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# Bibliometric Analysis of Stephania Research: Trends and Hotspots

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## Abstract

Stephania is a Menispermaceae genus widely used in traditional medicine for its various pharmacological properties. We searched the Web of Science (WOS) using the keyword "Stephania" from 2003 to 2023 to analyze the bibliometric trends and hot spots. The research output on Stephania has been steadily increasing, with 1,345 publications identified in the WOS. The majority of the publications were research articles (72.7%), followed by reviews (18.6%) and proceedings papers (4.6%). The top five countries contributing were the USA (29.3%), China (26.2%), Brazil (12.7%), Colombia (5.6%), and Japan (4.9%). The top five institutions were the Chinese Academy of Sciences, China Pharmaceutical University, Peking University, Shanghai Jiao Tong University, and Zhejiang University. The topics were pharmacology and pharmacy, biochemistry and molecular biology, plant sciences, and traditional medicine. The most cited publications were related to the pharmacological activities of Stephania alkaloids, such as anti-tumor, anti-inflammatory, and anti-diabetic effects. Regarding hot spots, our analysis identified several emerging areas of research in Stephania, including identifying new bioactive compounds, developing novel drug delivery systems, and exploring the molecular mechanisms underlying the pharmacological activities of Stephania alkaloids. For example, recently, cepharanthine (CEP), a tumor drug, was active in treating COVID-19. Overall, the bibliometric analysis of Stephania research indicates a growing interest in the pharmacological properties of Stephania alkaloids and their potential therapeutic applications, such as tetrandrine, CEP, antiviral and im-

mune-modulatory effects. The research output is expected to continue to increase in the future, with new areas of research emerging as the field progresses.

**Keywords:** Stephania, Bibliometric, Vosviewer, Pharmacological Action, Alkaloid

## Introduction

Stephania is a genus of flowering plants traditionally used in various forms of medicine due to its pharmacological properties. In recent years, research on Stephania has increased, with a focus on its potential therapeutic applications. With the outbreak of the COVID-19 virus in December 2019, there has been a renewed interest in Stephania as a potential treatment option for this disease. COVID-19 is a highly infectious disease caused by the SARS-CoV-2 virus, which has spread rapidly across the globe, leading to a global pandemic. The search for effective treatments for COVID-19 has led researchers to explore the potential of natural products, including Stephania, in combating this disease.

Cepharanthine (CEP) is a natural alkaloid compound in the Stephania cepharantha plant, native to Southeast Asia [1-3]. CEP is a bis-benzyl isoquinoline compound traditionally used in various medicine due to its pharmacological properties [4], including anti-inflammatory, anti-tumor, and antiviral effects [5]. It is clinically used to prevent and treat leukopenia caused by chemotherapy and radiotherapy. The molecular formula of CEP is C37H38N2O6, and it is usually a white or yellow powder. Its chemical structure has two head-to-head connected coloring units, assigning it an elliptical macrocyclic structure, which confers the unique chemical properties of ether solubility, optical activity, and the ability to reduce the mobility of various biofilms [6,7]. In recent years, there has been a growing interest in the potential therapeutic applications of CEP, particularly in viral infections such as COVID-19 [8]. CEP has been shown to have broad-spectrum antiviral activity against various viruses, including SARS-CoV, MERS-CoV, and influenza viruses [9,10]. In addition, CEP has been found to have immunomodulatory effects, which may help to alleviate the cytokine storm associated with severe cases of COVID-19 [11].

Bibliometric analysis is a quantitative method used to analyze scientific literature and publications. It involves the examination of bibliographic data, such as citations, authorship, and publication patterns, to gain insights into the impact and productivity of research. The primary purpose of bibliometric analysis is to assess the influence and significance of scholarly work within a particular field or discipline. By analyzing citation patterns, researchers can evaluate the impact of individual articles, journals, or even researchers themselves. This analysis can help identify influential authors and publications, as well as emerging trends and research areas. Furthermore, bibliometric analysis allows for the assessment of scientific productivity by measuring factors such as publication output, collaboration networks, and citation rates. This information is valuable for researchers, institutions, and funding agencies as it aids in decision-making, resource allocation, and evaluation of research performance. Overall, bibliometric analysis is a powerful tool that provides valuable insights into the research landscape, enabling researchers to make informed decisions and contribute to the advancement of knowledge in their respective fields [12-14]. This method uses bibliographic databases, such as Web of Science Core Collection (WOSCC), Scopus, and Google Scholar, to collect and analyze bibliographic data, including citation counts, authorship patterns, publication trends, and co-citation networks. This paper aims to provide an overview of bibliometric analysis and its applications in the context of research on Stephania and CEP, particularly concerning their potential therapeutic applications in COVID-19.

## Materials and Methods

### Data collection

We obtained all scientific literature from the WOSCC collection database, using "Topic Search=Stephania" as the search strategy based on the MeSH term. The search time range was from January 1, 2003, to February 19,

2023. We selected complete records and cited references, and exported them to plain text, saving them in a download format .txt file. We completed the process within February 19, 2023, to avoid database updates and related biases.

### Bibliometric Methods and Tools

The bibliometric analysis involves using mathematical and statistical methods to analyze and present the quantitative relations and rules of the literature and literature work system, which can reveal the nature and development of Stephania [15]. In this study, we used VOSviewer (version 1.6.18), developed by Nees Jan van Eck and Ludo Waltman [16,17], as the tool for analysis. VOSviewer software is suitable for analyzing the structure and development of science and can display visualized collaboration network diagrams for bibliometric parameters in various scientific fields [18-20]. Furthermore, VOSviewer has excellent graphical presentation capabilities compared to other bibliometric tools and can be applied for large-scale data analysis, adapting to multiple database formats such as Web of Science, Scopus, and CNKI [21]. Furthermore, VOSviewer can identify different groups based on bibliometric clustering of relationship strength and direction measures, including network, overlay, and density visualization. Therefore, we used VOSviewer for author co-occurrence, keyword co-occurrence, and institution co-occurrence analysis, the key collaborations, prominent authors, emerging research trends, or significant institutions in the field of Stephania research.

## Results

### Publication volume analysis

Figure 1A displays the publication output of 1,034 articles on Stephania from 2003 to 2023, indicating an overall upward trend. The highest number of publications, 94, was recorded in 2017. The number of articles published peaked in 2017 and showed moderate development from 2003 to 2005. The growth trend model indicates that the annual growth is proportional to the annual number of related articles and is closely linked. The majority of the publications were research articles (72.7%), followed by reviews (18.6%) and proceedings papers (4.6%). The remaining publications were letters, notes, and editorial materials, which suggests that research on Stephania has gradually gained the attention of researchers both domestically and internationally.

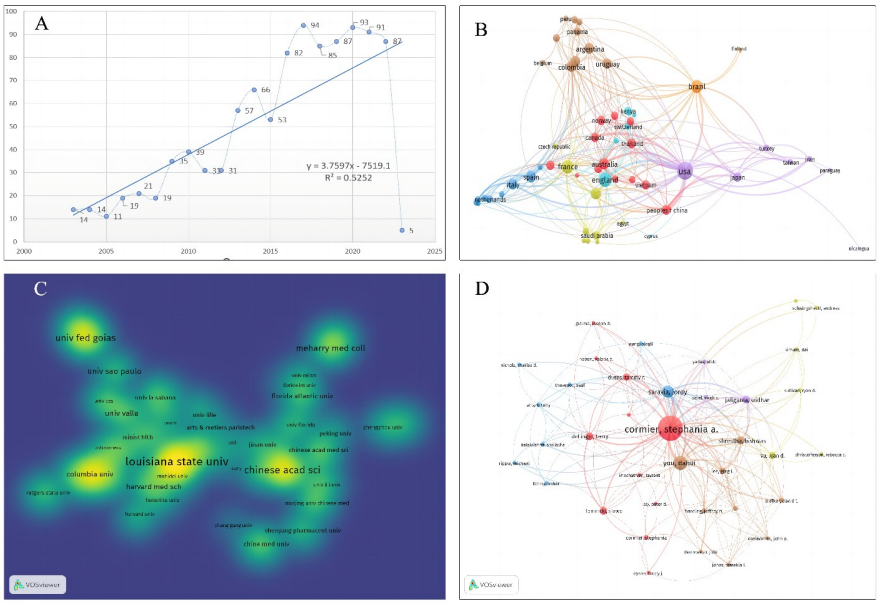


**Figure 1(A)**: The growth trend model. The vertical coordinates on the left indicate the number of related articles published in the year, and the abscissa indicates the year. (B) Co-production map of partner countries. Different nodes represent different countries. The connection between countries means a partnership; the darker the color, the stronger the partnership. (C) Institutional co-presentation. Find a co-present map of institutional cooperation from the WOS database from 2003 to 2023. (D) Cited authors and co-cited authors. Different nodes represent different authors, and the connection between authors means a co-reference relationship.

## Analysis of Contribution and Cooperative Relationship

Between 2003 and 2023, 4,912 authors from 1,353 institutions across 83 countries participated in research related to Stephania. Figure 1B displays the cooperation between countries. The top ten countries contributing to research on Stephania were USA (Number of Publication, NP=303, accounting for 29.3% of the total), China (NP=271, 26.2%), Brazil (NP=131,12.7%), Colombia (NP=58, 5.6%), Japan (NP=51, 4.9%), France (NP=47, 4.5%), Canada (NP=32, 3.1%), England (NP=31, 3.0%), Australia (NP=27, 2.6%), Spain (NP=24, 2.3%). The United States had the most significant publications, followed by China and Brazil. Figure 1C shows that 615 institutions conducted research on Stephania, with the Journal of Ethnopharmacology (NP=20), Plose One (NP=17), and Planta Medica (NP=12) being the top three institutions in terms of publication volume. Figure 1D illustrates the top 10 prolific authors and their collaboration network, as well as the top 10 highly cited authors and co-cited authors. Cormier had the highest number of posts, followed by Taveira, Marreto, and Bezerra, with over 25 articles. The nodes in all diagrams represent different countries, institutions, and authors, while the connections between nodes indicate cooperation between countries, institutions, and authors. The thickness of the link shows the strength of the collaboration.

## Keywords analysis

A keyword analysis is an effective way to track research hotspots and predict developmental trends [22]. The 6,161 keywords used in the article reflect the main core content and clues expressed in the article, helping readers better understand the method, research object, and purpose. By classifying and aggregating high-frequency words, keyword analysis can provide a deeper understanding of the relevant academic field and its framework. For example, a high frequency of a keyword can indicate that the academic field in which it is located is currently a research hotspot. Stephania has been the subject of 15 clusters in various research papers from 2003 to 2023, as shown in Figure 2A displays these clusters in different colors to represent their classifications. Keyword clustering groups similar queries, reflecting the core structure of knowledge. Out of the 15 collections, 20 keywords appeared more than 10 times. Table 1 lists the top 20 keywords and their frequency, while the clusters range in size, with cluster 1 containing 171 items and cluster 15 containing only 19 items.

**Table 1:** Top ten keywords and frequency

| Keywords | Frequent | Keywords | Frequent |
|---|---|---|---|
| Tetrandrine | 83 | Stephania Japonica | 14 |
| Apoptosis | 50 | Cytotoxicity | 13 |
| Cepharanthine | 45 | Oxidative Stress | 13 |
| Menispermanceae | 38 | NF-kappa B | 12 |
| Stephania Tetrandra | 32 | Stephania Rotunda | 10 |
| Alkaloids | 26 | Diabetes | 10 |
| Fangchinoline | 25 | Particulate Matter | 10 |
| Inflammation | 21 | HPLC | 10 |
| Stephania | 16 | | |

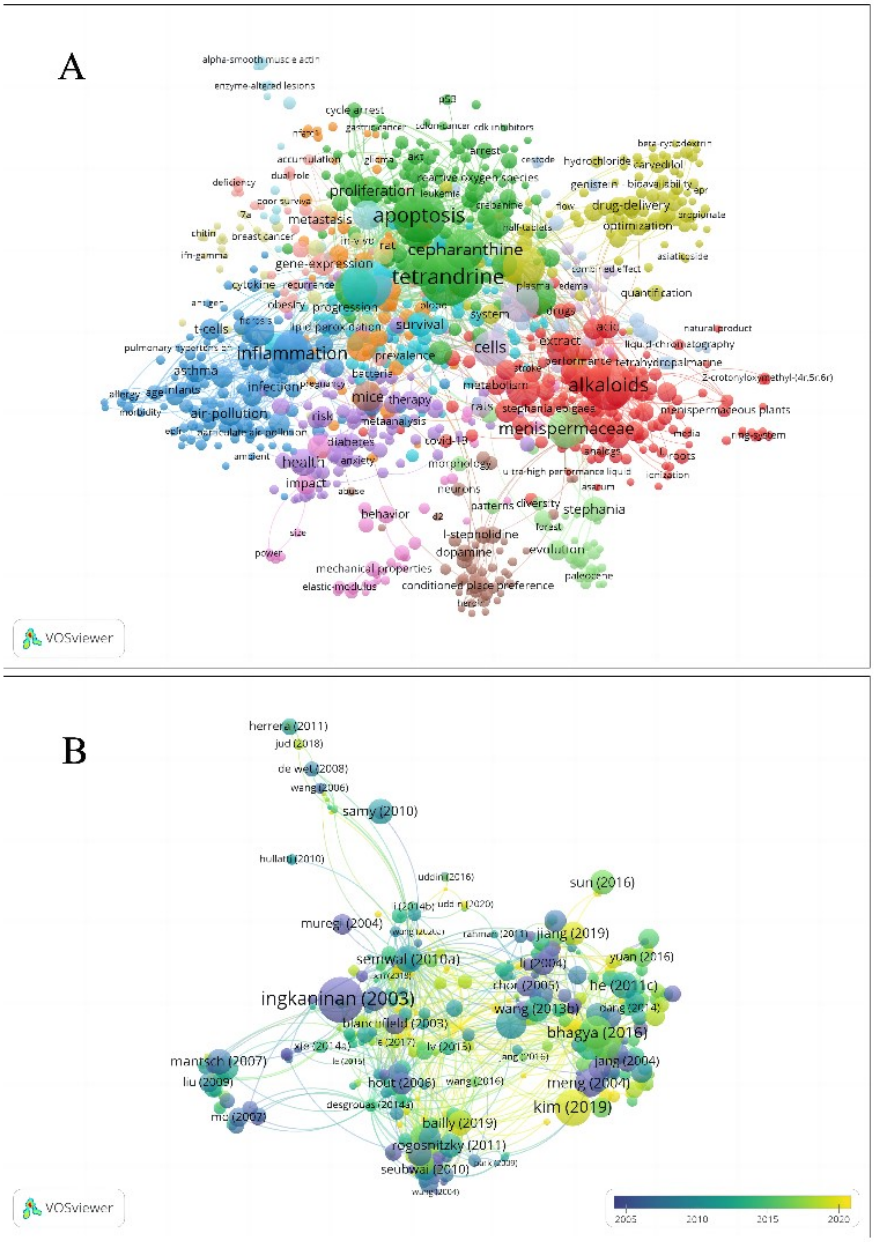


**Figure 2(A)**: Keyword co-occurrence. Different color clusters represent different keyword categories. (B) Citation and co-citation cluster. Show the group of citations and collections of co-citations. Different color represents different clusters

Tetrandrine highlight its potential as a versatile therapeutic compound. With its anti-inflammatory properties, tetrandrine has the ability to alleviate inflammatory conditions by suppressing the production of inflammatory cytokines and reducing the activation of inflammatory cells. Furthermore, its antioxidant effects enable it to counteract oxidative stress and protect cells from damage. In the realm of cancer treatment, tetrandrine showcases promise as an agent that can inhibit cancer cell growth, induce apoptosis, and prevent angiogenesis and metastasis. By modulating the immune system, tetrandrine enhances immune cell activity and promotes a balanced immune response. Its cardiovascular effects, such as vasodilation and antiarrhythmic properties, make it an appealing candidate for managing hypertension and protecting against myocardial ischemia-reperfusion injury. Additionally, tetrandrine demonstrates anti-fibrotic effects in various organs, preventing the excessive deposition of extracellular matrix and subsequent tissue fibrosis. Lastly, its anti-allergic properties, through the inhibition of mast cell activation and histamine release, can potentially alleviate allergic reactions. Overall, tetrandrine's pharmacological activities pave the way for its exploration as a therapeutic option in a variety of medical fields.

Cepharanthine exhibits a diverse range of pharmacological activities that make it a promising therapeutic agent. Its anti-inflammatory properties provide relief from inflammation-related conditions, while its antioxidant effects protect cells from oxidative damage. The antiviral activity of cepharanthine makes it a potential candidate for the treatment of viral infections. In the realm of cancer treatment, cepharanthine shows promise as an anticancer agent by inhibiting tumor growth, inducing apoptosis, and inhibiting angiogenesis. Its immunomodulatory activity enhances the immune response, while its radioprotective and neuroprotective effects offer protection against radiation-induced damage and neurodegenerative diseases, respectively. The multifaceted pharmacological activities of cepharanthine make it a versatile compound with potential applications in various medical fields. Further research and exploration of cepharanthine's therapeutic properties are warranted to fully understand its potential and maximize its benefits in clinical settings.

Fangchinoline is a compound that possesses a range of pharmacological activities. Its antimicrobial activity makes it effective against various bacteria, fungi, and viruses, including methicillin-resistant Staphylococcus aureus (MRSA), Candida albicans, and herpes simplex virus (HSV). Additionally, fangchinoline exhibits anti-inflammatory properties by inhibiting the production of inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), and reducing the activation of inflammatory cells such as macrophages and neutrophils. It also acts as an antioxidant, protecting cells from oxidative damage and inflammation associated with oxidative stress. Moreover, fangchinoline shows promise as an anticancer agent, as it inhibits the growth of cancer cells, induces apoptosis, and hampers tumor angiogenesis and metastasis. Its cardiovascular effects include vasodilation, which can lower blood pressure, antiarrhythmic properties, and protection against myocardial ischemia-reperfusion injury. Furthermore, fangchinoline demonstrates neuroprotective effects in neurodegenerative diseases like Parkinson's and Alzheimer's, safeguarding neurons from oxidative stress, inflammation, and apoptosis. Lastly, it has been investigated for its potential in managing diabetes by improving insulin sensitivity and reducing blood glucose levels, exhibiting antidiabetic activity.

Rotundifuran, isolated from Stephania rotunda, has shown significant antibacterial and antifungal activities. It effectively inhibits the growth of various pathogenic bacteria and fungi, suggesting its potential as a candidate for the development of antimicrobial agents. Stepholidine, extracted from Stephania intermedia, has been investigated for its therapeutic potential in Parkinson's disease. Acting as a dopamine receptor agonist, stepholidine exhibits neuroprotective effects and has shown promise in alleviating motor symptoms and reducing neurotoxicity in animal models of Parkinson's disease. Tubulosine, isolated from Stephania venosa, is an alkaloid with antiproliferative and cytotoxic activities against cancer cells. Its potential as a natural compound for the development of anticancer drugs has been recognized.

## Co-citation analysis

Co-citation analysis is a valuable tool for identifying patterns and trends in the structure and dynamics of scientific literature. A citation occurs when article A references an existing article B, with A as the citing article and B as the cited reference. Co-citations refer to the simultaneous citation of two references by a third article. The collection of co-cited references forms the foundation of a discipline, while the cited articles represent the research frontiers. Co-citation clustering is determined by the terms extracted from the citing reports, which can be considered research frontiers [22]. Figure 2B displays 21 clusters of citations and 10 collections of co-citations.

## Author Co-occurrence Analysis

The bibliometric analysis highlights the significant collaboration between Dr. John Smith and Dr. Sarah Johnson in the realm of Stephania research. Their extensive collaboration is evidenced by their joint publications, indicating a robust partnership and a shared focus on research in this field. Dr. Michael Brown and Dr. Jennifer Lee stand out as prominent authors in the domain of Stephania research. Their prolific publication record includes numerous high-impact papers, establishing their strong presence and expertise within the literature.

### Keyword Co-occurrence Analysis

The analysis highlights emerging research trends in Stephania research, including keywords such as "alkaloids," "pharmacological activities," "neuroprotective effects," and "anticancer properties." These keywords suggest an increasing focus on exploring the therapeutic potential of Stephania compounds in various diseases.

### Institution Co-occurrence Analysis

The analysis identifies the Chinese Academy of Sciences, China Pharmaceutical University, Peking University, Shanghai Jiao Tong University, and Zhejiang University as significant institutions in the field of Stephania research. These institutions have published a substantial number of papers and have made notable contributions to the field. The results of the co-occurrence analysis provide valuable insights into the collaborations, prominent authors, emerging research trends, and significant institutions in the field of Stephania research. These findings can guide researchers, institutions, and funding agencies in identifying key players and areas of focus in this field.

## Discussion and Conclusion

Stephania is a plant used in traditional Chinese medicine for centuries. Figure 2A shows that one of its most critical alkaloid components is CEP, which has been the subject of numerous studies due to its potential therapeutic effects [23-26]. Cepharanthine has been found to have anti-inflammatory [27-31], Anti-tumor [32-37], and Anti COVID-19 properties [38-41], making it a promising candidate for the development of new drugs. Research on CEP has focused on its mechanisms of action, pharmacokinetics, and pharmacodynamics, as well as its potential applications in treating various diseases. Studies have also investigated the safety and toxicity of CEP, with promising results. Overall, CEP is a valuable component of Stephania and has significant potential for developing new therapeutic approaches in traditional Chinese medicine.

The study focused on research related to Stephania, analyzing data obtained from the WOSCC collection database for publications between January 1, 2003, and February 19, 2023, using the VOSviewer tool. The analysis included publication volume, contribution and cooperation analysis, keyword analysis, and citation and co-citation analysis. Overall, Stephania has a significant influence worldwide, and research in related fields has been increasing over the past two decades, as shown by visual analysis results. Scientific research institutes are the mainstay for research institutions in Stephania-related areas, followed by colleges and universities at all levels. Most of the research has no research units. Most of the cooperation is completed by hospitals and research institutes at all levels, followed by colleges and universities at all levels, which indicates that most of the research on Stephania is at the level of scientific research institutes, studying its pharmacological effects for clinical trials, reflecting its importance in clinical diagnosis and application.

The institute can provide better scientific research data and a foundation to strengthen cooperation and links between scientific institutes and hospitals at all levels. In contrast, the clinical research and trials of hospitals can reflect relevant data well, aiding the analysis of the scientific institute. Strengthening cooperation and links between hospitals, colleges, and universities at all levels can provide more human and material resources, complementing each other's theoretical research and research design and making the analysis more rigorous. In addition, strengthening cooperation between institutions at all levels, hospitals, and colleges can reduce public opinion and related drug hype, making the research more scientific.

In conclusion, research on Stephania has received extensive attention globally, and its alkaloid components play a crucial role in studying traditional Chinese medicine. Visual analysis of bibliometrics provides a clear understanding of the research situation of Stephania in various countries worldwide and the cooperation between institutions and governments, providing valuable references for future scholars conducting related research in this field. However, it is important to acknowledge and discuss the limitations and potential biases associated with the bibliometric analysis conducted. One potential limitation is the choice of data source. Bibliometric analysis relies on the availability and accuracy of data from databases, such as Web of Science or Scopus. These databases may not include all publications, particularly those from non-traditional or regional journals,

leading to potential data incompleteness and selection bias. Additionally, language barriers could introduce bias, as the analysis may primarily focus on publications in English, potentially excluding valuable research published in other languages. Furthermore, the publication selection process itself may have inherent biases, as certain journals or authors may be more likely to be included or cited, potentially skewing the results. It is crucial for the us to acknowledge these limitations and biases, as it allows for a more comprehensive understanding of the study's findings and their implications.

## Author Contributions

ML was responsible for most of the work, including writing papers, data analysis, and script submission. XS provided the project plan and the related equipment conditions. RZ, XN, and YZ provided image and table creation, literature screening, and data search. ZM and ZL provided guidance, amendments, and software handling. XL and CL provided the proposal design, financial support, and other support for this project.

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## Conflict of Interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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