Bibliometrics Research on Immune of Traditional Chinese Medicine

Dongdong Bai¹, ², ³, Zhen Dong¹, ², ³, Xinpu Li¹, ², ³, Jinyin Luo¹, ², ³, Xurong Wang¹, ², ³, Hongsheng Li¹, ², ³, *

¹Key Laboratory of Veterinary Pharmaceutical Development, Ministry of Agriculture, Lanzhou, China
²Key Laboratory of New Animal Drug Project of Gansu Province, Lanzhou, China
³Lanzhou Institute of Husbandry and Pharmaceutical Sciences of Chinese Academy of Agricultural Science, Lanzhou, China

Email address:
lihsheng@sina.com (Hongsheng Li)
*Corresponding author

To cite this article:
Dongdong Bai, Zhen Dong, Xinpu Li, Jinyin Luo, Xurong Wang, Hongsheng Li. Bibliometrics Research on Immune of Traditional Chinese Medicine. *International Journal of Chinese Medicine*. Vol. 3, No. 4, 2019, pp. 52-58. doi: 10.11648/j.ijcm.20190304.11

Received: September 8, 2019; Accepted: September 24, 2019; Published: October 15, 2019

Abstract: Bibliometrics analysis is increasingly used for situation analysis in a certain field. We aimed to analyze the immunological aspects of traditional Chinese medicine (TCM) from 1995 to the present, such as study countries, institutions, journals, and hotspots. The web of science core collection was used to retrieve the articles related to TCM-Immune from 1995 to 2018, and the statistical analysis of those projects by the Excel, VOS viewer software. A total of 4005 kinds of literature on TCM-Immune were retrieved. It was found that the total number of papers published in recent years had increased rapidly, with China being the country with the largest number of publications, followed by the United States, South Korea, India, and Japan. Top 10 institutions except Kyung-hee University are based in China, and so are the authors of the top three. VOS viewer software divided the keywords into four clusters, the first cluster is immune in vitro, the second cluster is immune in vivo, the third cluster is TCM-Immune resistance, the fourth cluster is the mechanism of immune, the analysis shows that inflammation, oxidative stress, signal pathway, the mechanism of action is new hotspots in the future.

Keywords: Bibliometric Citation, Traditional Chinese Medicine, Immune, Hotspots

1. Introduction

Traditional Chinese medicine was widely used to prevent and treat human or animal diseases in China. In the theory of traditional Chinese medicine (TCM) or traditional Chinese veterinary medicine (TCVM), strengthening the body resistance is one of the basic principles of preventing and treating diseases [1]. With the progress of society, people pay more attention to human sub-health [2-4] and the development of proprietary Chinese medicine for human or animal use. Chinese medicine has rich experience in the prevention and treatment of the disease, especially in the immunity of traditional Chinese medicine. There are many reports have shown that immunity is related to disease [5-7], such as non-small cell lung cancer [8], cutaneous lupus erythematosus [9], systemic sclerosis [10], et al.

Bibliometrics refers to the quantitative analysis of all knowledge carriers by mathematical and statistical methods. VOS viewer is a free bibliometric analysis software developed by Nees Jan van Eck and Ludo Waltman of Leiden University in the Netherlands to construct and view bibliometric maps, which can draw scientific maps of various fields. It has been applied to the analysis of document information in many natural sciences. Compared with other Bibliometrics software, VOS viewer pays special attention to the graphical representation of bibliometrics map [11].

The objective was attempted to provide all-around insights on the current state of global TCM-Immune research. The distribution of the publications was analyzed as well as keywords and references to better understand the global trend
of research and to discover the hotspots in this field.

2. Materials and Methods

2.1. Bibliometric Dates and Search Strategy

A comprehensive bibliographic retrieval was performed online using the Web of Science Core Collection on 15 September 2018. In order to avoid errors caused by daily updates, the retrieval is completed in one day. The retrieval strategy was: TS = (Traditional Chinese medicine* OR Herb* OR TCM*) AND TS = (immunology* OR Immunity* OR Immune*). Language was selected as English. Articles and reviews that were normally peer-reviewed were included, but all others were excluded.

2.2. Date Collection

The original data downloaded from the web of science firstly imported into Microsoft Excel 2016, and then validated and evaluated by two independent researchers. Disagreement is United through discussion. Finally, the number of papers, citations and H-index bibliometric parameters were extracted. The collected data are imported into Microsoft Excel 2016 and VOS view software for quantitative and qualitative analysis.

2.3. Bibliometric Analysis

Firstly, Microsoft Excel 2016 is used to analyze the time trend of the number of publications, which can predict the future trend of the literature to a certain extent, in which the X-axis represents the time and Y axis to represent the amount of literature produced in the corresponding year. VOS viewer can be used for keyword mapping and clustering, and the frequency of hotspots [11].

3. Results

3.1. Contributions of Countries and Regions to Global Publications

Both the quantity and quality of publications were measured to evaluate the contributions of different countries and regions. A total of 4152 articles from 1995 to 2018 met the search criteria. After screening, a total of 4005 articles are available for analysis. We can see that TCM-Immune related articles have increased rapidly in recent years from Figure 1 A. Figure 1 B shows the trend of publications in five countries with the largest number of articles on TCM-Immune in recent years. China has the fastest growth and the largest number of papers since 2011. Although the number of papers issued by the United States, South Korea, India, and Japan has increased, there is still a big gap with China in this field, which may be related to national history, the cultural background and so on. The above-detailed information is shown in Table 1. People R China had the first place when ranking for the number of publications (1408, 35.16%), followed by USA (763, 19.05%) and the South Korea (313, 7.82%). The USA had the most citations with a number of 25158. People R China ranked 2nd with the citation number of 19154.

Figure 1. Contributive characteristics of TCM-Immune research. A Time-trend in the number of published documents in the studied field. B The total publications worldwide and five most productive countries in TCM-Immune. C The number of publications on TCM-Immune research from the top 10 contribution institutes. D The number of publications of the top 10 popular journals on TCM-Immune research.
Table 1. Publications in the 10 most productive countries.

| Country               | N  | %    | Total citations |
|-----------------------|----|------|-----------------|
| People R China        | 1408 | 35.16 | 19154          |
| USA                   | 763  | 19.05 | 25158          |
| South Korea           | 313  | 7.82  | 4278           |
| India                 | 239  | 6.017 | 4003           |
| Japan                 | 224  | 5.97  | 4350           |
| Taiwan                | 191  | 4.844 | 2926           |
| Germany               | 188  | 4.77  | 7126           |
| Canada                | 126  | 3.15  | 3110           |
| Iran                  | 108  | 2.69  | 1094           |
| Australia             | 95   | 2.37  | 2409           |

3.2. Journals Publishing TCM-Immune Research

After analysis the publication’s research on TCM-Immune by VOS viewer software, we know a journal of Ethnopharmacology published the most studies with 198 publications. There were 128 articles in evidence-based complementary and alternative medicine, 96 articles in PLoS one and 85 articles in international immunopharmacology on TCM-Immune research. The top 10 journals that published the most studies are listed in Figure 2.

Figure 2. Analysis of the top 17 references. Mapping of the top 17 co-cited references of 4055 publications on TCM-Immune research.

3.3. Institutes Publishing TCM-Immune Research

Publications from top 10 institutes accounted for 13.51% of all articles on TCM-Immune research. As can be seen from Figure 1 C, Chinese Academy of Sciences had the highest number of publications with a total of 97, thereby accounting for 2.42% of all published literature in this field, followed by China Medical University, Kyung Hee University, Fudan University and so on. Similarly, we can find that in the top 10 of the institutions, besides Kyung Hee University, they all belong to People R China (Table 2).

Table 2. Top 10 of institution engaging in research on TCM-Immune by frequency.

| Institution                      | Country               | N  | %    | Total citations |
|----------------------------------|-----------------------|----|------|-----------------|
| Chinese Acad Sci                 | People R China        | 97 | 2.42 | 1586           |
| China Med Univ                   | People R China        | 73 | 1.82 | 834            |
| Kyung Hee Univ                   | South Korea           | 55 | 1.37 | 931            |
| Fudan Univ                       | People R China        | 55 | 1.37 | 477            |
| Shanghai Univ Tradit Chinese Med | People R China        | 55 | 1.37 | 312            |
| Zhejiang Univ                    | People R China        | 47 | 1.17 | 580            |
| China Acad Chinese Med Sci       | People R China        | 43 | 1.07 | 473            |
| Beijing Univ Chinese Med         | People R China        | 41 | 1.02 | 193            |
| Nanjing Agr Univ                 | People R China        | 40 | 0.99 | 738            |
| Guangzhou Univ Chinese Med      | People R China        | 35 | 0.87 | 133            |

3.4. Authors Publishing TCM-Immune Research

Table 3. The top 10 authors with the most publications related to TCM-Immune research.

| Author | N  | Country               | Total citations |
|--------|----|-----------------------|-----------------|
| Wang, Y | 100 | People R China        | 814            |
| Li, J   | 78  | People R China        | 1094           |
| Li, X   | 75  | People R China        | 1045           |
| Zhang, Y | 69  | People R China        | 817            |
| Wang, J | 63  | People R China        | 860            |
| Wang, X | 62  | People R China        | 575            |
| Chen, J | 53  | People R China        | 720            |
| Wang, H | 50  | People R China        | 473            |
| Zhang, X | 43  | People R China        | 381            |
| Zhang, L | 43  | People R China        | 531            |

A total of 593 publications were from the top 10 authors, accounting for 14.81% of all publications related to the field. The 3 authors who published the most research was Wang, Y with 100 publications on TCM-Immune, followed by Li, J with 78 publications and Li, X with 75 publications (Table 3).

3.5. Analysis of References in TCM-Immune Publications

Reference analysis is used to examine the relationship between references and classify them. The top 17 references with more than 50 citations were selected for analysis of references by VOS viewer. Eventually, 17 papers were divided into two clusters. The first cluster consisted of 9 papers, mainly focusing on specific immunity of TCM, and the second cluster consisted of 8 papers, mainly focusing on innate immunity of TCM.
3.6. Analysis of Keywords in TCM-Immune Publications

The analysis of keywords can infer hotspots, and provide directions for future research. We cluster analysis on 90 keywords that appear at least 50 times in VOS viewer. 90 keywords were divided into four clusters: “Immune in vitro”, “Immune in vivo”, “TCM-Immune resistance” and “The mechanism of immune”. In “Immune in vitro” cluster, frequency keywords were: in-vitro (370 times), cells (364 times) and rats (167 times); In “Immune in vivo” cluster, frequency keywords were: mice (405 times), herbal medicine (149 times) and in-vivo (127 times). In “TCM-Immune resistance” cluster, frequency keywords were traditional Chinese medicine (281 times), immunity (273 times) and innate immunity (173 times). In “The mechanism of immune” cluster, frequency keywords were an expression (358 times), inflammation (279 times) and activation (277 times). The results indicate that there are four main directions in the research of traditional Chinese medicine immunity.

The statistic of keyword appearance time is done under the operation of VOS viewer software. Blue means that the keyword appeared earlier and red means that this keyword appears late (Figure 3). Before 2011, in the early stage of TCM-Immune research, the main popular hotspots were: cytokines, macrophages, induction and in-vivo, et al. According to Figure 4, we can know the latest trends, the newest keywords of the first cluster were oxidative stress, mechanism research; the second cluster included regulatory T cells; the third cluster involved herbivorous insects, Arabidopsis, growth performance, Aeromonas hydrophila, and the fourth cluster main included inflammation and signaling pathways. Clearly knowing these hotspots is of guiding significance for the subsequent research.

![Figure 3](image_url)

**Figure 3.** Distribution of keywords according to their time of appearance. The blue colour means the early appearance and red coloured keywords appeared later.

![Figure 4](image_url)

**Figure 4.** Mapping of the keywords in TCM-Immune research Mapping of the keywords in TCM-Immune research. The key words were divided into 4 groups according to different colours generated by default.
4. Discussion

China has the largest number of TCM-Immune publications in the world. In the early stage of TCM-Immune research, the United States has the largest number of papers, but since 2009, China has always maintained the number of the first, which is related to the history of China and the scientific research conditions at that time. After China, the United States, South Korea, India, and Japan, which also have more research on the TCM-Immune, are sending more papers. The quantity of TCM-Immune is the first in China, but the frequency of citation is the second, which is related to the policy of the evaluation system of Chinese scientific research [12], thus the quantity increases, but the quality is not very high [13].

More articles on TCM-Immune have been published in Journal of Ethnopharmacology, Evidence-based complementary and alternative medicine, Plos one and International Immunopharmacology. It is speculated that the new findings in this field will be published in these journals.

The research institutes and universities of China are the leading organizations in the research of TCM-Immune, which is closely related to the cultural and historical background of Chinese traditional medicine. Nine of the top 10 organizations, except Kyung Hee University, are based in China. This shows that China establishment of a world-class university is fundamental to improving the country scientific research capabilities [14].

Wang Y, Li Y, and Li X are three of the most published authors, and magazines that have the most frequently published new articles will obtain an update on the immunological research of traditional Chinese medicine (TCM).

According to bibliometrics analysis, we found the top 10 references. Plant immunity to insect herbivores [21] written by Howe GA was the most frequently cited, followed by Hormonal Modulation of Plant Immunity [22], Signal signature and transcriptome changes of Arabidopsis during pathogen and insect attack [23], Glucosinolate Metabolites Required for an Arabidopsis Innate Immune Response [24], Central memory self/tumor-reactive CD8(+) T cells confer superior antitumor immunity compared with effector memory T cells [25], Jasmonate Passes Muster: A Receptor and Targets for the Defense Hormone [26] Jasmonate passes musters: a receptor and targets for the defense hormone, et al. In recent years, inflammation [27], oxidative stress [28], signal pathway [29], mechanism of action [30], regulatory T cells [31-33] have been the focus of research (Table 4).

| Title                                                                 | First author | Journal                                          | Year | Citations |
|----------------------------------------------------------------------|--------------|--------------------------------------------------|------|-----------|
| Plant immunity to insect herbivores                                  | Howe GA      | Annual Review of Plant Biology                  | 2008 | 951       |
| Hormonal Modulation of Plant Immunity                                | Pieterse     | Annual Review of Cell and Developmental Biology | 2012 | 657       |
| Signal signature and transcriptome changes of Arabidopsis during pathogen and insect attack | De Vos       | Molecular plant-microbe interactions            | 2005 | 527       |
| Glucosinolate Metabolites Required for an Arabidopsis Innate Immune Response | Clay         | SCIENCE                                          | 2009 | 507       |
| Central memory self/tumor-reactive CD8(+) T cells confer superior antitumor immunity compared with effector memory T cells Jasmonate Passes Muster: A Receptor and Targets for the Defense Hormone | Klebanoff    | Proceedings of the national academy of sciences of the united states of america | 2005 | 484       |
| Health-promoting properties of common herbs                           | Browse       | Annual review of plant biology                  | 2009 | 443       |
| The scientific rediscovery of an ancient Chinese herbal medicine: Cordyceps sinensis Part I | Craig        | American journal of clinical nutrition          | 1999 | 366       |
| Induced Systemic Resistance by Beneficial Microbes                    | Zhu          | Journal of alternative and complementary medicine | 1998 | 312       |
| Pesticide mixtures, endocrine disruption, and amphibian declines: Are we underestimating the impact? | Pieterse     | Annual review of phytopathology                 | 2014 | 303       |
|                                                                      | Hayes        | Environmental health perspectives                | 2006 | 302       |

Bibliometrics method was used to analyze the development trend of TCM-Immune, and analyze the countries, institutions, authors, and magazines that have the most frequently published papers in this field and has important guiding significance for subsequent research. At the same time, this method also has some limitations. Firstly, the source of the literature comes from the web of the science core collection, not all databases. Second, the source of the literature is only English, and the literature of other languages is not statistically analyzed. Therefore, the source of literature on TCM-Immune is not comprehensive. In short, this study can provide very important guidance for future researchers in TCM-Immune.

5. Conclusion

At present, the research scope of TCM immunity is mainly focused on immune in vitro, immune in vivo, the TCM-Immune resistance, and the mechanism of immune. Through the analysis of this review shows that inflammation, oxidative stress, signal pathway, the mechanism of action is new hotspots in the future.
Acknowledgements

I wish to thank the timely help given by XPL, JYL, and XRW in analyzing the large number of samples. I wish to thank HSL for advice on experimental design and ZD for revision on the manuscript.

Statement of Ethics

Not Applicable.

Conflict of Interest

The authors have no conflicts of interest to declare.

Funding Sources

This research is supported by The National Key Research and Development Program of China (2017YFD0502200), International Science and Technology Cooperation Project of Gansu Province, China (17YF1WA169), the Agricultural Science and Technology Innovation Program (CAAS-ASTIP-2014-LIHPS-03).

Author Contributions

Dongdong Bai conducted the study and contributed to study design, data analysis, and preparation of the manuscript, Zhen Dong participated in the writing of the article and the revision and proofreading of the article. Xinpu Li, Jinyin Luo, Xurong Wang guide the writing. Hongsheng Li provided funding for the article. All authors gave their final approval of the manuscript.

References

[1] ZHAO J-X, LI X-F, WANG X-X. Effects of body-resistance strengthening and tumor-suppressing granules on immune adhesion function of red blood cells and expression of metastasis protein CD44 in tumor cells of patients with esophageal carcinoma [J]. World journal of gastroenterology: WJG, Baishideng Publishing Group Inc, 2007, 13 (32): 4360.

[2] ZHAO J, LIAO X, ZHAO H, et al. Evaluation on effectiveness and safety of Chinese herbs in treatment of sub-health: A systematic review and meta-analysis of randomized controlled trials [J]. Chinese journal of integrative medicine, Springer, 2018: 1–10.

[3] XU T, ZHU G, HAN S. Study of Zero-Inflated Regression Models in a Large-Scale Population Survey of Sub-Health Status and Its Influencing Factors [J]. Chinese Medical Sciences Journal, Elsevier, 2017, 32 (4): 218–225.

[4] SHEN J, AI B, SHEN M. Effectiveness of Mild Moxibustion for Sub-Health Conditions in Pre-and Post-Menopausal Women: A Randomized Controlled Clinical Trial [J]. Medical science monitor: international medical journal of experimental and clinical research, International Scientific Information, Inc., 2018, 24: 2907.

[5] CLARK R A. Resident memory T cells in human health and disease [J]. Science translational medicine, American Association for the Advancement of Science, 2015, 7 (269): 269rev1-269rev1.

[6] OLIVERA A, RIVERA J. Paradigm shifts in mast cell and basophil biology and function: an emerging view of immune regulation in health and disease [GJ]/Basophils and Mast Cells. Springer, 2014: 3–31.

[7] ROUND J L, MAZMANIAN S K. The gut microbiota shapes intestinal immune responses during health and disease.[J]. Nature reviews. Immunology, 2009.

[8] MIGNARD X, ANTOINE M, MORO-SIBILOT D, et al. IoNESCO trial: Immune neoajuvant therapy in early stage non-small cell lung cancer [J]. Revue des maladies respiratoires, 2018, 35 (9): 983–988.

[9] MARANO A L, CLARKE J M, MORSE M A, et al. Subacute cutaneous lupus erythematosus and dermatomyositis associated with anti - programmed cell death 1 therapy [J]. British Journal of Dermatology, Wiley Online Library, 2018.

[10] FUSCHIOTTI P. T cells and cytokines in systemic sclerosis [J]. Current opinion in rheumatology, LWW, 2018, 30 (6): 594–599.

[11] VAN ECK N, WALTMAN L. Software survey: VOSviewer, a computer program for bibliometric mapping [J]. Scientometrics, Akadémiai Kiadó, co-published with Springer Science+ Business Media BV …, 2009, 84 (2): 523–538.

[12] ZHAI X, WANG Q, LI M. Tu Youyou’s Nobel Prize and the academic evaluation system in China [J]. The Lancet, Elsevier, 2016, 387 (10029): 1722.

[13] GAO Y, WANG Y, ZHAI X, et al. Publication trends of research on diabetes mellitus and T cells (1997–2016): A 20-year bibliometric study [J]. PloS one, Public Library of Science, 2017, 12 (9): e0195347.

[14] HAN X, APPELBAUM R P. China’s science, technology, engineering, and mathematics (STEM) research environment: A snapshot [J]. PloS one, Public Library of Science, 2018, 13 (4): e0195347.

[15] ZHANG A, YANG Y, WANG Y, et al. Adjuvant-active aqueous extracts from Artemisia rupestris L. improve immune responses through TLR4 signaling pathway [J]. Vaccine, 2017.

[16] HE L X, REN J W, LIU R, et al. Ginseng (Panax ginseng Meyer) oligopeptides regulate innate and adaptive immune responses in mice via increased macrophage phagocytosis capacity, NK cell activity and Th cells secretion [J]. Food and Function, 2017.

[17] SHI H, HE J, LI X, et al. Isorhamnetin, the active constituent of a Chinese herb Hippophae rhamnoides L, is a potent suppressor of dendritic-cell maturation and trafficking [J]. International Immunopharmacology, 2018.

[18] MA A, YANG Y, WANG Q, et al. Anti-inflammatory effects of oxymatrine on rheumatoid arthritis in rats via regulating the imbalance between Treg and Th17 cells [J]. Molecular Medicine Reports, 2017.

[19] LI Y, WANG J, SONG X, et al. Effects of baicalein on IL-1β-induced inflammation and apoptosis in rat articular chondrocytes [J]. Oncotarget, Impact Journals, LLC, 2017, 8 (53): 90781.
[20] ZHANG W, HE W, SHI X, et al. An Asparagus polysaccharide fraction inhibits MDSCs by inducing apoptosis through toll-like receptor 4 [J]. Phytotherapy Research, 2018.

[21] HOWE G A, JANDER G. Plant immunity to insect herbivores [J]. Annu. Rev. Plant Biol., Annual Reviews, 2008, 59: 41–66.

[22] PIETERSE C M J, VAN DER DOES D, ZAMIOUDIS C, et al. Hormonal modulation of plant immunity [J]. Annual review of cell and developmental biology, Annual Reviews, 2012, 28: 489–521.

[23] DE VOS M, VAN OOSTEN V R, VAN POECKE R M P, et al. Signal signature and transcriptome changes of Arabidopsis during pathogen and insect attack [J]. Molecular plant-microbe interactions, Am Phytopath Society, 2005, 18 (9): 923–937.

[24] CLAY N K, ADIO A M, DENOUX C, et al. Glucosinolate metabolites required for an Arabidopsis innate immune response [J]. Science, American Association for the Advancement of Science, 2009, 323 (5910): 95–101.

[25] KLEBANOFF C A, GATTINONI L, TORABI-PARIZI P, et al. Central memory self/tumor-reactive CD8+ T cells confer superior antitumor immunity compared with effector memory T cells [J]. Proceedings of the National Academy of Sciences, National Acad Sciences, 2005, 102 (27): 9571–9576.

[26] BROWSE J. Jasmonate Passes Muster: A Receptor and Targets for the Defense Hormone [J]. Annual Review of Plant Biology, 2009.

[27] BRISLINGER D, DAXBÖCK C, ROSSMANITH E, et al. Bai Hu Tang, Si Ni Tang, and Xue Bi Tang amplify pro-inflammatory activities and reduce apoptosis in endothelial cells in a cell culture model of sepsis [J]. Journal of Ethnopharmacology, 2018.

[28] YAO B, ZHANG M, LENG X, et al. Antler extracts stimulate chondrocyte proliferation and possess potent anti-oxidative, anti-inflammatory, and immune-modulatory properties [J]. In Vitro Cellular and Developmental Biology - Animal, 2018.

[29] YANG L, WU H, QIU W, et al. Pulsatilla decoction inhibits Candida albicans proliferation and adhesion in a mouse model of vulvovaginal candidiasis via the Dectin-1 signaling pathway [J]. Journal of Ethnopharmacology, 2018.

[30] GUAN F, LAM W, HU R, et al. Majority of Chinese medicine herb category “Qing Re Yao” have multiple mechanisms of anti-inflammatory activity [J]. Scientific reports, Nature Publishing Group, 2018, 8 (1): 7416.

[31] ASTRY B, VENKATESHA S H, LAURENCE A, et al. Celastrol, a Chinese herbal compound, controls autoimmune inflammation by altering the balance of pathogenic and regulatory T cells in the target organ [J]. Clinical Immunology, 2015.

[32] ZHANG A, NING B, SUN N, et al. Indirubin increases CD4+CD25+Foxp3+ regulatory T cells to prevent immune thrombocytopenia in mice [J]. PLoS ONE, 2015.

[33] LI A, SHUAI X, JIA Z, et al. Ganoderma lucidum polysaccharide extract inhibits hepatocellular carcinoma growth by downregulating regulatory T cells accumulation and function by inducing microRNA-125b [J]. Journal of Translational Medicine, 2015.