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ORIGINAL RESEARCH

Bibliometric and Visualized Analysis of Artemisinin and Its Derivatives in Cancer

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Background: Artemisinin, found in the traditional Chinese medicine (TCM) *Artemisia annua*, has demonstrated remarkable efficacy in therapeutics and holds significant potential as a pharmaceutical drug in cancer. Until now, there have been no systematic scientometrics studies to analyze the research trend of artemisinin and its derivatives in cancer.

Aim of the Study: We conducted this bibliometric study with the aim of providing researchers in the field with an all-around summary of artemisinin and its derivatives in cancer, visualizing current research advances, identifying hotspots, and ultimately outlining cutting-edge trends for future development.

Methods: A total of 927 relevant publications from 1990 to 2023 were accessed from the WOSCC database and analyzed bibliometrically utilizing software including CiteSpace VOSviewer and Microsoft Excel.

Results: Global publications in artemisinin and tumor therapy have steadily increased. China is considered the leading country in terms of publication numbers, and Chinese scholars have been influential in the field of artemisinin and its derivatives in the prevention and treatment of cancer. Cluster analysis of co-cited references depicted artemisinin-type drugs, bax-mediated intrinsic pathways, and infected erythrocytes as the most noteworthy topics. In contrast, the keywords analysis revealed a strong emphasis on the issues of cancer, in-vitro, cycle arrest, anticancer activity, and plasmodium-falciparum.

Conclusion: This study provides a comprehensive overview of relevant research trends by explicitly analyzing the published literature associated with artemisinin and its derivatives in cancer. The results of this multifaceted analysis can provide valuable data that offers ample insights for the field and for researchers wishing to venture into the field.

Keywords: artemisinin, cancer, traditional Chinese medicine, therapeutic agent, bibliometric analysis

Introduction

Cancer constitutes a substantial global public health burden[1] and stands as the leading cause of mortality among non-communicable diseases (NCDs), as well as the foremost obstacle to enhancing life expectancy worldwide.[2] Even with technological advances, the incidence of some cancers continues to rise.[3] However, due to its complex nature and the resilience of malignant cells to current treatments, cancer continues to be a formidable challenge in the realm of medical research.[4,5] It is gratifying that traditional Chinese medicine has a more significant role in preventing and treating cancer,[6–8] with artemisinin-based drugs having a preventive and curative effect on a wide range of diseases.

Artemisinin, discovered in the traditional Chinese medicine (TCM) *Artemisia annua*,[9,10] is a compound identified as a sesquiterpene lactone that features an endoperoxide structure.[11] *Artemisia annua* has been recognized for its extensive application in traditional Chinese medicine, specifically for alleviating fevers and inflammatory conditions, with its utilization for malaria treatment tracing back over two millennia.[12] Artemisinin was discovered through research on

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traditional herbal medicine and is now an important drug for malaria treatment.[13] These plant-derived peroxides uniquely kill plasmodium in the pre-erythrocytic stage, blocking their advancement into mature periods with growing pathogenicity.[14,15] Beyond malaria, artemisinin and its derivatives, such as artesunate, exhibit broad therapeutic potential against parasitic diseases like schistosomiasis and clonorchiasis,[16] as well as bacterial infections,[17] inflammatory conditions (eg, SM934 tested in lupus patients),[18] and fibrosis[19] These compounds also demonstrate anti-inflammatory effects,[15,20] inhibit angiogenesis,[21] and suppress tumor cell growth by exerting antiproliferative and cytotoxic effects,[22] inhibiting cell migration and invasion, modulating gene expression and signaling pathways, and inducing cell cycle arrest and apoptosis.[13,23] Notably, research on fibrosis reveals mechanistic parallels with tumor stroma, offering cross-disciplinary insights for cancer therapy, which has garnered significant attention for their potential antitumor applications.[24]

Numerous studies have been released on using artemisinin and its derivatives in cancer treatment. Bibliometrics is a methodological framework that uses quantitative analysis to examine a large corpus of literature within a specific research domain.[25,26] It employs mathematical and statistical methodologies by utilizing visualization techniques to demonstrate various dimensions and trends characterizing the development of a scientific topic.[27–29] CiteSpace is a visual analysis software designed to visualize and analyze structural and temporal patterns in scientific literature.[30] It facilitates systematic scientometric reviews by providing an outline of the fundamental domain of knowledge, assisting in the recognition of primary subjects and patterns within research fields.[31] VOSviewer is designed to construct and visualize bibliometric networks of scientific publications, such as co-authorship networks and keyword co-occurrence networks, helping to reveal the structure and trends of a research field through graphical representations.[32] Pajek facilitated the adjustment and enhancement of the layout of the cluster map.[33,34]

Although crucial contributions have been made in researching artemisinin application and its derivatives in the field of malignancy, many challenges remain.[35,36] The selective study of artemisinin and its derivatives is not sufficiently in-depth. Although these compounds have shown cytotoxicity towards certain cancer cells, their lack of specificity may cause harm to healthy tissues.[14] Additionally, while their pharmacological effects have been tentatively elucidated,[37,38] the specific mechanisms of action remain unclear,[39] which limits the precise application of artemisinin and its derivatives in treating malignant neoplasm. Furthermore, despite the potential of artemisinin and its derivatives in anticancer therapy demonstrated by in vitro and animal tests, clinical research remains limited, with only a few trials and case reports demonstrating their efficacy as adjuvants or primary agents in cancer treatment.[40–43] Therefore, further research should focus on these areas. This research enhanced the understanding of artemisinin and its derivatives through bibliometric analysis. It improves current research and elevates anticancer investigations of the drug to a more sophisticated level of scientific understanding and practical implementation, thereby enabling its novel application within the realm of contemporary medicine.

Methods

Searching Strategy and Data Collection

The process of sourcing published materials was carried out by utilizing the Web of Science database (https://www.webofscience.com/wos/) on 4 January 2024. All publications were output within text-only files using the "Full Record and Cited References" format. The applied search formula was TS = (artemisinin*) AND TS = (cancer* OR anticancer* OR tumor* OR tumor* OR oncology OR neoplasm* OR carcinoma* OR lymphoma* OR sarcoma* OR leukemia*) AND DT = (Article OR Review) AND LA = (English) AND DOP = (1990–01-01/2023-12-31). Two investigators (Ting Bai and Yuqing He) regained and screened the papers. Any divergent viewpoints were resolved through constructive dialogue with the respective authors until a unanimous agreement had been reached. Figure 1A illustrates the flowchart for data collection and analysis.

Data Standardization

Nonstandardized keywords were screened in accordance with established standards to eliminate redundant repetition in the keyword co-occurrence graph. This is because inconsistencies in lexical categories and the forms of words in both

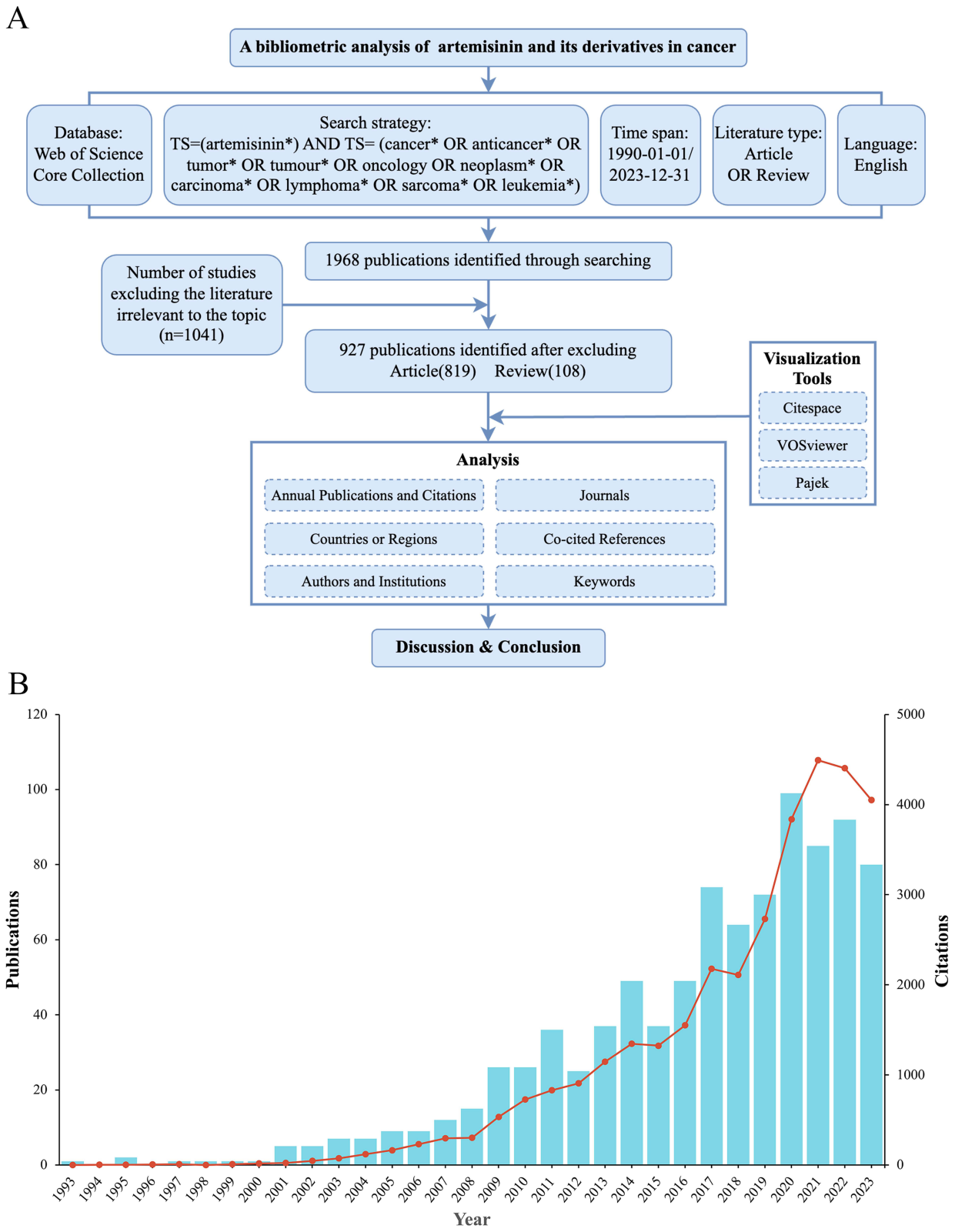

Figure 1 (**A**) Flowchart of bibliometric analysis. (**B**) The number of articles about Artemisinin and its Derivatives in cancer per year from 1993 to 2023.

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singular and plural can lead to such repetition. Additionally, countries/regions were standardized, such as the unification of England, Scotland, Northern Ireland, and Wales to form the United Kingdom and the incorporation of Taiwan into China.

Visualized Analysis

The software utilized in our investigation was as outlined below: CiteSpace (version 6.2. R7, Chaomei Chen, Drexel University, Philadelphia, PA, United States),[44] VOSviewer (version 1.6.20, Leiden University, Leiden, Netherlands),[32] Pajek (version 5.17, University of Ljubljana, Ljubljana, Slovenia).[33] The data was analyzed using these applications, and the results were transferred to multiple tables that condensed bibliometric parameters such as publication numbers and years, titles, countries and institutions, authors, journals, total and average citations, keywords, and references. The network maps, the time view, and the density view of the map were generated using VOSviewer. The VOSviewer map depicted that the nodes corresponding to weighting were the links indicating collaborations or co-occurring presences within a single piece of literature. The thickness of the link represented positive correlations with link strength. In the module visualizing networks, clusters were differentiated using colors. In the overlay visualization module, White symbolized the previous period of research, while purple denoted the current phase, and the colors of nodes were indicative of the average publication year. CiteSpace was utilized to generate burst maps, a dual map overlay of journals, and to identify co-citation references. The dark nodes represent older publications, while the bright nodes represent subsequent articles. Additionally, in the burst module, keywords and references were arranged based on the start of the year of the burst.

Results

Annual Publications and Citations

A total of 927 papers were involved, and the annual number of publications and citations were calculated. Figure 1B illustrates a consistent increase in publications and citations on artemisinin and tumor therapy from 1993 to 2023, with an accelerated growth rate after 2018. Specifically, annual publications increased from 62 in 2018 to 99 in 2020, reflecting heightened research interest, possibly due to emerging evidence of artemisinin's anticancer potential and increased funding for traditional Chinese medicine research. Citations peaked at 4493 in 2021, indicating growing academic impact. After screening up to the data collection cutoff date, the 2023 literature (n=80) did not set a new record in quantity, but still demonstrated sustained momentum.

Analysis of Cooperation Status

Countries/Regions

A total of 69 countries have contributed to the study of artemisinin and tumors. The most productive country/region was China (n = 536, 57.82%), in addition to the United States (n = 129, 13.92%), Germany (n = 90, 9.71%), India (n = 48, 5.18%), and South Korea (n = 33, 3.56%) (Figure 2A). The top 10 countries, such as one North American country, three European countries, five Asian countries, and one African country, have published 950 papers, constituting 80.85% of all published papers. Figure 2B displays the substantial collaboration among the top thirty countries/regions with the highest productivity. In general, among nations with a large number of publications and enhanced collaborative efforts, China is the most significant.

Institutions

Approximately 1000 institutions worldwide have conducted studies on the application of artemisinin and its derivatives in tumor research. Table 1 shows the top 10 institutions by the number of literature outputs and citations. Johannes Gutenberg University Mainz had the most important publications (n = 46, 4.96%), followed by the Chinese Academy of Sciences (n = 41, 4.42%). The main institutions and their collaborative relationships in the field are shown in Figure 2C. And the investigation of co-occurrent institutions found that close cooperation existed among institutions with many publications, and domestic collaboration exhibited greater frequency than international cooperation.

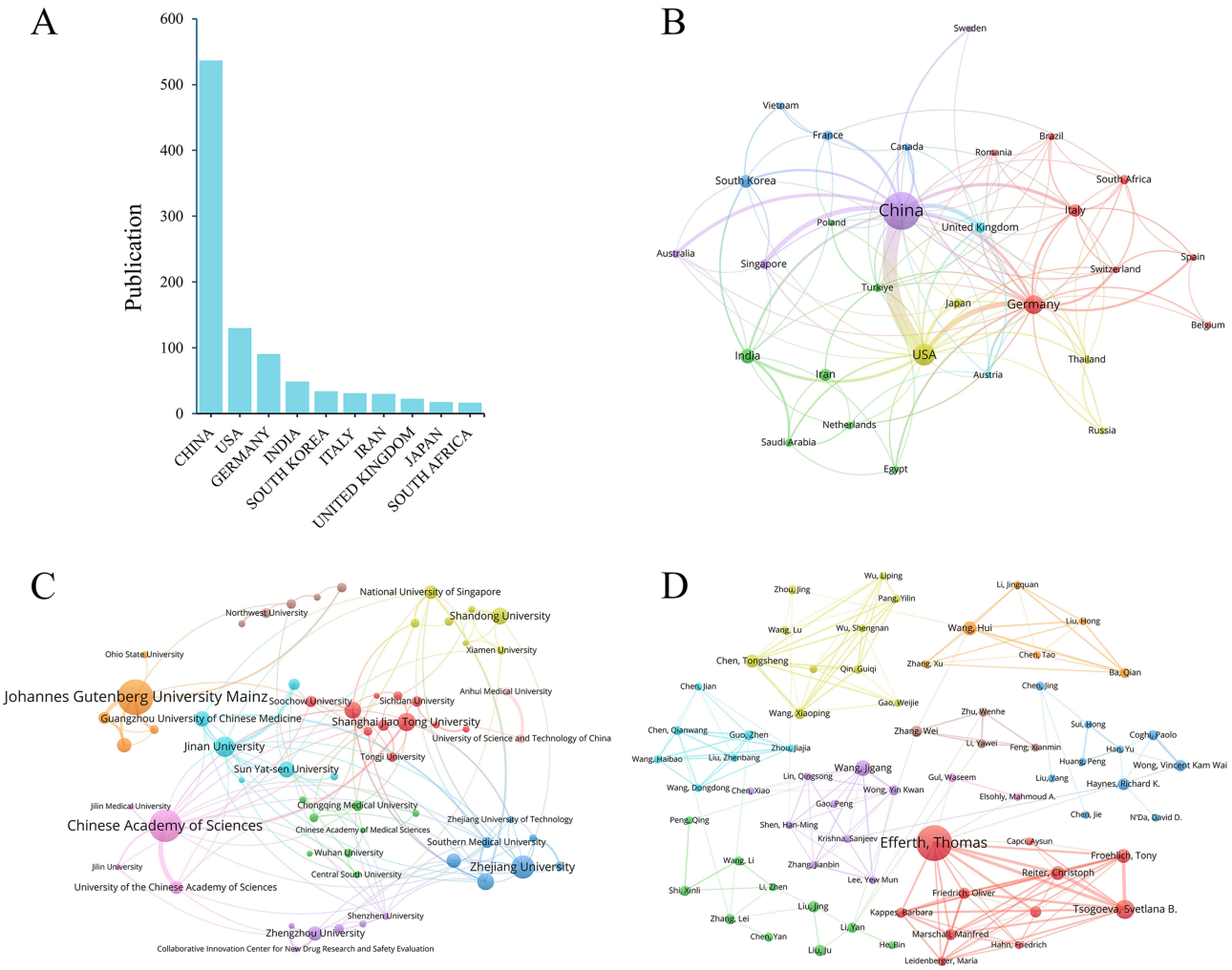

Figure 2 (**A**) The top 10 productive countries/regions. The network maps show countries/regions (**B**), institutions (**C**), and authors (**D**) involved in the research on Artemisinin and its Derivatives in cancer.

Authors

Over 4000 researchers engaged in research on artemisinin and tumors. Efferth, Thomas (n = 59) from Germany was the author with the most publications, followed by Tsogoeva, Svetlana B. (n = 17), and Sasaki, Tomikazu (n = 13) (Table 2). The analysis of author co-occurrence revealed multiple research groups and collaborative efforts between researchers in the field (Figure 2D). The nodes' size was positively associated with the publication number of a certain author, while the thickness of the lines between nodes indicated cooperation frequency.

Table 1 The Top 10 Productive Institutions

Institution	Publications	Citations
Johannes Gutenberg University Mainz	46	2952
Chinese Academy of Sciences	41	1533
University of Washington	28	2357
Zhejiang University	27	1116
Jinan University	23	640

(*Continued*)

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Table 1 (Continued).

Institution	Publications	Citations
Shanghai Jiao Tong University	20	340
China Academy of Chinese Medical Sciences	18	457
China Pharmaceutical University	18	411
Shandong University	18	392
Sun Yat-sen University	17	468

Table 2 The Top 10 Productive Authors

Name	Country	Publications	Total Citations	Per Citations
Efferth, Thomas	Germany	59	5090	86.27
Tsogoeva, Svetlana B.	Germany	17	871	51.24
Sasaki, Tomikazu	USA	13	1170	90.00
Wang, Jigang	China	12	524	43.67
Singh, Narendra P.	USA	11	775	70.45
Froehlich, Tony	Germany	10	563	56.30
Reiter, Christoph	Germany	10	683	68.30
Wang, Hui	China	10	680	68.00
Chen, Tongsheng	China	9	289	32.11
Noori, Shokoofe	Iran	9	206	22.89

Analysis of Journals

As of December 2023, 376 SCI journals have published articles on artemisinin and tumors. Table 3 provides a summary of the top 10 journals with the largest publication quantity arranged by total, accounting for 34.31% of the total citations. ANTICANCER RESEARCH was the most published journal (n = 17,4.52%), and CANCER LETTERS was the most cited (citations = 1141). JOURNAL OF MEDICINAL CHEMISTRY was the second most cited journal, with 1045 citations. The cited journal is on the left, and the cited journal is on the right of the map, which shows the topic distribution of journals by means of the dual map overlay of journals, as shown in Figure 3. The dual map overlay presents that almost all the articles about artemisinin and tumors were published in one discipline ("molecular biology immunology"). The primary sources of knowledge in this field are predominantly the two disciplines located on the right side of the map. ("molecular biology genetics" and "chemistry materials physics").

Analysis of Co-Cited References

Co-cited references indicate that they have been cited by multiple studies included in this study. In order to investigate the knowledge base and background of artemisinin and tumors, we conducted an analysis of reference co-citations through CiteSpace. In Figure 4A, the arrangement of co-cited references in the distribution network from 1993 to 2023 was depicted, including references cited more than 30 times on the map. Additionally, as indicated by the color bar, the more faded the color of the node, the later it was referenced. The top 10 co-cited references are listed in Table 4. Among them, the paper entitled the antimalarial artesunate is also active against cancer "has garnered the highest number of co-citations (n = 218).[45] The paper entitled" Qinghaosu (Artemisinin): an Antimalarial Drug from China ranked second (n = 182). The

Table 3 The Top 10 Journals of Publications on Artemisinin and Its Derivatives in Cancer (Sorted by Total Citations)

Journal	Category	Impact Factor (2022)	Total Publications (%)	Total Citations
Cancer Letters	Cancer Research & Oncology	9.7	11(2.93)	1141
Journal of Medicinal Chemistry	Molecular Medicine & Drug Discovery	7.3	12(3.19)	1045
Biochemical Pharmacology	Biochemistry & Pharmacology	5.8	12(3.19)	975
Anticancer Research	Oncology	2.0	17(4.52)	729
Phytomedicine	Pharmaceutical Science & Pharmacology	7.9	14(3.72)	707
International Journal of Oncology	Cancer Research & Oncology	5.2	5(1.33)	650
Biomaterials	Biochemistry; Genetics & Molecular Biology; Chemical Engineering; Engineering; Materials Science	14.0	8(2.13)	649
European Journal of Medicinal Chemistry	Chemistry; Medicinal	6.7	23(6.12)	647
Bioorganic & Medicinal Chemistry	Organic Chemistry	3.5	15(3.99)	646
PLOS ONE	Multidisciplinary	3.7	12(3.19)	626

first was published in the International Journal of Oncology, and the second was published in SCIENCE. All of the top 10 co-cited references were published in 1985, with around two-thirds published in the last two decades.

A total of 18 clusters were identified, as stated in the log-likelihood ratio algorithm of CiteSpace. The 10 largest clusters among them are shown in Figure 4B. In the timeline view, the cluster labels are at the far end of the line, and different colored nodes on the same line represent references from different years within a cluster, with the nodes closer to the right representing the latest references. Modularity Q (0.851) is above the threshold of 0.3, and Mean Silhouette (0.9306) values surpass 0.7, indicating that the clusters are compelling and hold structural significance. The 10 largest clusters were identified as "artemisinin-type drug" (cluster #0), "bax-mediated intrinsic pathway" (cluster #1), "infected erythrocyte" (cluster #2), "potential synergism" (cluster #3), "biological action" (cluster #4), "inhibits hypoxia" (cluster #5), "tumor cell" (cluster #6), "kaposis sarcoma xenograft tumor" (cluster #7), "botanical compound" (cluster #8) and

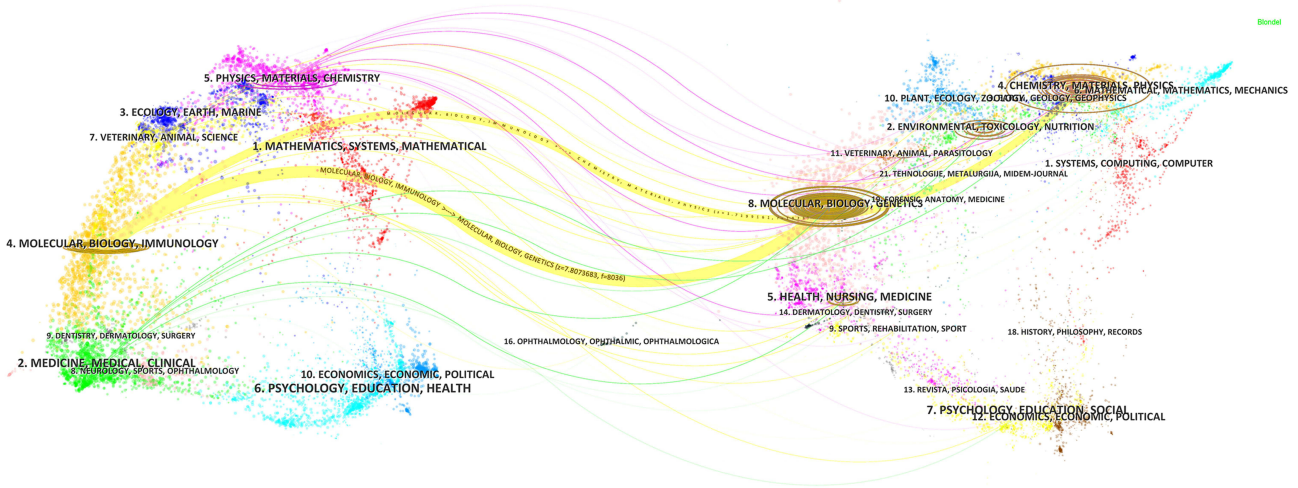

Figure 3 The dual map overlay of journals.

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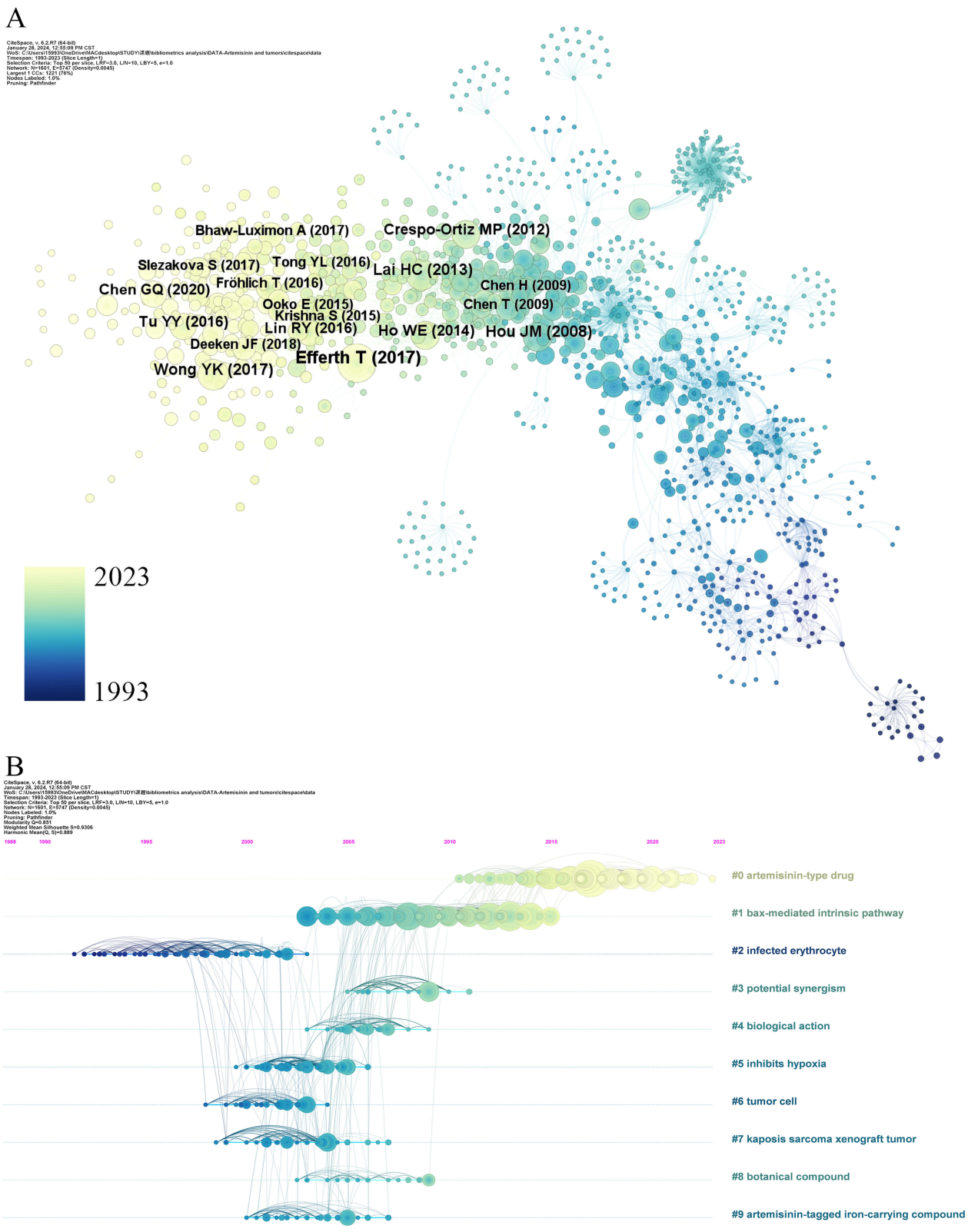

Figure 4 The map of co-citation references (**A**) and the largest 10 clusters (**B**).

Table 4 The Top 10 Co-Cited References

First Author	Year	Journal	Title	Co-Citations
Efferth et al[45]	2001	InternatioInternational Journal of Oncologynal	The anti-malarial artesunate is also active against cancer	218
Klayman et al[16]	1985	Sciences	Qinghaosu(Artemisinin): an Antimalarial Drug from China	182
Hou et al[9]	2008	Clinical Cancer Research	Experimental Therapy of Hepatoma with Artemisinin and Its Derivatives: In vitro and In vivo Activity, Chemosensitization, and Mechanisms of Action	158
Efferth et al[46]	2004	Free Radical Biology and Medicine	Enhancement of cytotoxicity of artemisinins toward cancer cells by ferrous iron	143
Efferth et al[47]	2003	Molecular Pharmacology	Molecular Modes of Action of Artesunate in Tumor Cell Lines	131
Singh et al[48]	2001	Life Sciences	Selective toxicity of dihydroartemisinin and holotransferrin toward human breast cancer cells	130
Efferth et al[49]	2017	Seminars in Cancer Biology	From ancient herb to modern drug: Artemisia annua and artemisinin for cancer therapy	111
Woerdenbag et al[50]	1993	Journal of Natural Products	Cytotoxicity of Artemisinin-Related Endoperoxides to Ehrlich Ascites Tumor Cells	106
Lai et al[51]	1995	Cancer Letters	Selective cancer cell cytotoxicity from exposure to dihydroartemisinin and holotransferrin	105
Dell'Eva et al[52]	2004	Biochemical Pharmacology	Inhibition of angiogenesis in vivo and growth of Kaposi's sarcoma xenograft tumors by the anti-malarial artesunate	104

"artemisinin-tagged iron-carrying compound" (cluster #9), respectively. The largest and most recent cluster, Cluster #0, comprises 245 references.

The citation burst in a reference is when those references are cited significantly more often than usual over time, and this type of study can facilitate the exploration of how research hotspots have evolved over the years. The top 50 with the most robust citation burst are shown in Figure 5, where the red bar indicates a high frequency of citations, and the blue bar indicates a low citation frequency.

The reference with the most robust burst strength (strength = 35.07, burst period = 2018–2023) is "From ancient herb to modern drug: Artemisia annua and artemisinin for cancer therapy",[49] published by Efferth T. Table 5 shows the references that remain in a state of the burst.

Analysis of Keywords

Keywords serve as the fundamental components of articles. Utilizing co-occurrence analysis of keywords can effectively pinpoint active research areas in the field. Among 3440 keywords in 927 papers, the keywords with a frequency of occurrence greater than 15 times were extracted and clustered, and 109 keywords were obtained (Figure 6A). The average publishing year was between 2009 and 2021. The nodes' different colors represent the five clusters found, including 36, 23, 18, 18, and 14 keywords, respectively. Cluster 1 (red) is mainly correlated with drug application. Keywords in this cluster include "cancer", "in-vitro", "cycle arrest", "anticancer activity", and "plasmodium-falciparum". Cluster 2 (green) contains keywords associated with the pharmacological mechanism of artemisinin in the treatment of tumors, such as "artemisinin", "dihydroartemisinin", "mechanism", "cell" and "ferroptosis". Cluster 3 (blue), Cluster 4 (yellow), and Cluster 5 (purple) emphasize artemisinin drugs, expression, and outcome, respectively. In the density view (Figure 6B), "artemisinin", "apoptosis", "artesunate", "dihydroartemisinin" and "in-vitro" exhibited a high density on the map, demonstrating the importance of these topics and the possible interests of research in the field of artemisinin and tumors.

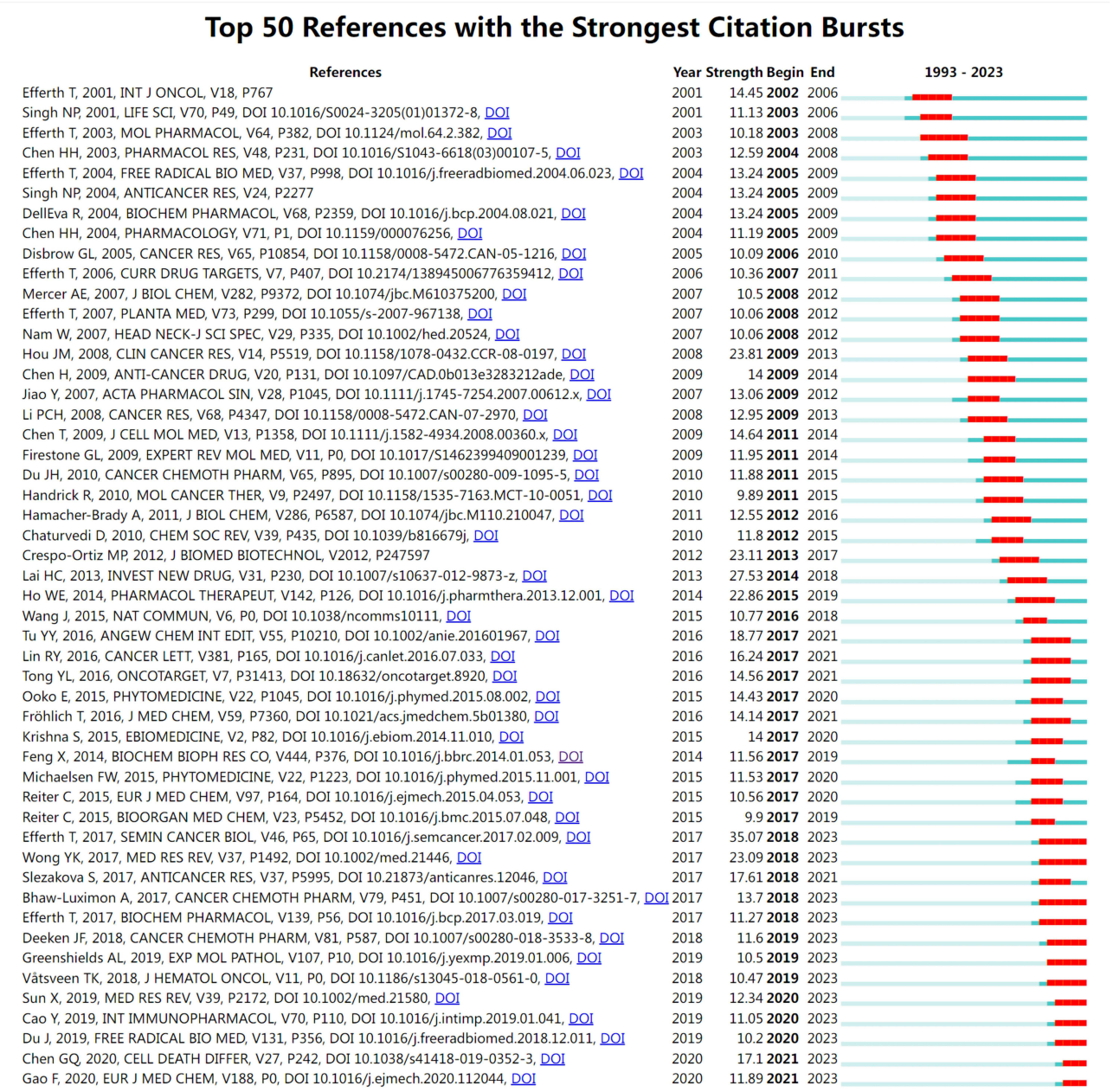

Figure 5 Visual analysis of reference bursts.

We employed the keyword burst and time view tools to investigate the progression of research trends, anticipate emerging topics, and discover potential hotspots. Keywords in Figure 6C were color-coded based on their average publishing year. Keywords that appear early are displayed in white, while recent keywords are in dark purple. The latest keywords involved “hybrid molecule”, “cell death”, “oral artesunate”, “colorectal cancer”, “phase”, “ferroptosis”, and “autophagy”. Figure 6D shows the keyword burst in artemisinin and tumors over the last three decades. The keywords that continued to exhibit a state of burst are “nanoparticles”, “therapy”, “oral artesunate”, “cycle arrest”, “metabolism”, “mechanism”, “autophagy”, “cell death”, “combination”, “ferroptosis”, “hybrid molecule”, “colorectal cancer”, “lung cancer”, indicating the potential research hotspots in the future.

Table 5 References Currently in a State of Burst

Burst Period	First Author	Year	Journal	Title
2018–2023	Efferth et al,[49]	2017	Seminars in Cancer Biology	From ancient herb to modern drug: Artemisia annua and artemisinin for cancer therapy
2018–2023	Wong et al,[53]	2017	Medicinal Research Reviews	Artemisinin as an anticancer drug: Recent advances in target profiling and mechanisms of action
2018–2023	Bhaw-Luximon et al,[54]	2017	Cancer Chemotherapy and Pharmacology	Artemisinin and its derivatives in cancer therapy: status of progress, mechanism of action, and future perspectives
2018–2023	Efferth et al,[55]	2017	Biochemical Pharmacology	Cancer combination therapies with artemisinin-type drugs
2019–2023	Deeken et al,[56]	2018	Cancer Chemotherapy and Pharmacology	A Phase I study of intravenous artesunate in patients with advanced solid tumor malignancies
2019–2023	Greenshields et al,[57]	2019	Experimental and Molecular Pathology	The anti-malarial drug artesunate causes cell cycle arrest and apoptosis of triple-negative MDA-MB-468 and HER2-enriched SK-BR-3 breast cancer cells
2019–2023	Våtsveen et al,[58]	2018	Journal of Hematology & Oncology	Artesunate shows potent anti-tumor activity in B-cell lymphoma
2020–2023	Sun et al,[59]	2019	Medicinal Research Reviews	Targeting autophagy enhances the anticancer effect of artemisinin and its derivatives
2020–2023	Cao et al,[60]	2019	International Immunopharmacology	Artemisinin enhances the anti-tumor immune response in 4T1 breast cancer cells in vitro and in vivo
2020–2023	Du et al,[61]	2019	Free Radical Biology and Medicine	DHA inhibits proliferation and induces ferroptosis of leukemia cells through autophagy dependent degradation of ferritin
2021–2023	Chen et al,[62]	2020	Cell Death & Differentiation	Artemisinin compounds sensitize cancer cells to ferroptosis by regulating iron homeostasis
2021–2023	Gao et al,[63]	2020	European Journal of Medicinal Chemistry	Artemisinin-derived hybrids and their anticancer activity

Discussion

Our study conducts a bibliometric analysis focusing on the recent advances, research hotspots, and future trends of artemisinin and its derivatives in cancer treatment. We conducted a systematic literature review of articles published in the WOSCC database from 1990 to 2023 associated with the application of artemisinin and its derivatives in cancer. Our comprehensive bibliometric evaluation included 927 papers from 376 journals from 69 countries/regions. By analyzing tables, visualized results, and statistics on countries, regions, authors, institutions, and keywords in the field, we offered valuable perspectives on emerging hotspots and trends in this area of research.

Bibliometric Information

As illustrated in Figure 1B, the number of publications generally exhibits an annual upward trend. The publication curve with dots peaked in 2020. Additionally, the figure illustrates that the rate of increase in citations exceeds that of publications and exhibits a similar trend to the publication volume.

Artemisinin was discovered in the 1970s, and Tu Youyou and her team successfully extracted it from the *Artemisia annua* plant in 1972. This discovery provided a novel effective drug for malaria treatment.[64] For over 40 years, this drug class has continued attracting widespread attention from researchers as a novel therapeutic agent.[65] Artemisinins are a novel class of compounds that demonstrated potent therapeutic effects in inflammation,[15] immune diseases,[66]

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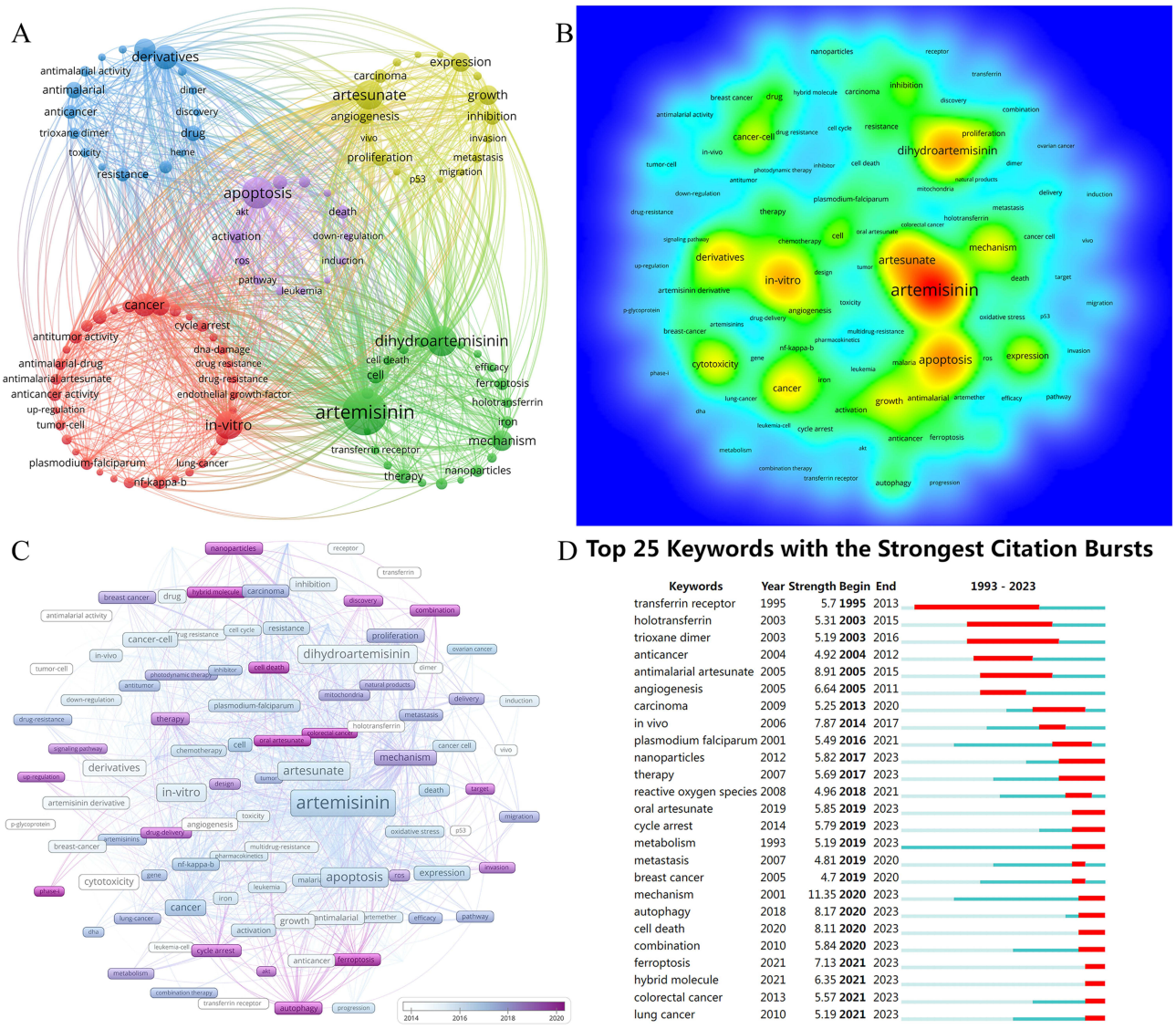

Figure 6 (**A**) The network map of occurrence over 15 times with 5 clusters. (**B**) The density view and (**C**) the time view of the map of keywords. (**D**) The keywords with strong citation bursts in articles related to Artemisinin and its Derivatives in cancer.

shock,[67,68] cancer,[7,55,69] and other conditions.[70] In recent years, with the global epidemic of cancer, the repurposing of "old" drugs for new indications has gradually gained popularity. The emerging research field of using artemisinin and its derivatives for cancer treatment has also developed rapidly. Between 1993 and 2000, the research on artemisinin-based drugs in cancer therapy did not attract much attention. Since 2001, this field has attracted growing interest, and the number of related research reports has rapidly increased. The clinical application of artemisinin and its derivatives in cancer is a current research direction, which will provide insightful perspectives for the future development of safe and reliable anticancer drugs.

Efferth, Thomas, who received the Willmar Schwabe Award in 2006, is the most productive author (59 papers). He and his team mainly focus on applying artemisinin-based drugs in cancer treatment, including the anti-multidrug resistance capability of artesunate and its mechanism of action.[59,71,72] Chinese scholars have published the most research, four times that of the second-ranked United States. Eight out of the top ten most productive institutions are in China, which may be related to China's large population base. Additionally, China is one of the countries with a high incidence and mortality rate of cancer, which can also contribute to this outcome. Hence, it is unsurprising that Chinese researchers are the most active in cancer research. Notably, among the top 18 most-cited articles, 10 were written by Chinese

Table 6 The Top 10 Most Cited Articles

Title	First Author	Journal	Year	Total Citations	Citations Per Year
What made sesquiterpene lactones reach cancer clinical trials?	Ghantous et al,[74]	Drug Discovery Today	2010	495	35.36
The anti-malarial artesunate is also active against cancer	Efferth et al,[45]	International Journal of Oncology	2001	476	20.70
Nrf2 inhibition reverses the resistance of cisplatin-resistant head and neck cancer cells to artesunate-induced ferroptosis	Roh et al,[75]	Redox Biology	2017	367	52.43
From ancient herb to modern drug: Artemisia annua and artemisinin for cancer therapy	Efferth et al,[49]	Seminars in Cancer Biology	2017	350	50.00
Flavonoids from Artemisia annua L. as Antioxidants and Their Potential Synergism with Artemisinin against Malaria and Cancer	Ferreira et al,[73]	Molecules	2010	319	22.79
Artemisinin and its derivatives: a novel class of anti-malarial and anti-cancer agents	Chaturvedi et al,[76]	Chemical Society Reviews	2010	294	21.00
Experimental therapy of hepatoma with artemisinin and its derivatives: In vitro and in vivo activity, chemosensitization, and mechanisms of action	Hou et al,[9]	Clinical Cancer Research	2008	270	16.88
Antitumor Activity of Artemisinin and Its Derivatives: From a Well-Known Antimalarial Agent to a Potential Anticancer Drug	Crespo-Ortiz et al,[77]	Journal of Biomedicine and Biotechnology	2012	268	22.33
Anti-cancer natural products isolated from Chinese medicinal herbs	Tan et al,[78]	Chinese Medicine	2011	261	20.08
Artemisinin derivatives induce iron-dependent cell death (ferroptosis) in tumor cells	Ooko et al,[79]	Phytomedicine	2015	257	28.56

scholars. This indicates, to some extent, the influence of Chinese scholars on artemisinin and its derivatives in cancer prevention and treatment.

Among the top 10 most cited publications (Table 6), Efferth et al were the first to propose the anticancer effects of artemisinin-based drugs. They suggested that artesunate could be a potential candidate for cancer chemotherapeutics.[45] In 2008, Hou et al investigated the in vivo and in vitro anticancer effects of Artesunate and Dihydroartemisinin and their impact on cell proliferation and apoptosis-related gene protein expression. They concluded that their use alone or in combination with other therapies has a promising therapeutic effect on human liver cancer.[9] In 2010, Ghantous et al explored the application of sesquiterpene lactones in clinical cancer trials and considered them hopeful candidates in cancer drug discovery.[73] As the anticancer effects of artemisinin-based drugs are gradually uncovered, these drugs are increasingly favored in cancer prevention and treatment.

Furthermore, as shown in Table 1, although most institutions publishing research on artemisinin and its derivatives are based in China, the most co-cited articles originate from leading journals such as International Journal of Oncology and Science. These highly cited papers, such as "The antimalarial artesunate is also active against cancer" (co-cited 218 times) and "Qinghaosu (Artemisinin): an Antimalarial Drug from China" (co-cited 182 times), are frequently referenced due to their pioneering contributions to the field. For instance, the former, published by Efferth et al, was among the first to systematically demonstrate artesunate's anticancer potential across multiple cancer cell lines, establishing a foundational framework for subsequent studies. Similarly, the latter, published in Science, provided a comprehensive overview of artemisinin's discovery and its pharmacological properties, serving as a seminal reference for both malaria

and cancer research. These papers are highly cited because they introduced novel concepts, provided robust experimental evidence, and were published in high-impact journals, enhancing their visibility and influence. This suggests that the global impact of research in this field is driven by studies that combine innovative insights with rigorous methodologies, regardless of the authors' geographical origins.

Overall, the bibliometric results indicate that studies on artemisinin and its derivatives in cancer prevention and treatment are still thriving. Researchers from diverse nations are driving forward this field from different perspectives, collectively contributing to a rapid academic revolution that will continue from the present into the future.

Detection of Research Hotspots and Future Directions

Specific Mechanisms of Action of Artemisinin and Its Derivatives Against Cancer

The classification of specific anticancer mechanisms covers multifaceted interventions targeting cancer biological processes and molecular mechanisms, of which the regulation of signaling pathways is central. These mechanisms include intervening in the cell cycle to block tumor cell proliferation, activating apoptosis to induce tumor cell death, inhibiting key signaling pathways to limit tumor growth and division, adopting anti-angiogenic measures to reduce the blood supply to tumors, utilizing immune modulation to enhance the body's attack on tumors, influencing gene expression in tumor cells through genetic and epigenetic regulation, and depriving metabolic reprogramming of energy required by cancer cells.[24,80]

Artemisinin and its derivatives have important roles in the regulation of anticancer signaling pathways, the main ones of which are suppression of PI3K/AKT/mTOR pathway, which affects the cell cycle, cell dormancy, and proliferation;[81,82] activation of AMPK signaling pathway, which regulates cell growth and metabolic reprogramming;[83] inhibition of STAT3 signaling pathway, which affects cancer cell growth, survival, and immune escape;[84–87] activation of JNK signaling pathway, which promotes cell apoptosis and autophagy;[88,89] inhibition of NF-κB activity, which reduces tumor cell sensitivity to apoptosis and promotes tumor growth. Pathway promotes apoptosis and autophagy.[90–93]

The PI3K/AKT/mTOR pathway is a significant cell survival and proliferation signaling pathway, and artemisinin and its derivatives can reduce the viability and proliferation rate of cancer cells by inhibiting this pathway. This signaling pathway is also intimately connected with the progression of the cell cycle. By blocking the PI3K/AKT/mTOR pathway, artemisinins and their derivatives can lead to cell cycle arrest and prevent the proliferation of cancer cells.[94] In some cases, artemisinin and its derivatives possess the capacity to trigger autophagy and cancer cell apoptosis by inhibiting mTOR activity,[95–97] an important mechanism of their anticancer effects. The PI3K/AKT/mTOR pathway has also been related to drug resistance in cancers, and artemisinin and its derivatives, by inhibiting this pathway, may help overcome the resistance of certain cancers to chemotherapeutic drugs.[98,99] The cancers it affects include breast cancers,[100,101] prostate cancers,[102,103] ovarian cancers,[104,105] pancreatic cancers,[106,107] lung cancers,[108,109] stomach cancers[110,111] and liver cancers.[112]

Artemisinin and its derivatives may directly inhibit the function of PI3K, AKT, or mTOR kinases, thereby blocking signaling. They may also interfere with interactions between critical molecules in the signaling pathway, such as preventing AKT's phosphorylation or inhibiting the mTOR complex's assembly. Artemisinin and its derivatives may also affect the PI3K/AKT/mTOR pathway by modulating factors upstream or downstream of the pathway, such as inhibiting the activity of growth factor receptors or modulating the expression of downstream effector molecules. By inhibiting the PI3K/AKT/mTOR pathway through these mechanisms, artemisinin and its derivatives hinder the proliferation and survival of cancer cells at various levels, providing an important basis for their action as potential anticancer drugs.

Artemisinin and its derivatives belong to the class of sesquiterpene lactones, and in the most cited article, "What made sesquiterpene lactones reach cancer clinical trials?" Ghantous et al summarized the specific mechanism of action of sesquiterpene lactones, including artemisinin, on tumors and cancer stem cells and pointed out that in clinical trials for cancer, sesquiterpene lactones (SLs) can diffuse through the cell membrane and selectively target specific signaling pathways and mechanisms in cancer cells. These include the NF-kB pathway, sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) pump, high intracellular iron content, cell surface transferrin receptors, and epigenetic regulation mechanisms. Glutathione can also diffuse through the cell membrane and interact with the SERCA pump through lipophilic interactions, inhibiting its function of transporting Ca^{2+} from the cytoplasm to the endoplasmic reticulum. Numerous cancer cells exhibit elevated levels of intracellular iron and transferrin receptors. Intracellular

iron can bind to the endoperoxide bridge of artemisinin, leading to its activation and the production of toxic reactive oxygen species. Additionally, artemisinin can inhibit the activity of NF-kB. NF-kB is a vital transcription factor within cells that regulates various cellular processes, including inflammation, immune responses, cell growth, and death. In the development of cancer, the activity of NF-kB is abnormally elevated and closely associated with tumor formation, advancement, metastasis, and resistance to anticancer treatments. Therefore, inhibiting the activity of NF-kB is considered a potential anticancer strategy. The specific effects of inhibiting NF-kB include suppressing tumor cell proliferation and survival, reducing tumor growth promoted by inflammatory responses, blocking tumor metastasis and invasion, and enhancing the effectiveness of anticancer therapies.

STAT3 serves as a downstream mediator of various cytokines, such as IL-6 and IL-4, and growth factors, including EGF and hypoxia. It has become a significant target due to its role in enhancing the stemness of tumor cells, triggering abnormal proliferation and malignant transformation, and evading apoptosis metastasis and immune responses.[113] Phosphorylated STAT3 dimers in cancer cells stimulate the gene transcription related to the regulation of cell cycle, adhesion, angiogenesis, and metastasis. Sustained STAT3 activation is an adverse prognostic factor in certain cancers. In immune cells, IL-6 triggers STAT-3 phosphorylation to facilitate IL-10 secretion, which leads to both maintenance of a robust immunosuppressive microenvironment and autocrine activation of immune STAT-3. ARTs can polarize monocytes to adopt a tumoricidal phenotype by inhibiting STAT3 in human primary monocytes. Additionally, suppressing Fas downregulation mediated by STAT3 or decreasing phosphorylated STAT3 can hinder tumor proliferation and metastasis while inducing cell apoptosis.[114]

Artemisinin and its derivatives exert their effects on the MAPK pathway through various mechanisms. MAPKs, which include c-Jun N-terminal kinase (JNK), ERKs, and p38 MAPK, play a significant role in multiple cellular processes.[115,116] VEGF's downstream signaling pathways can activate ERKs, promoting cell survival and proliferation. By interacting with endothelial cells (ECs) receptors phosphorylating Raf and activating MEK1/2 and ERKs, VEGF can enhance EC survival and proliferation.[115] JNK and p38 MAPK are involved in both cytotoxic and cytoprotective activities.[116–118] JNK, a protein enhancing angiogenesis, responds to stressors, phosphorylating c-jun of AP-1, leading to nuclear translocation and upregulating pro-angiogenic stimuli. p38 MAPK responds similarly to stress stimuli.[117–123] Additionally, both JNK and p38 MAPK also mediate apoptosis.[124–126] Impeding ERK-related cytoprotective activities can inhibit angiogenesis.

Artemisinin compounds exhibit both cytotoxic and cytostatic effects on cancer cells and cause cell cycle arrest in multiple cell types. Inhibitors such as the Cyclin-dependent kinase-associated protein (CIP) and kinase-inhibitory protein (KIP), including p57, p21, and p27,[127] participate in regulating cell division. Artemisinin and its derivatives disrupt cell division by interfering with different phases of the cell cycle. Artemisinin has been found to typically cause growth arrest during the G0/G1 to S transition. Nevertheless, growth arrest during all stages of the cell cycle has been frequently observed. ARTs also trigger apoptotic cell death in several cell types, where the mitochondrial-mediated apoptotic signaling pathways exert a crucial role.[123,128]

Directions of Artemisinin and Its Derivatives in Tumor Therapy

Artemisinin and its derivatives, such as dihydroartemisinin (DHA), artesunate (ARS), and artemether, have emerged as promising candidates in cancer therapy due to their multifaceted antitumor effects, including induction of apoptosis, ferroptosis, cell cycle arrest, and inhibition of angiogenesis. Preclinical studies have demonstrated efficacy across a broad spectrum of cancers, including breast, colorectal, lung, liver, and cervical cancers. However, significant challenges remain in translating these findings into clinical practice, including suboptimal bioavailability,[129] and limited clinical trial data. To overcome these hurdles and maximize the therapeutic potential of artemisinin-based compounds, future research should prioritize the following specific development directions, which aim to enhance efficacy, specificity, and clinical applicability.

Optimization of Drug Delivery Systems: one of the primary limitations of artemisinin and its derivatives is their poor pharmacokinetic profile, characterized by low solubility, rapid metabolism, and short half-life in vivo.[130] These factors reduce the drugs' ability to reach therapeutic concentrations at tumor sites while increasing the risk of systemic toxicity. Future research should focus on developing advanced drug delivery systems to address these challenges. Nanomedicine

offers a promising avenue, with approaches such as nanoparticles, liposomes, micelles, and dendrimers showing potential to enhance tumor-specific delivery. For example, transferrin-eight-arm-polyethylene glycol–dihydroartemisinin nanoparticles (TF-8armPEG–DHA NPs) have demonstrated improved tumor accumulation and reduced off-target effects in preclinical models of non-small cell lung cancer (NSCLC).[131] Expanding on such models, researchers could explore stimuli-responsive nanoparticles that release artemisinin in response to tumor-specific cues, such as pH, hypoxia, or enzyme activity, thereby improving precision and efficacy. Additionally, organelle-targeted delivery systems hold significant promise. Artemisinin's mechanism of action, particularly its induction of reactive oxygen species (ROS) via interaction with intracellular iron, suggests that targeting mitochondria or endoplasmic reticulum could amplify its cytotoxic effects.[14] Conjugates like triphenylphosphonium (TPP)-linked artemisinin have shown enhanced mitochondrial localization and cytotoxicity in cancer cells.[132] Future studies should investigate novel conjugates and nanoparticle designs to optimize subcellular targeting, potentially increasing potency while minimizing damage to healthy tissues. These advancements could pave the way for clinical trials by providing formulations that achieve higher therapeutic indices.

Combination Therapies to Overcome Resistance: cancer's heterogeneity and propensity for developing resistance to monotherapies underscore the need for combination strategies. Artemisinin and its derivatives are well-suited for this approach due to their ability to modulate multiple signaling pathways, including PI3K/AKT/mTOR,[82] NF-κB,[133] STAT3,[84] and MAPK,[134] which are often implicated in tumor progression and drug resistance. Future research should systematically evaluate artemisinin-based combinations with conventional chemotherapeutics, targeted therapies, and immunotherapies to identify synergistic effects. For instance, preclinical studies have shown that combining artesunate with cisplatin enhances cytotoxicity in ovarian cancer cells.[135] Similarly, DHA has been reported to sensitize pancreatic cancer cells to gemcitabine, suggesting potential for combination regimens in cancers with poor prognosis.[136] Beyond chemotherapeutics, integrating artemisinin with immunotherapies, such as immune checkpoint inhibitors (eg, anti-PD-1/PD-L1 antibodies), could exploit its immunomodulatory properties.[82] Artemisinin's ability to suppress regulatory T cells and myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment (TME) suggests it could enhance T-cell-mediated antitumor immunity.[137] Clinical trials exploring these combinations, particularly in immunologically "cold" tumors like pancreatic or liver cancer, could establish artemisinin as a versatile adjuvant. To accelerate progress, high-throughput screening platforms, as demonstrated in recent studies could be employed to identify optimal drug pairings and dosing schedules, minimizing trial-and-error in clinical settings.[138]

Elucidation of Molecular Mechanisms: while artemisinin's antitumor effects—such as induction of apoptosis, ferroptosis, autophagy, and cell cycle arrest—are well-documented, the precise molecular interactions driving these outcomes remain incompletely understood. This knowledge gap hinders the rational design of more potent and selective derivatives. Future research should leverage advanced omics technologies, including genomics, transcriptomics, proteomics, and metabolomics, to comprehensively map artemisinin's interactome in cancer cells. Moreover, understanding the role of tumor-specific factors, such as iron metabolism or oxidative stress, could guide the development of derivatives tailored to particular cancer types. Computational modeling and machine learning approaches could further predict artemisinin's efficacy across diverse genetic backgrounds, enabling personalized treatment strategies. By elucidating these mechanisms, researchers can design analogs with enhanced specificity, reducing off-target effects and paving the way for precision oncology applications.

740Clinical Trial Expansion and Biomarker Development: The scarcity of clinical trials remains a critical bottleneck in artemisinin's development as a cancer therapeutic. While preclinical data are robust, only a handful of studies have evaluated artemisinin or its derivatives in human patients, often as adjuvants rather than primary agents. Future research should prioritize designing and conducting phase I/II clinical trials to assess safety, pharmacokinetics, and preliminary efficacy in specific cancer types with strong preclinical evidence. These trials should incorporate rigorous endpoints to establish clinical utility. Equally important is the identification of biomarkers to predict treatment response and guide patient selection. Artemisinin's efficacy is closely tied to factors like intracellular iron levels, antioxidant enzyme activity and expression of signaling molecules like VEGF or EGFR. Developing assays to measure these biomarkers in patient samples could enable stratification, ensuring that artemisinin is administered to those most likely to benefit. Collaborative

efforts between academia and industry will be essential to fund and execute these trials, bringing artemisinin closer to regulatory approval.

Targeting the Tumor Microenvironment: The tumor microenvironment plays a pivotal role in cancer progression, immune evasion, and therapy resistance. Artemisinin's ability to modulate the TME, particularly through inhibition of immunosuppressive cells like Tregs and MDSCs, offers a unique opportunity to enhance antitumor immunity. Future research should explore how artemisinin derivatives can reshape the TME to favor immune activation. Additionally, artemisinin's anti-angiogenic effects, mediated through pathways like NF-κB and VEGF, suggest it could disrupt the vascular niche that supports tumor growth. Research should focus on combining artemisinin with anti-angiogenic agents, such as bevacizumab, to starve tumors of nutrients and oxygen. Furthermore, the role of cancer-associated fibroblasts (CAFs) and extracellular matrix remodeling in the TME remains underexplored in the context of artemisinin therapy. Investigating these interactions could uncover novel therapeutic targets, broadening artemisinin's applicability across solid tumors.

Development of Novel Derivatives: To address limitations like low potency and non-specific cytotoxicity, future research should focus on synthesizing novel artemisinin derivatives with improved pharmacological properties. Structure-activity relationship (SAR) studies could guide the design of analogs that retain the critical endoperoxide bridge—essential for ROS generation—while enhancing lipophilicity, stability, or receptor affinity.

By pursuing these six development directions—optimized delivery, combination therapies, mechanistic elucidation, clinical trials, TME modulation, and novel derivatives—artemisinin and its derivatives can transition from promising preclinical agents to cornerstone therapies in oncology. These efforts will require interdisciplinary collaboration, integrating expertise in pharmacology, bioengineering, immunology, and clinical research.

Limitations

Our study retrieved literature from the WOSCC database through reliable retrieval strategies, but the limitations still need to be considered: All the data in our article were obtained from a single database, which may lead to some incomplete initial data. The algorithm used to generate the results inevitably has its flaws. Due to the limited time frame for retrieving relevant research, some recently published articles may not appear in the search results we provide. Therefore, further in-depth exploration is needed to elucidate the hotspots and scientific trends in the research of artemisinin and its derivatives in cancer. Nevertheless, this bibliometric analysis still delves deeply into the existing data and provides valuable insights into the origin and advancement of applicating artemisinin and its derivatives in cancer, thus enhancing the lucidity of potential hotspots and guiding directions for future study.

Conclusions

We conducted a bibliometric analysis to assess the outcomes and impacts of relevant research. Our study summarized the most recent advancements in artemisinin and its derivatives in the field of cancer, identified research hotspots, and explored the prospects for development in this area. Artemisinin and its derivatives have undoubtedly become a significant research direction in cancer prevention and treatment. Currently, the drug repurposing of artemisinin for various types of cancer is a popular research topic, and studies on various clinical settings and combination therapies are crucial. Moreover, delving into the mechanisms of activity of artemisinin and its derivatives on multiple cancers is a current research hotspot. In cancer treatment research, artemisinin and its derivatives, serving as safe, reliable, and cost-effective drugs, have already achieved encouraging results in preclinical studies. Future research in this field should focus on combination therapeutics involving artemisinin and its derivatives, drug resistance in cancer, and other key issues, utilizing multidisciplinary approaches and omics technologies to foster active collaboration among different research groups.

Abbreviations

NCD, non-communicable disease; TCM, traditional Chinese medicine; WOSCC, Web of Science Core Collection; PI3K, Phosphoinositide 3-kinase; AMPK, Adenosine Monophosphate-activated Protein Kinase; STAT3, Signal Transducer and Activator of Transcription 3; JNK, c-Jun N-terminal kinase; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; mTOR, mammalian Target of Rapamycin; AKT, Protein Kinase B; MAPK, Mitogen-Activated

Protein Kinase; VEGF, Vascular Endothelial Growth Factor; ERK, Extracellular Signal-Regulated Kinase; CIP, Cyclin-dependent kinase-associated protein; KIP, Kinase-Inhibitory Protein; SERCA, Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase; IL-6, Interleukin-6; IL-4, Interleukin-4; EGF, Epidermal Growth Factor; IL-10, Interleukin-10; ARTs, Artemisinin and its derivatives; ECs, Endothelial Cells; AP-1, Activator Protein 1; DHA, Dihydroartemisinin; ARS, Artesunate; ROS, Reactive Oxygen Species; NSCLC, Non-Small Cell Lung Cancer; TPP, Triphenylphosphonium; MDR, Multidrug Resistance; MDSCs, Myeloid-Derived Suppressor Cells; TME, Tumor Microenvironment; CAFs, Cancer-Associated Fibroblasts; SAR, Structure-Activity Relationship.

Data Sharing Statement

All data generated or analyzed during this study are included in this article.

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Author 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; 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.

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Disclosure

The authors declare that they have no competing interests.

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