Current status and trends for natural products on hyperuricemia research: a scientometric visualization analysis from 2000 to 2021

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Abstract. – **OBJECTIVE:** Hyperuricemia (HUA) is a metabolic disease caused by abnormal purine metabolism in the body. It also shows a trend of high incidence among younger people worldwide. More and more studies have shown that natural products can be used to treat HUA, and the literature in this field has been increasing in recent years. However, few bibliometric analyses have systematically examined this field. Our study aims to analyze the published literature to identify trends and hotspots in natural product therapy for HUA, present the research status and summarize critical topics.

MATERIALS AND METHODS: A literature search was conducted through the Web of Science Core Collection (WOSCC) database, using Bibliometric R, VOS Viewer, and CiteSpace to examine the eligible publications. A total of 1,201 publications (1,040 articles and 161 reviews) concerning natural product therapy for HUA research between 2000 and 2021 were ultimately included.

RESULTS: In recent years, research articles in this field have increased. China and the United States are the main driving forces in this field and have a high academic reputation. China published the most relevant articles, while the United States cited the most. Chinese Acad Sci is the institution with the most relevant research results. Flavonoids, xanthine oxidase, antioxidant activity, and gout are the current research hotspots and future research trend topics.

CONCLUSIONS: Our results provide a general overview of the leading research directions of natural products in HUA research. The mechanisms of natural products, especially those related to xanthine oxidase, antioxidant activity, and gout, may soon become hot spots and should be closely watched. The field of natural product therapy for HUA is going through rapid development, and our research provides a valuable reference for clinical researchers and practitioners.

Key Words:
   Natural product, Hyperuricemia, Bibliometric, Visual analysis, Research frontier.

Introduction

With the changes in the dietary structure of modern people, the incidence of hyperuricemia (HUA) is increasing yearly. HUA is a metabolic disease caused by abnormal purine metabolism in the body. According to statistics, the total prevalence of HUA in China is 13.3%[1]. The absolute majority in the United States is also 14.6%[2], showing a trend of high incidence among young people worldwide. HUA is the biochemical basis of the pathogenesis of gout. Gout occurs when urate is deposited in human tissues, causing damage to the body. At the same time, HUA is also closely related to chronic kidney disease, cardiovascular and cerebrovascular diseases, and metabolic syndrome. The pathogenesis of HUA mainly includes primary HUA, secondary HUA, increased uric acid production, and decreased uric acid excretion. The onset of HUA is also accompanied by hypertension, obesity, atherosclerosis, etc., posing a threat to human life safety.

Currently, the clinical treatment of HUA is mainly based on small-molecule synthetic drugs, such as allopurinol and febuxostat, which inhibit the production of uric acid, and benzbromarone, which promotes the excretion of uric acid. Although these drugs have apparent effects on reducing serum uric acid levels, there are adverse reactions such as severe allergic reactions and liver and kidney damage. Natural products have a wide range of sources, low toxicity, and side effects, and they are an essential source of drug discovery. More and more natural organisms have been found[3] to have a wide range of uric acid-lowering activities and high safety. It has become an important direction for the discovery of new drugs for the treatment of HUA. In recent

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years, natural products have had a remarkable curative effect in treating HUA, and they have gradually become dominant drugs. Studies[4-17] have shown that natural product extracts, including Shanchahua, Danshen, Yejuhua and Rougui, Tianyeju, Mugua, Juhua, Lamuye, Xunma, Qinpi, Duzhong, Tufuling, Qincaizi, Shihu, etc. can inhibit the production of uric acid and promote the excretion of uric acid, thereby reducing uric acid. At present, the more widely studied natural product monomers also have good uric acid-lowering activity, and compounds such as flavonoids, saponins, and coumarins are outstanding, including quercetin, galangin, apigenin, chrysin, luteolin, herbalin, osthole, diosgenin, ellagic acid, etc[18-28].

Bibliometrics is an interdisciplinary science that quantitatively analyzes knowledge carriers, taking the literature system and bibliometric characteristics as the research object. Bibliometrics has been carried out in a wide range of research topics, including the medical field[29,30]. Several bibliometrics tools have been developed and are frequently used, including VOS Viewer, CiteSpace, Excel, etc. These tools enable researchers to quickly assess the discipline's current state and identify hotspots, especially for novice and non-specialist researchers[31,32]. In recent years, several papers have been published on natural products for the treatment of HUA. However, to our knowledge, there has yet to be any study that outlines it from a bibliometric perspective. Therefore, we performed a bibliometric analysis to understand the research trends of natural products in the treatment of HUA from multiple aspects, including the number of papers published each year, prolific countries, essential journals, key references, and research priorities. This study is intended to be a reference for clinical researchers and practitioners.

Materials and Methods

Data Source

Data were downloaded from the Science Citation Index (WoSCC) on the day of December 31, 2021. The following search terms were used: TS=("Natural Product*" OR "Natural Compound*" OR "Natural Molecule*" OR "Phytochemical*" OR "Secondary metabolite*") AND TS=("Acid, Uric*" OR "2,6,8-Trihydroxypurine*" OR "Trioxopurine*" OR "Potassium*" OR "Urate*" OR "Urate, Potassium*" OR "Ammonium Acid Urate*" OR "Acid Urate, Ammonium*" OR "Urate, Ammonium Acid*" OR "Sodium Urate Monohydrate*" OR "Monohydrate, Sodium Urate*" OR "Urate Monohydrate, Sodium*" OR "Monosodium Urate Monohydrate*" OR "Monohydrate, Monosodium Urate*" OR "Urate Monohydrate, Monosodium*" OR "Sodium Acid Urate Monohydrate*" OR "Sodium Urate*" OR "Urate, Sodium*" OR "Monosodium Urate*" OR "Urate, Monosodium*" OR "Sodium Acid Urate*" OR "Acid Urate, Sodium*" OR "Urate, Sodium Acid*" OR "Hyperuricemia*"). Non-English language, non-article, and non-review publications were excluded. All data, including titles, author information, abstracts, keywords, journals, and references, were downloaded on the same day[32]. This query yielded 1,201 records, which were obtained for this study. Data involving full records and cited references were downloaded in txt format. Microsoft Excel Office 2019 was applied to manage data. The study was performed following the PRISMA guidelines **(Annex 1)**.

Data Collection

All records were retrieved from WoSCC, including the annual number of publications, output by country, institution, journal, author, frequency of citations, etc. Data was converted into Microsoft Excel 2019, VOS Viewer, and CiteSpace V to analyze fundamental indicators.

Statistical Analysis

Annual publication production, total and average citations, citations per article, and complete citations by country were analyzed and plotted using Microsoft Excel v. 2019 and organized the essential characteristics of publications and citations data. Statistically significant differences between means are marked in each graph. $p < 0.05$ was considered statistically significant. VOS observers were used to create network visualization maps to analyze collaborations among countries, institutions, and authors of highly cited literature. In addition, the VOS Viewer can categorize keywords with high co-occurrence frequency into several clusters and simultaneously color them according to the time course. Co-occurrence analysis identified research hotspots and trends. We choose "author keywords" as the unit of analysis. We performed citation analysis of journals and clusters using CiteSpace V, which captures keywords with strong citation bursts and builds a visual map of all entries. The surge in citations is a key indicator for identifying emerging trends.

Results

## Publication Output and Temporal Trend

After analysis, 1,201 publications met the inclusion criteria, including 1,040 articles and 161 reviews. The annual production of publications in this field of study increased steadily until 2008, and since then has grown substantially from 2009 to 144 in 2020, more than seven times the annual production in 2008 (Figure 1A).
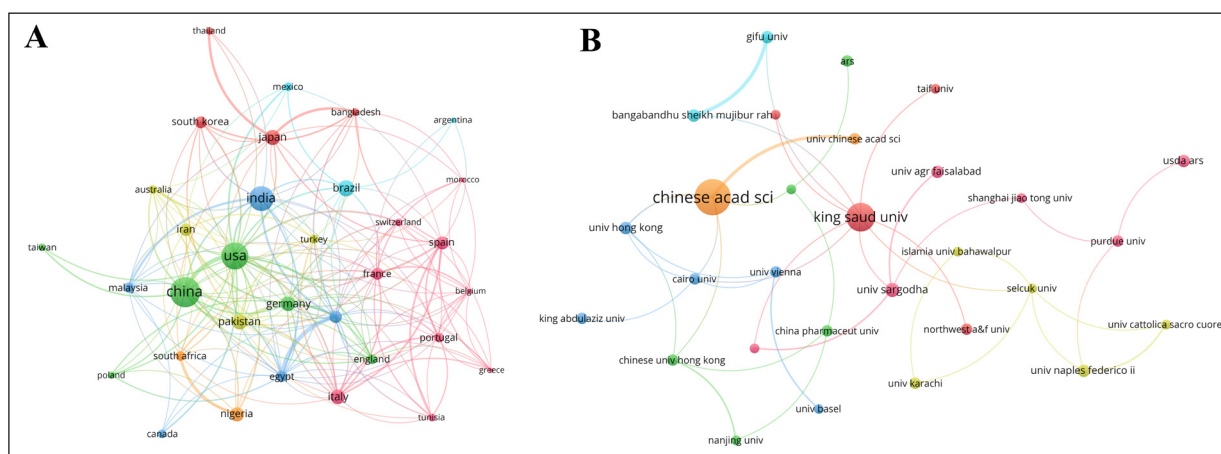
Distribution by Country/Region and Institution

All publications were distributed to 94 countries/regions and 1,729 institutions (**Supplementary Table I** and **Supplementary Table II**). China has the highest document production with 180 copies (14.98%), followed by the United States (151 copies, 12.57%), India (128 copies, 10.67%), Brazil (63 copies, 5.25%), and Japan (58 copies, 4.83%) (Figure 1B). We further identified the top 10 countries with the highest number of citations, with the United States ranking first (7,555 times), followed by China

(3,558 times), India (1,897 times), Germany (1,639 times), and England (1,468 times) (Figure 1C). All articles were cited 28,030 times, and the H-index was 77. After our analysis, we found that the number of publications in the United States is not the highest among all countries and regions. Still, citations are the highest, nearly twice as high as second-ranked China. At the same time, it is found that the number of publications in Germany and England is 54 and 29, but with 1,639 and 1,468 citations, indicating higher sources in these two countries. A global visualization map was used to indicate the research depth of each country or region in this research area, with darker colors showing higher publication volume in that country or region (Figure 1D).

Using VOS Viewer to investigate international collaborations, we constructed a network visualization map for publications on natural product therapy for HUA research. Figure 2A shows cooperation among countries that have published more than ten documents (33 of 94 papers). Countries with higher co-occurrence rates are classified as the same color. Countries with similar colors,
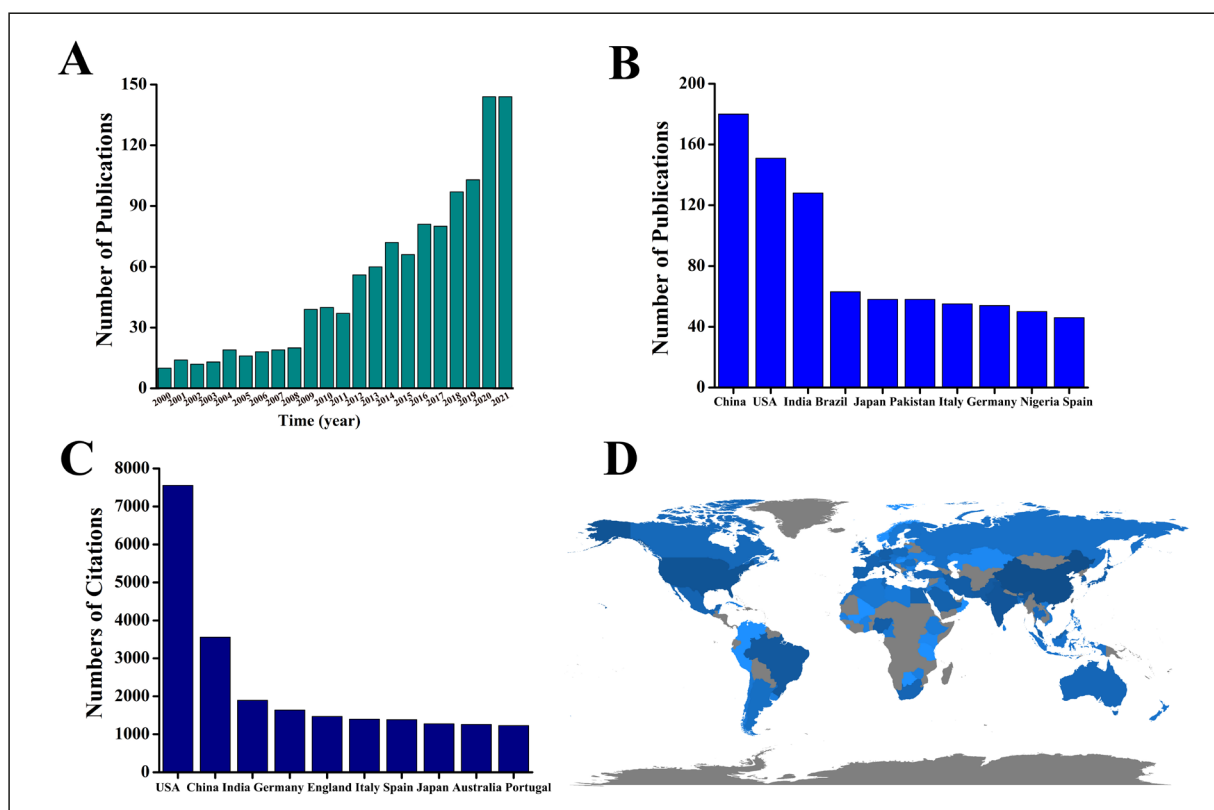
Figure 1. Trends in the number of publications and analysis of country/regions in natural products on HUA research. **A**, The annual worldwide publication output. **B**, The annual national publication output of the 10 most productive countries/regions. **C**, The 10 most-cited countries/regions. **D**, Regional distribution.

Figure 2. VOS Viewer network visualization map of country/regions and institutions involved in natural products on HUA research. **A**, Collaboration analysis of countries/regions. Of the 94 countries/regions, 33 had at least 10 publications. **B**, Collaboration analysis of institutions. Of the 1,729 institutions, 37 had at least 5 publications.

which we consider more closely partnered, form clusters. The width of the line represents the size of the collaboration. The USA has the highest overall link strength, which indicates that it is involved in the most collaborations with the rest of the world (**Supplementary Table III**). The ten institutions with the most relevant research results are shown in Table I. Leading institutions are Chinese Acad Sci (27), King Saud Univ (20), Univ Sao Paulo (12), and Univ Porto (11). We performed a co-authorship analysis using the VOS Viewer to reveal potential collaborative relationships between institutions (Figure 2B, **Supplementary Table IV**).
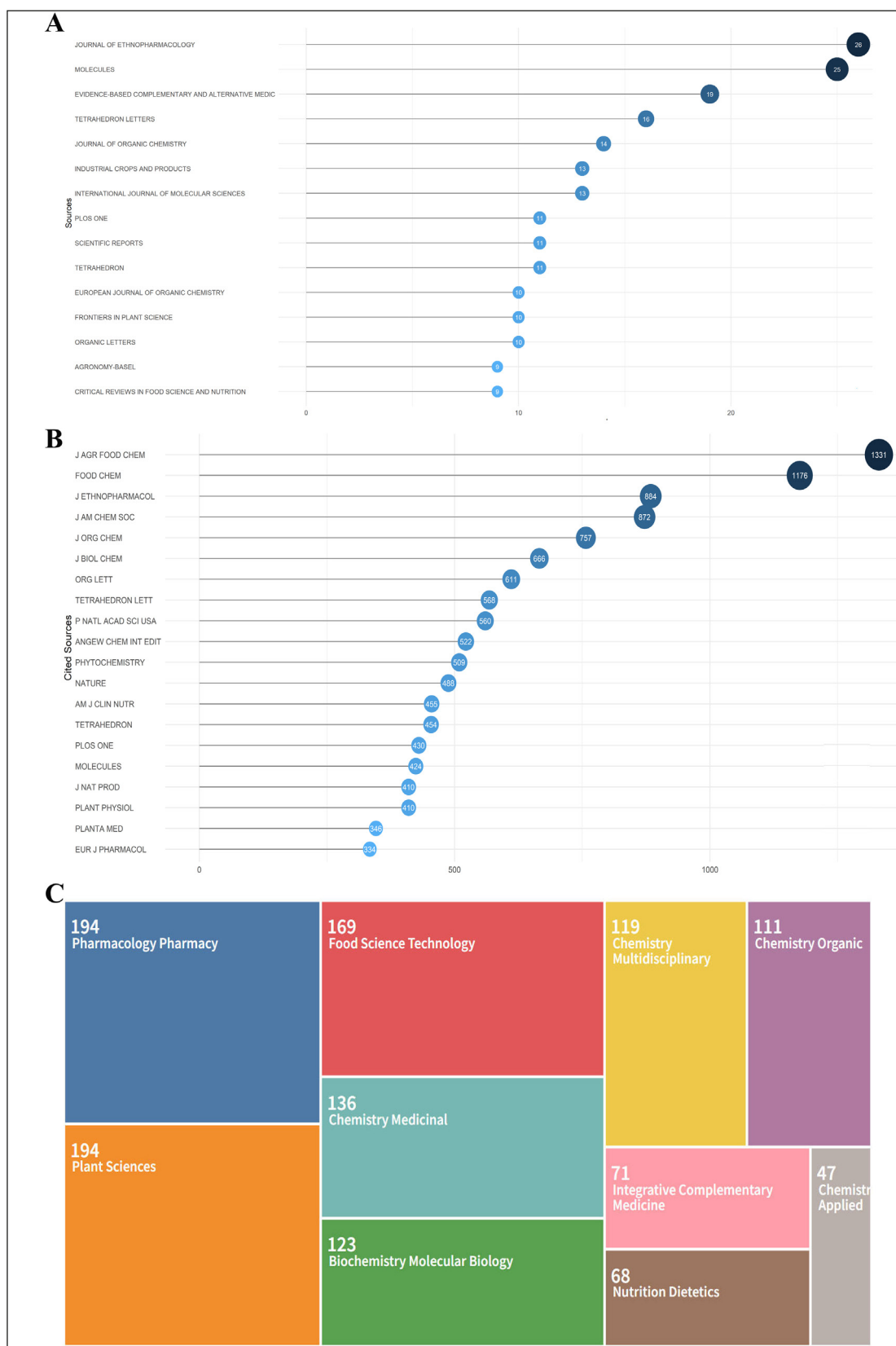
Distribution by Journal

1,201 papers on natural products for the treatment of HUA were published in 558 academic journals. This study lists the 10 most productive journals (Figure 3A). Journal of Ethnopharmacology pub-

lished the most papers (26 publications), followed by Molecule (25 publications), Evidence-Based Complementary and Alternative Medicine (19 publications), Tetrahedron Letters (16 publications), and Journal of organic chemistry (14 publications). These are the 10 journals with the most locally cited source (Figure 3B), Journal of Agricultural and Food Chemistry local cited source is the highest (1,331 times), followed by Food Chemistry (1,176 times), Journal of Ethnopharmacology (884 times), Journal of the American Chemical Society (872 times), Journal of Organic Chemistry (757 times). The results of Web of Science categories show that Pharmacology Pharmacy and Plant Sciences have the highest proportions (194, 16.15%), followed by Food Science Technology (169, 14.07%), Chemistry Medicinal (136, 11.32%) and Biochemistry Molecular Biology (123, 10.24%) (Figure 3C, **Supplementary Table V**).

Table I. Top 10 productive authors and co-cited authors in natural products on HUA Research.

Rank	Author	Count	Rank	Co-cited author	Citation
1	Gasparotto Junior A	9	1	Sarker U	152
2	Oba S	7	2	Aoac	73
2	Rouphael Y	7	2	Ueda M	73
2	Sarker U	7	4	Molander GA	70
5	Calloi Palozi RA	6	5	Bubnov YN	57
5	Saito N	6	6	Denmark SE	54
5	Signor Tirloni CA	6	7	Nicolaou KC	53
5	Suwanborirux K	6	8	Wang Y	51
5	Ueda M	6	9	Singleton VL	48
10	Cho SS	5	10	Harborne JB	40

A

B

C

Figure 3. The results of journal distribution about natural products on HUA research. **A**, the 10 most productive journals. **B**, 10 journals with the most locally cited source. **C**, The categories of Web of Science.
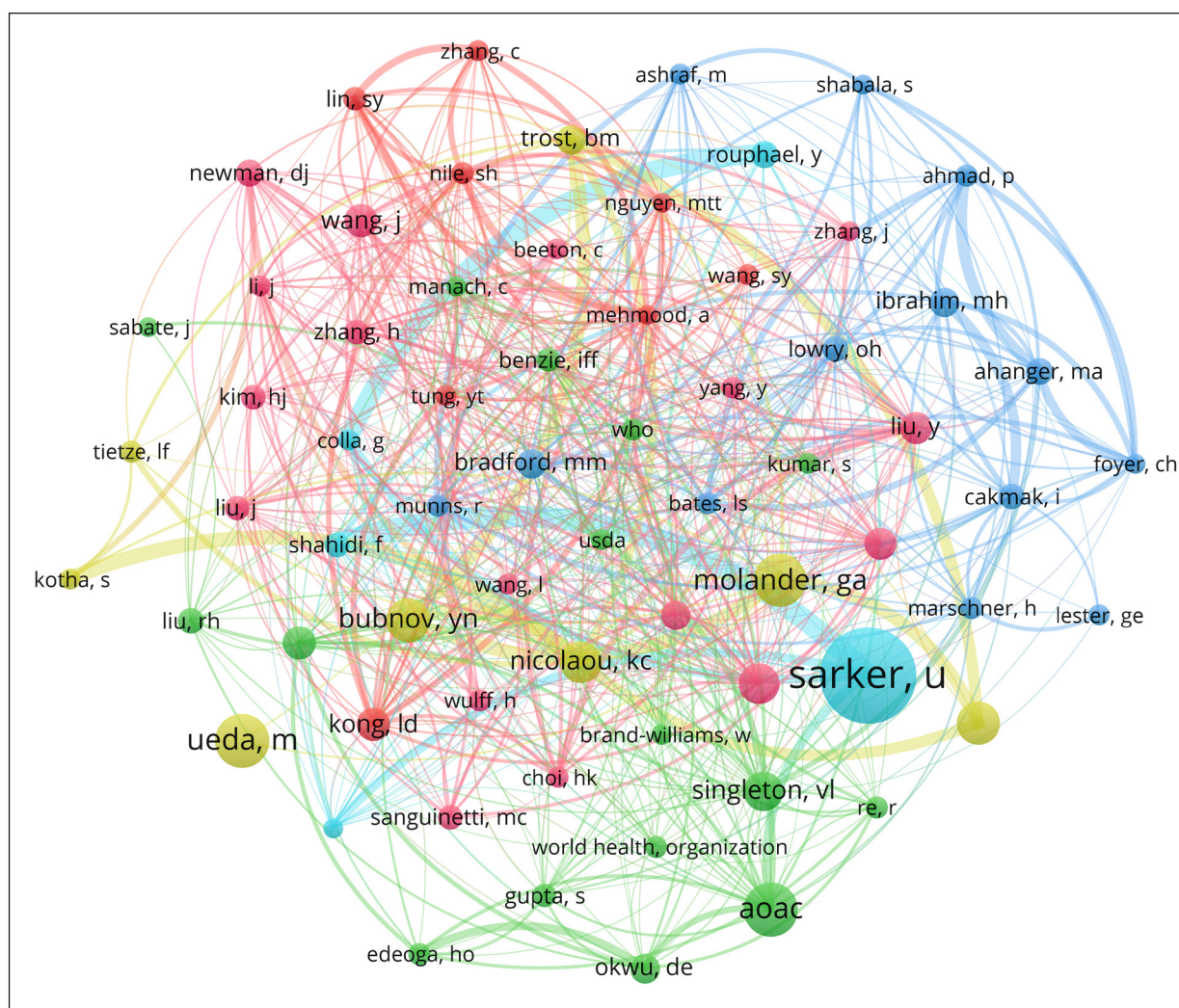
Figure 4. VOS Viewer network visualization map of co-cited authors of the articles related to natural products on HUA research. Of the 5,956 co-cited authors, 69 had at least 20 citations.
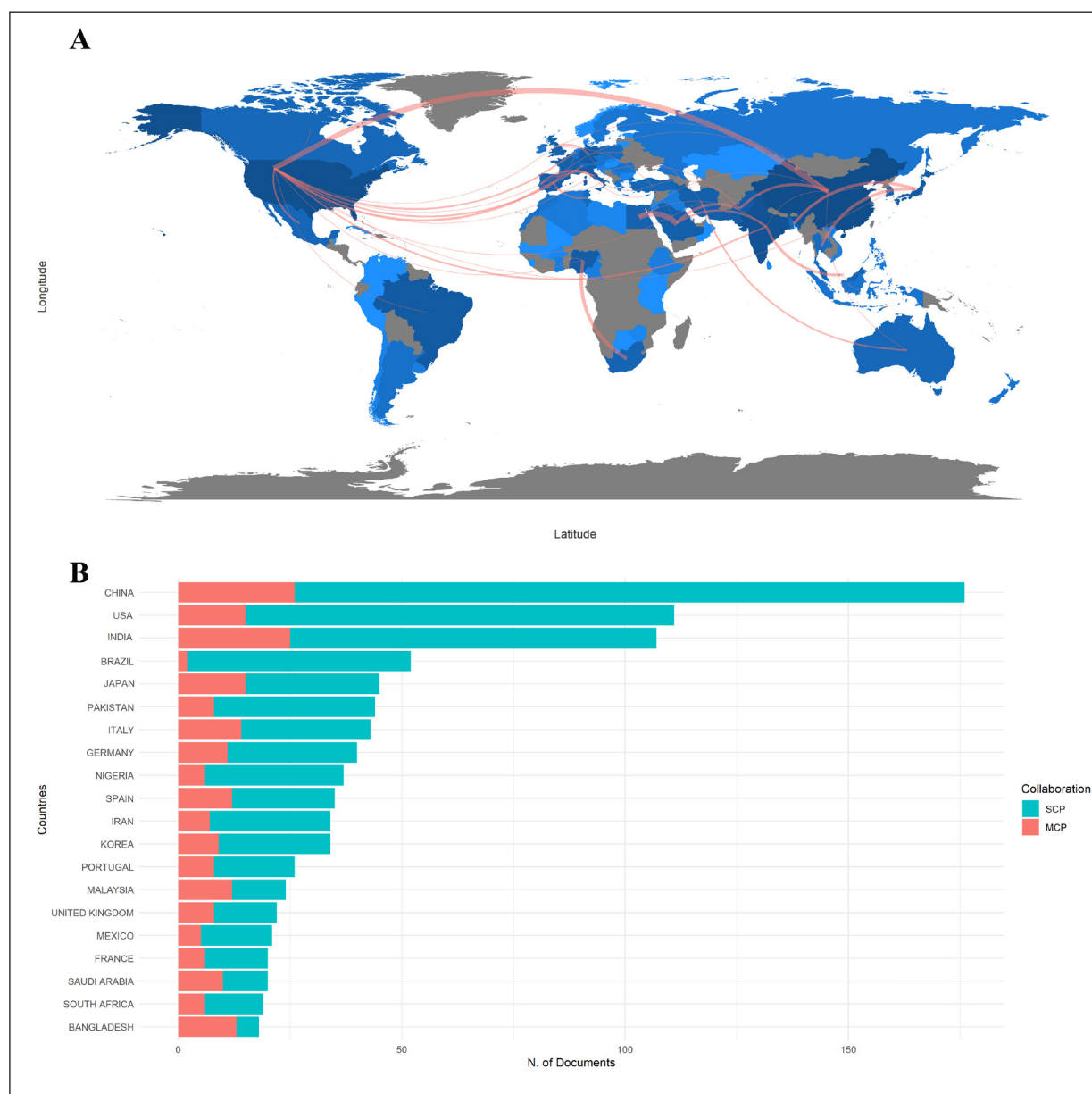
Distribution by Author

In our study, 5,986 authors contributed to all outputs (**Supplementary Table VI**). Table I lists the 10 most prolific authors. With 9 publications, Gasparotto Junior A has the highest number of publications, followed by Oba S (7 publications), Rouphael Y (7 publications), and Sarker U (7 publications). Calloi Palozi RA, Saito N, Signor Tirloni CA, Suwanborirux K, and Ueda M (6 publications) tied for fifth. Network visualization of the cited authors is shown in Figure 4. The most significant nodes are associated with the most frequently cited authors, including Sarker U (152 citations), Oac A (73 citations), Ueda M (73 citations), Molander GA (70 citations), and Bubnov YN (57 citations). Two of the 10 most prolific authors (Sarker U, Ueda M) are among the most frequently cited (**Supplementary Table VII**).

Analysis of Cooperative Relationship

In our research on HUA treatment with natural products, we found that research in this field has more cooperation in various countries and regions. Figure 5A shows the cooperation relationship of different countries on a global scale. The country of the corresponding author is analyzed in this study (Figure 5B). We found that 153 of the 180 publications have authors from the same country, and the results of the multiple country publications analysis show that China (27 publications) and the United States (25 publications), and other countries/regions have published more papers.

Figure 5. Regional distribution (**A**), and the country of the corresponding author (**B**), related to natural products on HUA research.

Analysis of Keyword Co-Occurrence Clusters

We created a keyword co-occurrence knowledge map using the VOS Viewer with 110 terms (defined as terms with more than five occurrences). The size of the circle indicates how often the keyword appears; the more significant the process, the more frequently the keyword appears. Keywords for natural product treatment HUA are shown in Figure 6A. Figure 6B shows an overlay visualization of keywords arranged by time. Pur-

ple, blue, green, and yellow on the time course correspond to the occurrence of keywords in the average time from earlier years to the most recent years. In the current research stage of HUA, "antioxidant activity", "uric acid", and "gout" are the main topics in this field.

Analysis of Burst Keywords

We use CiteSpace to detect emergent keywords, identify hotspots, and research fronts over time. Among the top 100 most cited keywords in
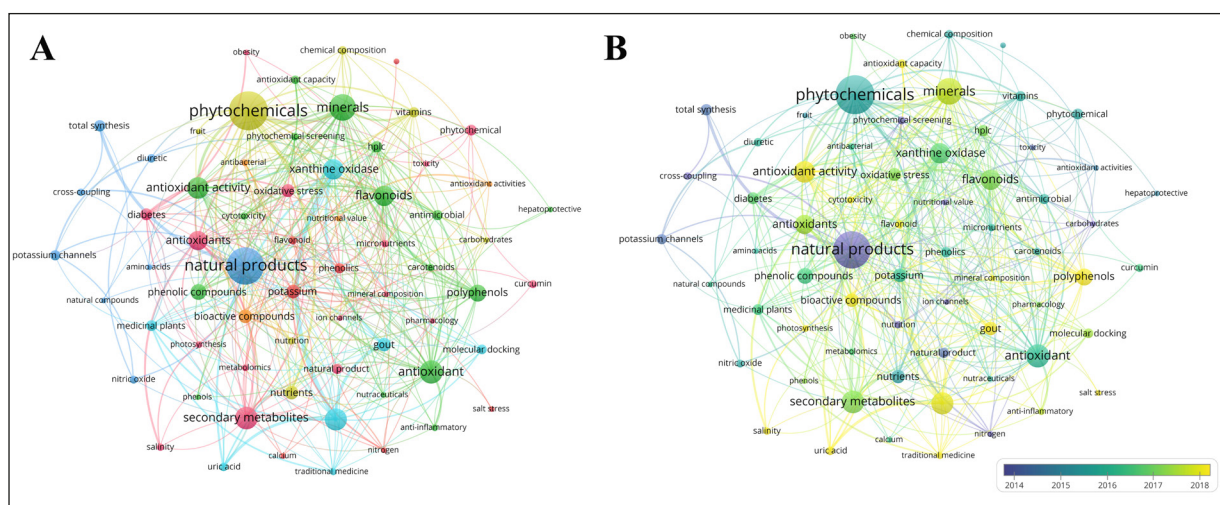
Figure 6. Analysis of keywords in publications related to natural products on HUA research. **A**, VOS Viewer network visualization map of keywords. **B**, VOS Viewer overlay visualization of keywords by time.

this field, we are particularly interested in those that have exploded since 2000 (Figure 7). "protein" (burst strength of 6.28), "potassium channel" (burst strength of 6.3), etc. are the most concerned; research results in recent years have shown that "flavonoid" (burst strength of 4.34), "xanthine oxidase" (burst strength of 3.73) and "plant growth" (burst strength of 4.26) are the critical points of the current study.

Discussion

This study identified 1,201 publications related to natural products in HUA research through the Web of Science Core General Information Collection database from 2000 to 2021. The annual publication output increased steadily. Referring to the distribution of countries/regions, China and the United States were the main driving force with a high academic reputation in natural products on HUA research, which was confirmed by the following characteristics: number of publications, number of citations, H-index value, the total and citations per publication (CPP). In recent years, publications on natural product treatment for HUA have increased yearly, and annual publications in China have also increased substantially. Although China's total publication volume exceeds that of the United States, the CPP of Chinese publications is lower. The United States ranks first in the world in terms of total citations. It indicates that China and the United States influence the natural product treatment of HUA. Ger-
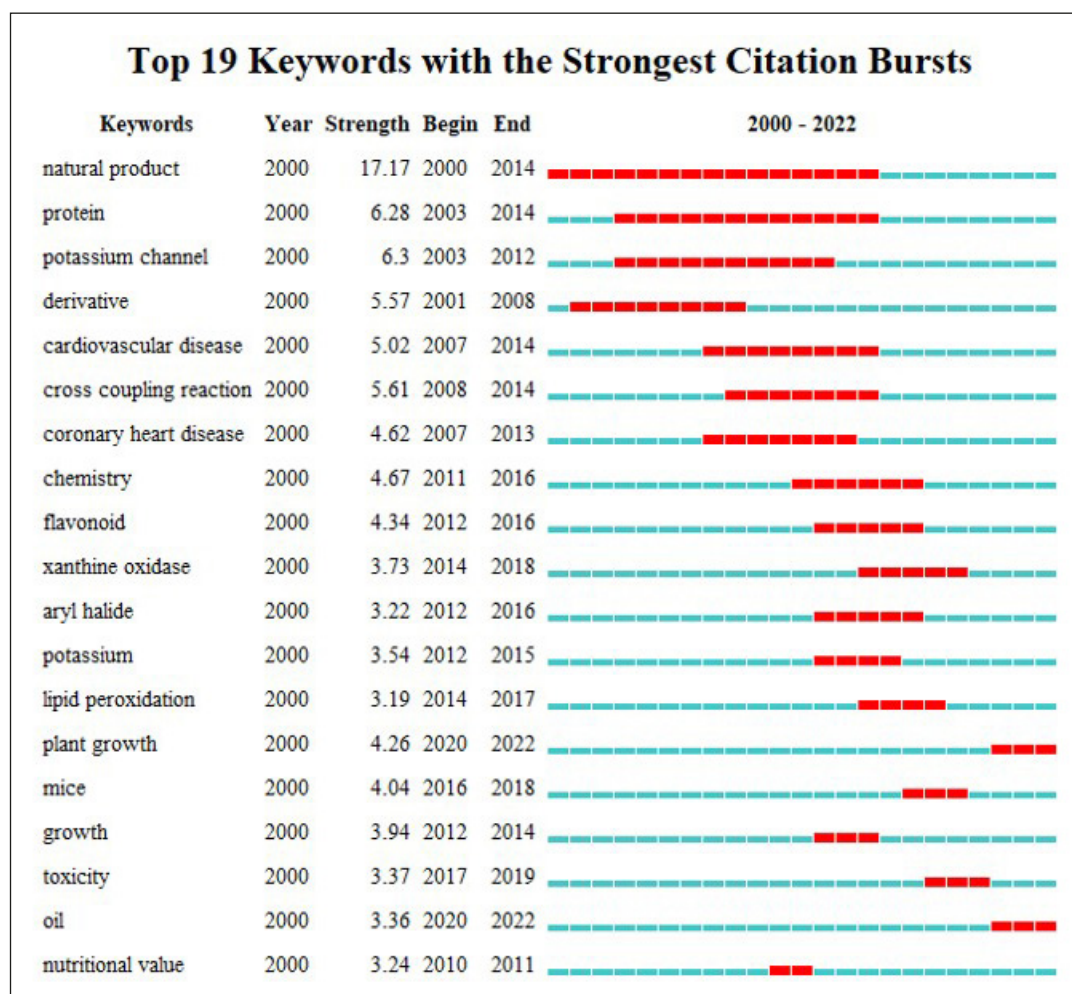
many and England have a relatively small number of publications, which has gradually increased in recent years, and the total number of citations is among the highest in the world. It reflects the significant progress these countries have made in this field, closely related to their strong cooperation with the United States.

General Trends, Influential Countries/ Institutions/Authors, and Academic Collaboration in Natural Product Treatment of HUA Research

In addition, most of the top ten productive colleges and universities are from the United States, which shows the solid academic influence of the United States in this field. The Chinese Academy of Sciences is the most productive institution in the world. It cooperates closely with many other Chinese institutions, which shows that it has a high academic reputation in this field in China. At the same time, it shows that it produces more high-quality publications and plays a crucial role in promoting the development of the area.

1,201 papers on the treatment of HUA with natural products were published in 558 academic journals, among the 10 most active journals, Journal of Ethnopharmacology (26 publications), Molecule (25 publications), Evidence-Based Complementary and Alternative Medicine (19 publications), reflecting that they are both essential information resources. In addition, most of the literature focuses on three categories, including pharmacology, chemopharmaceuticals, and biochemical molecular biology, suggesting

Top 19 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2000 – 2022
natural product	2000	17.17	2000	2014	
protein	2000	6.28	2003	2014	
potassium channel	2000	6.3	2003	2012	
derivative	2000	5.57	2001	2008	
cardiovascular disease	2000	5.02	2007	2014	
cross coupling reaction	2000	5.61	2008	2014	
coronary heart disease	2000	4.62	2007	2013	
chemistry	2000	4.67	2011	2016	
flavonoid	2000	4.34	2012	2016	
xanthine oxidase	2000	3.73	2014	2018	
aryl halide	2000	3.22	2012	2016	
potassium	2000	3.54	2012	2015	
lipid peroxidation	2000	3.19	2014	2017	
plant growth	2000	4.26	2020	2022	
mice	2000	4.04	2016	2018	
growth	2000	3.94	2012	2014	
toxicity	2000	3.37	2017	2019	
oil	2000	3.36	2020	2022	
nutritional value	2000	3.24	2010	2011	

Figure 7. Keywords with periods of burst from 2000 onward among the top 19 burst keywords in articles related to natural products in HUA research.

that these categories are highly recommended for tracking knowledge of natural substances in HUA research. Journal of Agricultural, Food Chemistry, Food Chemistry, and Journal of Ethnopharmacology are the journals with the most locally cited sources in this field, and this also shows that researchers can focus on the information in these journals and keep abreast of the latest research trends in this field.

In the research of the treatment of HUA with natural products, it is found that various countries and regions have more cooperation, and China has the full publications and multiple country publications. This shows that China has a strong influence in this field and at the same time cooperates with other countries. Most collaborations have contributed to the advancement of research in this field.

Topics Evolution and Future Outlook

Co-occurrence and burst analysis of keywords are widely used to identify research hotspots and predict research fronts[34,35]. This study tracked the thematic evolution and future outlook of natural product therapy HUA research from multiple perspectives and various visualizations. The burst analysis of keywords shows that flavonoid and xanthine oxidase are strong burst terms in the study of this field in recent years. Trending topics extracted from keywords show flavonoids, xanthine oxidase, phytochemicals, and antioxidant activity as the latest issues of HUA research. Indicating that these may be emerging topics in HUA research on natural products, its future research frontiers may be as follows (Figure 8):
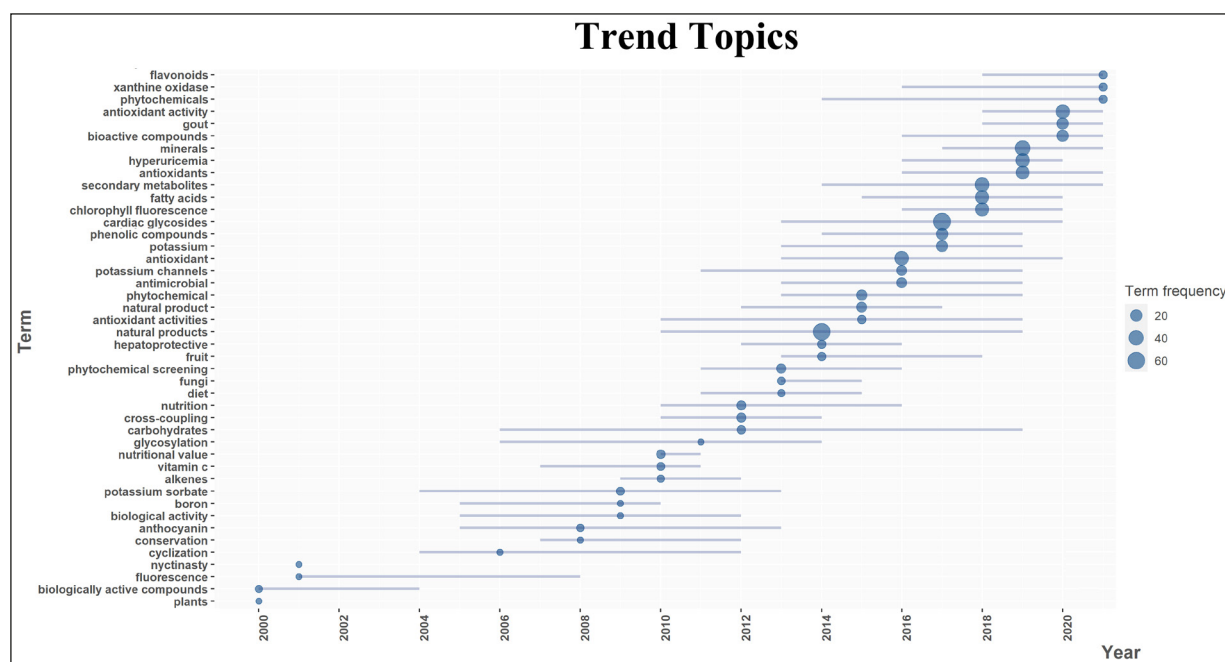
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Trend Topics

Figure 8. The trend topics related to natural products in HUA research.

1) HUA and flavonoids

Flavonoids are two benzene rings with phenolic hydroxyl groups (A and B rings) connected through the central three carbon atoms and have special biological activities. Research[36] shows that flavonoid compounds generally have inhibitory effects on xanthine oxidase activity, and different flavonoids have different inhibitory abilities on xanthine oxidase activity. Flavonoids are the strongest, followed by flavonols. Data analysis showed that hydrophobic force is the leading force for binding flavonoids to xanthine oxidase, and the double bond between C-2 and C-3 that maintains the planar structure of flavonoids is the key to inhibiting the activity of xanthine oxidase. In addition, because xanthine oxidase contains a molybdenum pterin active center, hydrogen bonds are easily formed between the hydroxyl moieties on flavonoids C-5 and C-7 and the active site of xanthine oxidase, and the inhibitory ability of the activity of xanthine oxidase is also vital. It can be used to prevent and treat HUA caused by the elevated expression level of xanthine oxidase[37-40].

2) HUA and xanthine oxidase

Xanthine oxidase is a vital purine metabolizing enzyme that converts hypoxanthine to xanthine, which further catalyzes the production of uric acid from xanthine. It plays a crucial role in the pathogenesis and treatment of HUA. Currently, the most commonly used xanthine oxidase inhibitors are allopurinol and febuxostat, which can reduce uric acid. The xanthine oxidase inhibitory activity is also widely used in screening uric acid-lowering drugs. In-depth research on xanthine oxidase can contribute to developing the field of natural product treatment of HUA and further promote the conversion of natural products into new medicines to prevent and treat HUA[41-44].

3) HUA and antioxidant activity

HUA is closely related to oxidative stress. Oxidative stress is the body's imbalance of oxidation and anti-oxidation, resulting in acute tissue damage or potential damage caused by increased reactive oxygen species generation or reduced clearance. Uric acid acts as a pro-oxidant to amplify oxidative stress damage in the body. This suggests that antioxidant activity is vital in treating HUA with natural products and may also serve as a way to screen urate-lowering drugs. Oxidative stress may exist in the HUA state, and antioxidant activity is crucial in HUA treatment[45-47].

4) HUA and gout

Gout is a progressive and disabling metabolic disease related to high blood uric acid and urate

deposition. It has become the second-largest metabolic disease in China and shows a trend of high incidence among young people around the world. The guideline[1] for the diagnosis and management of hyperuricemia and gout in China refers to "subclinical gout" as HUA with uric acid crystals without clinical symptoms. As a result, it has broken through the previous knowledge of joint localization of gout. It regards urate deposition diseases such as HUA and gouty arthritis as different clinical stages of a disease. This shows that HUA and gout are closely related, and HUA is also the biochemical basis of gout[48,49]. In the research and development of uric acid-lowering drugs, their anti-inflammatory activity can be further screened to further exert the drug's efficacy and protect patients' health. To our knowledge, this bibliometric analysis is the first to explore natural product development and trends in HUA.

Limitations

This study also has certain limitations. First, the data in this study were only extracted from the WoSCC database, as we consider this database to be a reliable service for publications and citations. However, it may contain fewer documents and journals than other databases like Google Scholar or Scopus. Second, non-English articles were excluded from the database and analysis, potentially leading to source bias. Furthermore, we selectively analyzed the features of the information. Therefore, we may overlook some key points and details.

Conclusions

The number of annual publications on natural product therapy HUA research has grown between 2000 and 2021. China has the most significant number of publications, while the United States is most frequently involved in international cooperation. The Chinese Academy of Sciences is the institution that contributes the most, taking the lead in research cooperation. Keyword analysis showed that exploring flavonoid "xanthine oxidase" is still a hotspot for future HUA research. Future research direction about HUA may be related to phytochemistry, flavonoids, xanthine oxidase, antioxidant activity, and gout. This study will provide valuable research references and cutting-edge directions for future researchers in the field of HUA.

Availability of Data and Materials
The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Authors' Contributions
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All the authors took part in drafting, revising or critically reviewing the article, gave final approval of the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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

Ethics Approval and Informed Consent
Not applicable.

References

1) Ni Q. Guideline for diagnosis and treatment of hyperuricemia and gout. World J Tradit Chin Med 2021; 16: 183-189.
2) Singh G, Lingala B, Mithal A. Gout and hyperuricemia in the USA: prevalence and trends. Rheumatology 2019; 58: 2177-2180.
3) Zhang Z, Liang R, Zhao T, Xu S, Liu X, Zhan P. Research progress of natural products for the treatment of hyperuricemia and gout. Acta Pharmaceutica Sinica 2022; 57: 1679-1688.
4) Yoon IS, Park DH, Kim JE, Yoo JC, Bae MS, Oh DS, Shim JH, Choi CY, An KW, Kim EI, Kim GY, Cho SS. Identification of the biologically active constituents of Camellia japonica leaf and anti-hyperuricemic effect in vitro and in vivo. Int J Mol Med 2017; 39: 1613-1620.
5) Kim JK, Kim WJ, Hyun JM. Salvia plebeia extract inhibits xanthine oxidase activity in vitro and reduces serum uric acid in an animal model of hyperuricemia. Planta Med 2017; 83: 1335-1341.
6) Lee YS, Kim SH, Yuk HJ, Kim DS. DKB114, a mixture of Chrysanthemum indicum linne flower and Cinnamomum cassia (L.) J. presl bark extracts, improves hyperuricemia through inhibition of xanthine oxidase activity and increasing urinel excretion. Nutrients 2018; 10: 1381.

7) Mehmood A, Zhao L, Wang C, Hossen I, Raka RN, Zhang H. Stevia residue extract increases intestinal uric acid excretion via interactions with intestinal urate transporters in hyperuricemic mice. Food Funct 2019; 10: 7900-7912.

8) Zhang R, Zhan S, Li S, Zhu Z, He J, Lorenzo JM, Barba FJ. Anti-hyperuricemic and nephroprotective effects of extracts from Chaenomeles sinensis(Thouin) Koehne in hyperuricemic mice. Food Funct 2018; 9: 5778-5790.

9) Peng A, Lin L, Zhao M, Sun B. Identifying mechanisms underlying the amelioration effect of Chrysanthemum morifolium Ramat.' Boju' extract on hyperuricemia using biochemical characterization and UPLC-ESI-QTOF/MS-based metabolomics. Food Funct 2019; 10: 8042-8055.

10) Tian Y, Lin L, Zhao M, Peng A, Zhao K. Xanthine oxidase inhibitory activity and antihyperuricemic effect of Moringa oleifera Lam. leaf hydrolysate rich in phenolics and peptides. J Ethnopharmacol 2021; 270: 113808.

11) Han S, Wei R, Han D, Zhu J, Luo W, Ao W, Zhong G. Hypouricemic effects of extracts from Urtica hyperborea Jacq. ex Wedd. in hyperuricemia mice through XOD, URAT1, and OAT1. BioMed Res Int 2020; 2020: 2968135.

12) Zhou Y, Zhang X, Li C, Yuan X, Han L, Li Z, Tan X, Song J, Wang G, Jia X, Feng L, Qiao X, Liu J. Research on the pharmacodynamics and mechanism of Fraxini Cortex on hyperuricemia based on the regulation of URAT1 and GLUT9. Biomed Pharmacother 2018; 106: 434-442.

13) Fang C, Chen L, He M, Luo Y, Zhou M, Zhang N, Yuan J, Wang H, Xie Y. Molecular mechanistic insight into the anti-hyperuricemic effect of Eucommia ulmoides in mice and rats. Pharm Biol 2019; 57: 112-119.

14) Wang S, Fang Y, Yu X, Guo L, Zhang X, Xia D. The flavonoid-rich fraction from rhizomes of Smilax glabra Roxb. ameliorates renal oxidative stress and inflammation in uric acid nephropathy rats through promoting uric acid excretion. Biomed Pharmacother 2019; 111: 162-168.

15) Li S, Li L, Yan H, Jiang X, Hu W, Han N, Wang D. Anti-gouty arthritis and anti-hyperuricemia properties of celery seed extracts in rodent models. Mol Med Rep 2019; 20: 4623-4633.

16) Lou XJ, Wang YZ, Lei SS, He X, Lu TT, Zhan LH, Chen X, Chen YH, Li B, Zheng X, Lv GY, Chen SH. Beneficial effects of macroporous resin extract of Dendrobium candidum leaves in rats with hyperuricemia induced by a high-purine diet. Evid Based Complement Altern Med 2020; 2020: 3086106.

17) Zhang KH, Wang MQ, Wei LL, Feng CJ, Zhang YS, Teng JB. Investigation of the effects and mechanismsof Dendrobium loddigesii Rolfe extract on the treatment of gout. Evid Based Complement Altern Med 2020; 2020: 4367347.

18) Chen HQ, Zhou X, Wang XX. Study on the mechanism of quercetin in treating hyperuricemia. Guangming J Chin Med 2019; 9: 1340-1344.

19) Ou R, Lin L, Zhao M, Xie Z. Action mechanisms and interaction of two key xanthine oxidase inhibitors in galangal: combination of in vitro and in silico molecular docking studies. Int J Biol Macromol 2020; 162: 1526-1535.

20) Li Y, Zhao Z, Luo J, Jiang Y, Li L, Chen Y, Zhang L, Huang Q, Cao Y, Zhou P, Wu T, Pang J. Apigenin ameliorates hyperuricemic nephropathy by inhibiting URAT1 and GLUT9 and relieving renal fibrosis via the Wnt/B-catenin pathway. Phytomedicine 2021; 87: 153585.

21) Miao MX, Wang X, Lu X. Mechanism study effects of apigenin on reducing uric acid and renal protection in oteracil potassium-induced hyperuricemia mice. China Pharm 2016; 27: 4794-4797.

22) Chang YH, Chiang YF, Chen HY, Huang YJ, Wang KL, Hong YH, Ali M, Shieh TM, Hsia SM. Anti-inflammatory and anti-hyperuricemic effects of chrysin on a high fructose corn syrup-induced hyperuricemia rat model via the amelioration of urate transporters and inhibition of nlrp3 inflammasome signaling pathway. Antioxidants 2021; 10: 564.

23) Lin Y, Liu PG, Liang WQ, Hu YJ, Xu P, Zhou J, Pu JB, Zhang HJ. Luteolin-4'-O-glucoside and its aglycone, two major flavones of Gnaphalium afine D.Don,resist hyperuricemia and acute gouty arthritis activity in animal models. Phytomedicine 2018; 41: 54-61.

24) Zhang Y, Jin L, Liu J, Wang W, Yu H, Li J, Chen Q, Wang T. Effect and mechanism of dioscin from Dioscorea spongiosa on uric acid excretion in animal model of hyperuricemia. J Ethnopharmacol 2018; 214: 29-36.

25) Wu FP, Jin P, Pu YC. Study on chemical constituents and kidney protection of Gynostemma pentaphylum. China J Med Chem 2020; 30: 153-158.

26) Tashiro Y, Sakai R, Hirose-Sugiura T, Kato Y, Matsuo H, Takada T, Suzuki H, Makino T. Effects of osthol isolated from Cnidium monnieri fruit on urate transporter 1. Molecules 2018; 23: 2837.

27) Chen M, Ye C, Zhu J, Zhang P, Jiang Y, Lu X, Wu H. Bergenin as a novel urate-lowering therapeutic strategy for hyperuricemia. Front Cell Devel Biol 2020; 8: 703.

28) Sun ZR, Liu HR, Hu D, Fan MS, Wang M. Ellagic acid exerts beneficial effects on hyperuricemia by inhibiting xanthine oxidase and NLRP3 inflammasome activation. J Agric Food Chem 2021; 69: 12741-12752.

29) Tran BX, Vu GT, Ha GH, Vuong QH, Ho MT, Vuong TT. Global evolution of research in artificial intelligence in health andmedicine: a bibliometric study. J Clin Med 2019; 8: 360.

30) Ke L, Lu C, Shen R, Lu T, Ma B, and Hua Y. Knowledge mapping of drug-induced liver injury: a scientometric investigation (2010–2019). Front Pharmacol 2020; 11: 842.

31) Zhang P, Yan FW, and Du CQ. A comprehensive analysis of energy management strategies for hybrid electric vehicles based on bibliometrics. Renew Sustain Energy Rev 2015; 48: 88-104.

32) Yang S, Sui J, Liu T, Wu W, Xu S, Yin L. Trends on PM2.5 research, 1997-2016: a bibliometric study. Environ Sci Pollut Res Int 2018; 25: 12284-12298.

33) Chen H, Li R, Zhang F, Yao Q, Guo Y. A Scientometric Visualization Analysis for Natural Products on Cancer Research from 2008 to 2020. Front Pharmacol 2021; 12: 650141.

34) Guo J, Gu D, Zhao T, Zhao Z, Xiong Y, Sun M. Trends in piezo channel research over the past decade: A bibliometric analysis. Front Pharmacol 2021; 12: 668714.

35) Song Y, Ma P, Gao Y, Xiao P, Xu L, Liu H. A bibliometrics analysis of metformin development from 1980 to 2019. Front Pharmacol 2021; 12: 645810.

36) Rahaman MS, Siraj MA, Islam MA, Shanto PC, Islam O, Islam MA, Simal-Gandara J. Crosstalk between xanthine oxidase (XO) inhibiting and cancer chemotherapeutic properties of comestible flavonoids- a comprehensive update. J Nutr Biochem 2022; 110: 109147.

37) Paul C, Li Y, M. C, Jia P, Hu K. Cimanga. Structure-activity relationship and classification of flavonoids as inhibitors of xanthine oxidase and superoxide scavengers. J Nat Prod 1998; 61: 71-76.

38) Lin S, Zhang G, Liao Y. Dietary flavonoids as xanthine oxidase inhibitors-structure-affinity and structure-activity relationships. J Agric Food Chem 2015; 63: 7784-7794.

39) Xia DZ, Zhang Y, Lv GY. Research progress of flavonoids in prevention and treatment of hyperuricemia and gout. Chin Pharm J 2009; 44: 721-723.

40) Qong YH, Cheng Q, Zhang Y. Review on natural products against hyperuricemia. Nat Prod Res Dev 2018; 30: 243.

41) Miljana B, Bozidar B, Adelin A, Eric R, Regis P, France L. Does oxidative stress play a role in altered chara-cteristics of diabetic bone A systematic review. Calcif Tissue Int 2017; 101: 553-563.

42) Paschou E, Gavrilaki E, Papaioannou G. Febuxostat hypersensitivity:another cause of DRESS syndrome in chronic kidney disease .Eur Ann Allergy Clinl Immunol 2016; 48: 251-255.

43) Kostic DA, Dimitrijevic DS, Stojanovic GS. Xanthine oxidase:isolation, assays of activity,and inhibition. J Chem 2015; 2015: 294858.

44) Li DQ, Zhao J, Wu D, Li S. Discovery of active components in herbs using chromatographic separation coupled with online bioassay. J Chromatogr B 2016; 1021: 81-90.

45) Xie L, Zhu B, Hu YQ, Tao L; Gao Y. Mitochondrial DNA oxidative damage triggering mitochondrial dysfunction and apoptosis in high glucose-induced HRECS. Invest Ophthalmol Vis Sci 2008; 49: 4203-4209.

46) Venla Kurra, Arttu Eräranta, Pasi Jolma, Tuija I, Vehmas, Asko Riutta. Hyperuricemia, oxidative stress, and carotid artery tone in experimental renal insufficiency. Am J Hypertens 2009; 22: 964-970.

47) Sautin YY, Johnson RJ. Uric Acid: The oxidant-antioxidant paradox. Nucleosides Nucleotides Nucleic Acids 2008; 27: 608-619.

48) Pineda C, Louthrenoo W, Edwards NL, Andrés M, Vargas-Santos AB, Roddy E, Pascart T, Lin CT, Perez-Ruiz F, Tedeschi SK, Kim SC, Harrold LR, McCarthy G, Kumar N, Chapman PT, Tausche AK, Vazquez-Mellado J, Gutierrez M, da Rocha Castelar-Pinheiro G, Richette P, Pascual E, Fisher MC, Burgos-Vargas R, Robinson PC, Singh JA, Jansen TL, Saag KG, Slot O, Uhlig T, Solomon DH, Keenan RT, Scire CA, Biernat-Kaluza E, Dehlin M, Nuki G, Schlesinger N, Janssen M, Stamp LK, Sivera F, Reginato AM, Jacobsson L, Lioté F, Ea HK, Rosenthal A, Bardin T, Choi HK, Hershfield MS, Czegley C, Choi SJ, Dalbeth N. Gout, Hyperuricemia, and Crystal-Associated Disease Network Consensus Statement Regarding Labels and Definitions for Disease Elements in Gout. Arthritis Care Res (Hoboken) 2019; 71: 427-434.

49) Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet 2016; 388: 2039-2052.