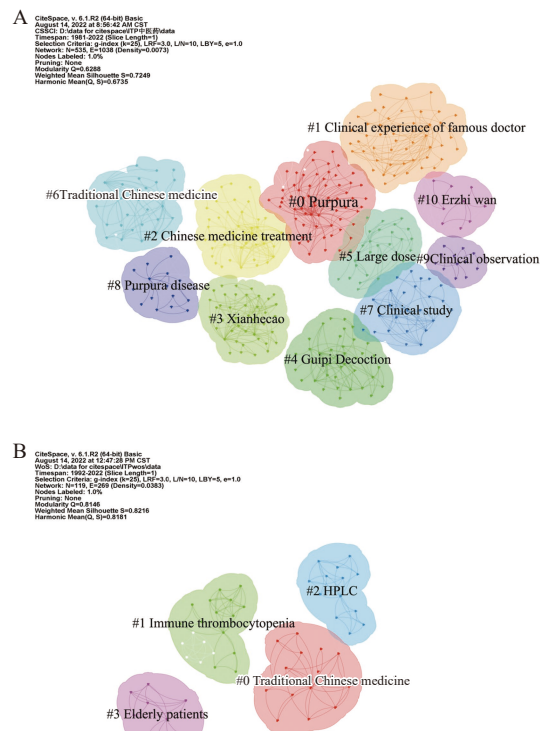
**Table 5** Classification of high frequency keywords in the Chinese articles on TCM treatment of ITP

Classification	Keyword	Frequency	Centrality
Basic words	Chinese medicine treatment	177	0.28
	Purpura	156	0.28
	ITP	102	0.46
	Treatment based on syndrome differentiation	57	0.10
	Blood disorders	29	0.06
Research type	Clinical experience summary	83	0.12
	Clinical trial research	61	0.03
	Review	28	0.04
	Animal research	7	0.01
	Data mining	4	0.01
Chinese medicine treatment	Guipi Decoction (归脾汤)	26	0.03
	Xianhecao (Agrimoniae Herba)	16	0.07
	Purpura Granule (紫癜颗粒)	9	0.01
	Shengxueling (生血灵)	8	0.01
	Erzhi Pill (二至丸)	7	0.02
	Ziqian Capsule (紫茜胶囊)	6	0.01
	Shengban Decoction (升板汤)	5	0.01
	Bazhen Decoction (八珍汤)	5	0.01
	Nvzhenzi (Ligustri Lucidi Fructus)	4	0.01
	Xiaochaihu Decoction (小柴胡汤)	3	0.01
	Zhongjiefeng (Sarcandrae Herba)	3	0.01
	Huangqi (Astragalus Propinquus)	2	0.01
Western medicine treatment	Shengxue Powder (生血散)	2	0.01
	Prednisone	40	0.04
Research subject	Child	52	0.07
	Animal model	35	0.05
Treatment based on syndrome differentiation	Removing heat from blood to stop bleeding	19	0.06
	Clearing heat to cool the blood	13	0.03
	Activating blood circulation to remove blood stasis	12	0.01
	Qi failing to control blood	12	0.04
	Treatment from spleen	8	0.01
	Treatment from liver	6	0.01
	Strengthening the spleen and kidney	2	0.01
	Kidney deficiency	2	0.01
Mechanism research	Platelets	21	0.03
	Immune function	14	0.03
	Megakaryocytes	11	0.02
	Cytokines	10	0.01
	CD86	2	0.01
	Bone Marrow	2	0.01
	NK cell	2	0.01

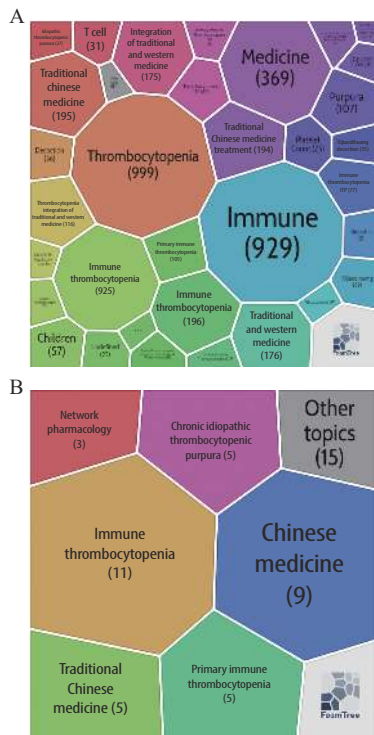
**Table 6** Classification of high frequency keywords in the English articles on TCM treatment of ITP

Classification	Keyword	Frequency	Centrality
Basic words	Immune thrombocytopenia	12	0.57
	Traditional Chinese medicine	8	0.37
	Network pharmacology	3	0.13
Chinese medicine or ingredients	Panaxadiol saponin	2	0.10
Mechanism research	Receptor agonist	2	0.13

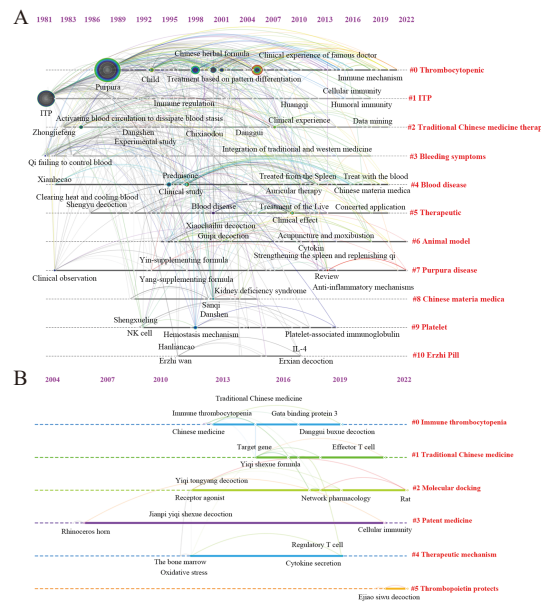




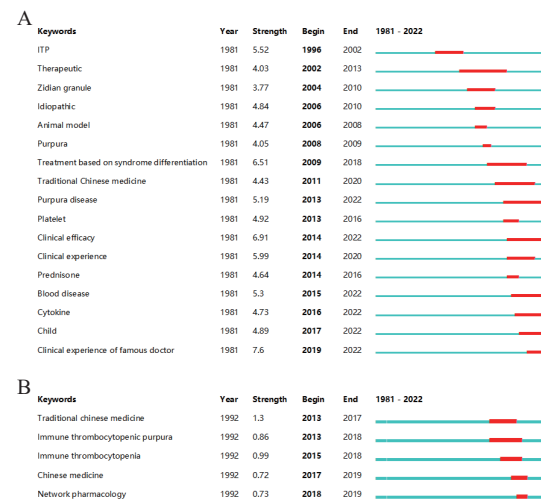
**Figure 6** Keyword clustering analysis for TCM treatment of ITP by CiteSpace  
A, clustering analysis of keywords in Chinese articles. B, clustering analysis of keywords in English articles. Each color represents a keyword cluster.



**Figure 7** Keyword clustering analysis for TCM treatment of ITP by Carrot2  
A, clustering analysis of keywords in Chinese articles. B, cluster analysis of keywords in English articles. Each color represents a keyword cluster, and the occurrence frequency of keywords is in brackets after keywords in the figure.



**Figure 8** Timeline distribution map for TCM treatment of ITP  
A, time zone distribution of Chinese articles. B, time zone distribution of English articles. The nodes with connections between keywords are selected in the timeline distribution map for display. Each node in the figure represents a keyword, the line represents the connection between keywords, the same color represents the close connection of this kind of keywords. The horizontal axis represents the appearance time of keywords, and the vertical axis represents keyword clustering, focusing on showing the development of clustering throughout the timespan.



**Figure 9** Bursting keywords for TCM treatment of ITP  
A, top 17 keywords with the strongest citation bursts in Chinese articles. B, top five keywords with the strongest citation bursts in English articles.

4 Discussion

4.1 Research overview

Results from the multi-software visual map analysis of TCM treatment of ITP suggest that, in terms of the number of publications per year, a rising trend can be observed, which has entered a stage of maturation and



relatively stable development in the recent 15 years, but the overall number of articles published is less than other diseases. Chinese research focuses on clinical research and clinical experience summary. From the year 2007 to 2010, the number of articles on clinical research and clinical experience summary increased significantly, and the annual publications reached their peak in 2010. Although the overall number of published articles has fluctuated and declined since the year of 2010, articles on animal research have gradually increased. The number of articles published dropped sharply in 2013 and 2018, but considering the literature classification and journal classification, it is found that the number of articles on clinical research and clinical experience summary dropped sharply, and the number of articles published in ordinary journals also dropped, whereas the number of articles published in core journals stayed stable. It is speculated that the change in research types and the emphasis on article quality may have led to a sharp drop in the number of articles. Researches published in English journals mainly focus on clinical research and experimental research. The journals with the largest number of articles in Chinese and English are Liaoning Journal of Traditional Chinese Medicine and Chinese Journal of Integrated Traditional Chinese and Western Medicine (English version), respectively. Keyword analysis showed that integrated traditional Chinese and western medicine treatment, clinical research, experience of famous doctors, TCM treatment, cellular immunity, and humoral immunity are the main research fields. The core teams for the Chinese articles are represented by CHEN Xinyi, ZHOU Yongming, BAI Yusheng, HU Xiaomei, MA Rou, CHEN Zhixiong, and YU Huiping, while the English core teams are represented by MA Rou, LI Lin, GAO Ruilan and ZHANG Aijun. The authors with the most articles in Chinese and English are CHEN Xinyi and MA Rou, respectively. Dongzhimen Hospital of Beijing University of Chinese Medicine and Xiyuan Hospital of China Academy of Chinese Medical Sciences are the research institutions with the most published articles in Chinese and English, respectively, and there is a lack of cross-regional and international cooperation between the institutions. The above results suggest that there are relatively few research articles on TCM treatment of ITP, and a lack of close communication and cooperation among institutions, which may stem from the absence of communication platform between institutions and the limited number of studies. Following the research results in other fields [32, 33], inter-institutional cooperation should be strengthened, and cross-regional and inter-institutional cooperation can significantly increase research results and promote research progress.

## 4.2 Research hotspots

The research hotspot of TCM treatment of ITP mainly lies in the clinical syndrome differentiation of ITP, the

therapeutic effect of TCM prescriptions on ITP, and the mechanism of ITP treatment.

(i) Clinical syndrome differentiation of ITP. Studies have shown that the common syndromes of ITP are blood-heat, fire flaming from Yin deficiency, failure of Qi to control blood, existence of blood stasis, etc. NIE et al. [34] have proved that Xijiao Dihuang Decoction can promote the expression of recombinant indoleamine 2,3-dioxygenase (IDO) in peripheral blood mononuclear cells of ITP rats through JAK1/STAT1 signal molecules and reduce platelet immune damage, which suggests that Xijiao Dihuang Decoction can be used for treating the blood-heat syndrome. Qianggen Powder (茜根散) is recommended for the syndrome of fire flaming from Yin deficiency. ZHOU et al. [35] have found that Qianggen Powder combined with prednisone can improve the TCM symptoms of ITP patients with fire flaming from Yin deficiency more effectively than western medicine treatment alone, by up-regulating the ratio of CD4 + T lymphocytes, down-regulating the ratio of CD8 + T lymphocytes, and improving the immune dysfunction of patients. Guipi Decoction is recommended for the syndrome of Qi failing to control blood. WU et al. [36] have shown that Guipi Decoction may inhibit the activation and proliferation of self-reactive T cells and B cells, and prevent the production of anti-platelet antibodies by increasing the number of regulatory T cells (Treg) and the expression of tumor growth factor (TGF)- $\beta$ 1 in peripheral blood of ITP mice. Xuefu Zhuyu Decoction (血府逐瘀汤) is recommended for blood stasis syndrome. XU [37] found that Xuefu Zhuyu Decoction combined with western medicine has a good effect for patients with idiopathic thrombocytopenic purpura, and also has a positive regulatory effect on cytokines and immune status for this kind of patients, showing a high value for clinical practice. In addition, Professor HU Xiaomei's team noticed from the perspective of disease differentiation and syndrome differentiation that the clinical treatment of ITP is inseparable from treating blood, Qi, and fire. Based on the relationship among blood, Qi, and fire, it is proposed that "treating from Qi" can be used as the clinical idea for ITP [38]. ZENG Yingjian of our team also pointed out that the pathogenesis of refractory ITP was damp-heat stasis, spleen deficiency, and Qi stagnation, and its core was the loss of Qi in spleen and stomach, which can be treated from Qi and blood [39, 40]. Therefore, ITP clinical syndrome differentiation analysis followed by study of prescriptions based on syndrome type is still the main means of research at present.

(ii) Study on the therapeutic effect of TCM prescriptions on ITP. Analysis of the research status shows that Guipi Decoction, Xiaochaihu Decoction, Bazhen Decoction, Erzhi Pill, Zidian Shengyu Powder (紫癜圣愈散), Shengxueling, Jianpi Shengxue Decoction (健脾生血汤) are commonly used TCM prescriptions, while Xianhecao

(Agrimoniae Herba), Mohanlian (Ecliptae Herba), Zhongjiefeng (Sarcandrae Herba), Nvzhenzi (Ligustri Lucidi Fructus), Dihuang (Rehmanniae Radix), and Shudihuang (Rehmanniae Radix Praeparata) are commonly used herbs. In the clinic, the effect of improving ITP symptoms by TCM prescriptions is obvious, such as increasing platelet count, reducing the side effects of chemotherapy drugs, and regulating immune function. In the study carried out by HU Xiaomei's team [19, 41], 33 ITP patients were given Yiqi Shuxue Formula (益气舒血方) [Renshen (Ginseng Radix et Rhizoma), Zhigancao (Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle), fried Baizhu (Atractylodis Macrocephalae Rhizoma), Fuling (Poria), Danggui (Angelicae Sinensis Radix), Chuanxiong (Chuanxiong Rhizoma), Baishao (Paeoniae Radix Alba), Shudihuang (Rehmanniae Radix Praeparata) and Ejiao (Asini Corii Colla)]. The results showed that Yiqi Shuxue Formula could remove "Yin fire" by reinforcing Qi to improve the body state, increase platelets, inhibit bleeding, and reduce hormones to achieve the therapeutic effect eventually. Based on the TCM theories with the clinical characteristics of ITP, CHEN Xinyi proposed that "treating from spleen" was the basic principle for ITP treatment. After treating the ITP mouse model with formulas targeting spleen [Jianpi Yiqi Shexue Extract (健脾益气摄血浸膏), Jianpi Yiqi Extract (健脾益气浸膏), and Guipi Decoction Extract (归脾汤浸膏)], it is found that the peripheral platelets of mice were increased, the bleeding was reduced, and the bleeding symptoms were improved [42-44]. SUN et al. [45] gave Qihuang Decoction (芪黄汤) [(Dihuang (Rehmanniae Radix), Shudihuang (Rehmanniae Radix Praeparata), Tusizi (Cuscutae Semen), Gouqi (Lycii Fructus), Shanzhuyu (Corni Fructus), Mohanlian (Ecliptae Herba), Nvzhenzi (Ligustri Lucidi Fructus), Huangqi (Astragalus Propinquus), Fuling (Poria), Taizishen (Pseudostellariae Radix), and Shanyao (Dioscoreae Rhizoma)] to 42 ITP patients and found that Qihuang Decoction combined with hormone therapy could significantly increase platelet count and platelet hematocrit, improving the immunity of ITP patients. ZHONG et al. [46] also found that Jianpi Shengxue Decoction [Huangqi (Astragalus Propinquus), Danggui (Angelicae Sinensis Radix), Dangshen (Codonopsis Radix), Baizhu (Atractylodis Macrocephalae Rhizoma), Huangjing (Polygonati Rhizoma), Xiaoji (Cirsii Herba), Baimaogen (Imperatae Rhizoma), Xianhecao (Agrimoniae Herba), Huangqin (Scutellariae Radix), Huangbai (Phellodendri Chinensis Cortex), and Gancao (Glycyrrhizae Radix et Rhizoma)] can improve the TCM symptoms, and effectively increase the platelet count of chronic ITP patients characterized by Qi failing to control blood. To sum up, there are more and more studies on the treatment of ITP with TCM prescriptions under the guidance of TCM theories, which promote the development of TCM and improve life quality. However, researchers

should also pay attention to the research on the therapeutic material basis and mechanism in the future.

(iii) Study on the mechanism of ITP treatment. Keywords co-occurrence analysis found that the current research focused on humoral immunity, cytokines, immune regulation, target genes, etc. The research on the mechanism of Qingdai (Indigo Naturalis) in the treatment of ITP has made some progress. ZHAO et al. [47] have determined the potential new mechanism of Qingdai (Indigo Naturalis) in the treatment of ITP by regulating the homeostasis of CD4+ T cells in PD1/PTEN/AKT signaling pathway. At the same time, SHAO et al. [48] found that Qingdai (Indigo Naturalis) might inhibit inflammation in ITP by activating thrombopoietin receptor (c-MPL) and normalizing the expression of tumor necrosis factor (TNF), and play a direct role in platelet production. In addition, the research on the therapeutic mechanism of TCM prescriptions for ITP is gradually intensifying. XU et al. [14] found that Jianpi Zishen Xiehuo Formula (健脾滋肾泻火方) was effective in treating ITP model mice, and its therapeutic mechanism may be related to reducing the number of dendritic cells (DC) in mouse spleen, the expression of co-stimulating cluster of differentiation (CD) 86 on DC surface, and the secretion of interleukin (IL) 12p70. HUANG et al. [49] found that the mechanism of Jianpi Yiqi Shexue Formula in treating ITP might be related to regulating secretory immunoglobulin A (sIgA) content in intestinal mucus, down-regulating tumor antigen p53 protein expression, reducing lymphocyte apoptosis rate and improving intestinal immune function. LI et al. [50] found that the Guipi Decoction might exert an therapeutic effect on ITP by reducing the expression of CD80 and CD86 in spleen, inhibiting the activation of B lymphocytes, and reducing the production of platelet autoantibodies, which results in protection of platelets.

In addition, in the area of mechanism, network pharmacology technology has attracted much attention at present. As a new discipline, the integrity and systematicness of its drug-target-pathway network structure are consistent with the holistic view of TCM. Adopting network pharmacology, HU Xiaomei's team [51, 52] found that Yiqi Shexue Formula could treat ITP by regulating immunity and related biological processes in 2019, and found in 2020 that Bazhen Decoction treated ITP mainly through the TNF signaling pathway. In 2021, HUANG et al. [53] discovered that through network pharmacology, Bazhen Decoction may interact with core proteins such as Raf proto-oncogene serine/threonine-protein kinase (RAF1), phosphoinositol 3 kinase  $\gamma$  (PIK3CG), and inhibitor of nuclear factor kappa B kinase subunit  $\beta$  (IKKBK) to regulate immunity and related signaling pathways, so as to treat ITP. In addition, the recent articles of HU Xiaomei's team published in *Frontiers in Medicine* confirmed that through network pharmacology, molecular docking, high-performance liquid chromatography, and

experimental verification, Ejiao Siwu Decoction (阿胶四物汤) may down-regulate inflammatory factors and reduce vascular endothelial injury by regulating vascular endothelial growth factor (VEGF), advanced glycation end products and their receptors (AGE-RAGE), complement and coagulation cascade signaling pathways to treat ITP [54]. Therefore, on the basis of combining the keyword co-occurrence analysis results of target genes, cytokines, and immune regulation, the material basis of pharmacological effects and potential mechanisms of the single Chinese herb and prescriptions can be accurately analyzed through network pharmacology, bioinformatics, and molecular docking, which can improve the research efficiency significantly. However, due to the different database types, updates, and timeliness in network pharmacology, the molecular mechanism should be further verified in combination with analysis of proteomics, metabolomics, and post-translational modifications.

### 4.3 Research trends

It is found that the future trends of this field lie in the retrospective research of famous doctors' experiences, data mining, and the mechanism research of TCM treatment of ITP, and the trend analysis was carried out in combination with high-frequency keywords.

(i) Retrospective study. The retrospective study of medical records and database literature of famous TCM doctors is helpful for summarizing the effective prescriptions and their mechanism in this field. ZHOU Yongming's team [55] found that TCM treatment of ITP focused on invigorating spleen, invigorating Qi and absorbing blood, clearing heat, cooling blood and stopping bleeding, and paying attention to tonifying liver, spleen, and kidney, or promoting blood circulation and removing blood stasis for chronic illness. Some scholars have shown that the therapeutic principle of TCM treatment of ITP is "invigorating Qi and nourishing Yin, harmonizing blood and softening liver", the core drugs are Huangqi (*Astragalus Propinquus*), Dihuang (*Rehmanniae Radix*) and Danggui (*Angelicae Sinensis Radix*), and the compatibility of drug pairs follows the principle of "treating Qi, fire, and blood" [38, 56]. In addition to using TCM prescriptions, therapies such as auricular points and acupoint application [57], acupuncture [58], and massage can also be used to relieve symptoms, promote patients' recovery, and reduce complications. Through retrospective study, the resources of TCM classic prescriptions and TCM treatment technologies can be easily collected, and the advantages of TCM in treating ITP can be further developed.

(ii) Study on therapeutic mechanism. The traditional mechanism studies of treating ITP with the single Chinese herb and TCM prescription are mainly based on humoral immunity, cytokines, and immune regulation,

as is exemplified by the studies on Qingdai (Indigo Naturalis), Jianpi Yiqi Shuxue Formula, Guipi Decoction, etc. With the development of molecular biology, bioinformatics, and network pharmacology, many scholars have begun to focus on the specific molecular mechanism of the single Chinese herb and prescriptions. Represented by HU Xiaomei, scholars have started to conduct network pharmacology-based research related to the treatment of ITP with TCM prescriptions, such as Yiqi Shuxue Formula, Bazhen Decoction, and Ejiao Siwu Decoction. Future research on the mechanism of TCM treatment of ITP may be based on network pharmacology combined with *in vitro* and *in vivo* pharmacodynamic experiments for deeper understanding of the mechanism.

(iii) The analysis of high frequency keywords trend. High frequency keywords such as clinical experience summary, clinical research, review, Xianhecao (*Agrimoniae Herba*), Guipi Decoction, prednisone, platelets, immune function, cytokines, and megakaryocytes were obtained through the keyword co-occurrence map. Among them, clinical experience summaries and clinical research have kept certain popularity in this field. After entering the 21st century, with the modernization of TCM, the research direction has changed from clinical efficacy observation to clinical trial research [59], *in vitro* experiment, and animal research [60]. The above research shows that TCM has obvious advantages in treating ITP from the perspective of etiology and pathogenesis of modern medicine. In the future, we should focus on the research between TCM prescriptions and the mechanism of immunotherapy for ITP. On the basis of existing research, modern science and technology should be used to conduct data mining, network pharmacology, experimental research, etc., to obtain better and newer core mechanisms of related prescriptions, and give full play to the advantages of TCM.

## 5 Conclusion

The current study shows that TCM treatment of ITP is in a stable and rising trend at present, but the lack of cross-regional and international research is especially disturbing. This study analyzes and concludes that the research hotspots of TCM treatment of ITP are focused on the clinical syndrome differentiation of ITP, the therapeutic effect of TCM prescription on ITP, and the mechanism of ITP; the research trends are retrospective research like summarizing the experience of famous doctors, data mining, and studies on the therapeutic mechanism such as humoral immunity and cellular immunity cytokines, etc. Later, the advantages of TCM such as the multi-target, multi-faceted and individualized characteristics should be given full play in order to provide new ideas for future research.



## Fundings

Jiangxi Traditional Chinese Medicine Administration Clinical Research Base Construction Project (Jiangxi TCM Science and Education Letter [2021] No. 3), Jiangxi Traditional Chinese Medicine Young and Middle-aged Backbone Talents (First Batch) Training Program Project (Jiangxi TCM Science and Education Letter [2020] No. 2), and Jiangxi Traditional Chinese Medicine Administration Science and Technology Program Project (2021B050).

## Competing interests

The authors declare no conflict of interest.

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## 中医药治疗免疫性血小板减少症的研究热点与趋势可视化分析

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**【摘要】目的** 通过文献计量学和可视化分析对中医药治疗免疫性血小板减少症(ITP)的相关文献进行梳理, 展示该领域的整体研究进展、热点及发展趋势, 为 ITP 的进一步研究提供参考。**方法** 检索中国知网、万方、维普、WOSCC、PubMed 数据库中关于中医药治疗 ITP 的文献信息, 检索时限为建库至 2022 年 7 月 31 日。运用 VOSviewer、CiteSpace、Carrot2 及 NoteExpress 软件对发文量、文献类型、期刊分布进行数据分析, 并对研究热点、作者、机构及关键词等进行可视化分析。**结果** 经过筛选最终纳入中文文献 1493 篇、英文文献 40 篇。中文文献研究以临床试验研究和临床经验总结为主, 英文文献以临床试验研究和动物实验研究为主。中文文献共发表在 317 种中文期刊中, 英文文献共发表在 29 种英文期刊中。研究热点主要集中在 ITP 的临床辨证、中药复方对 ITP 治疗效果研究、ITP 的治疗机制研究等方面。关键词分析表明中西医结合治疗、临床研究、名医经验、中医药治疗、细胞免疫、体液免疫方面研究成果较多。中、英文发文量最多的作者分别是陈信义教授和麻柔教授。中、英文发文量最多的研究机构分别是北京中医药大学东直门医院和中国中医科学院西苑医院。临床用于治疗 ITP 的常见中药包括仙鹤草、女贞子、墨旱莲、肿节风等, 中药复方有归脾汤、犀角地黄汤、八珍汤、二至丸及小柴胡汤。发展趋势主要集中在回顾性研究、机制研究及数据挖掘等方面。**结论** 中医药治疗 ITP 的研究已进展到稳步上升期, 但研究内容仍需深入, 且研究机构之间应加强合作交流, 以此推动中医药在 ITP 领域的现代化发展。

**【关键词】** 免疫性血小板减少症; 中医药; 文献计量学; 可视化分析; CiteSpace; VOSviewer; Carrot2; 研究热点