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REVIEW ARTICLE

# Research trends and visualization of cinobufagin in oncology treatment: A bibliometric analysis

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## Abstract

**Introduction**: Cinobufagin shows promise in cancer therapy, particularly for hepatocellular carcinoma, with an emerging focus on survival outcomes and combination strategies.

**Objective**: This study employed bibliometric methods to analyze and visualize research trends and hotspots related to cinobufagin in oncology using CiteSpace (v.6.2) and VOSviewer (v.1.6.20).

Methods: Publications in Science Citation Index and Emerging Sources Citation Index journals indexed in the Web of Science database from inception to September 3, 2024, were retrieved. Visual analyses with CiteSpace and VOSviewer were conducted to identify co-cited authors, institutions, journals, countries, keywords, references, and research trends.

**Results**: Of 179 relevant English-language documents retrieved, 172 met the inclusion criteria after excluding conference abstracts, unpublished articles, duplicates, and irrelevant studies. The most prolific and cited authors were Inagaki Yoshinori, Kokudo Norihiro, and Tang Wei. *Cancer Science* had the highest total citations, while Shanghai University of Chinese Medicine was the leading research institution. China produced the largest number of publications. Co-cited literature mainly focused on cinobufagin's pharmacological properties and anti-tumor mechanisms, particularly in hepatocellular carcinoma. Frequently used keywords included "cinobufagin toxin base," "hepatocellular carcinoma," "toad toxin," "apoptosis," and "gene expression." Emerging hotspots highlight cinobufagin's pharmacological activity and pharmacokinetics, mechanisms across multiple cancers, effects on patient survival, and potential synergy with chemotherapy.

**Conclusion**: This study mapped research trends on cinobufagin in cancer therapy, emphasizing its role in tumor cell cycle inhibition and signaling pathways. Key research areas include hepatocellular carcinoma, colon cancer, and lung cancer, with a growing focus on survival outcomes. Safety, side effects, and risk management strategies remain critical areas for future research.

***Keywords:*** Cinobufagin; Bibliometrics; Visual analysis; Anti-tumour mechanism; Chinese medicine

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## 1. Introduction

Cancer is one of the leading causes of death worldwide. According to the World Health Organization, millions of people die annually from various types of cancer. In oncology, the limitations of conventional therapies have driven researchers to explore new therapeutic strategies. Cinobufagin, an active molecule extracted from the epidermis of the toad, has garnered attention due to its remarkable anti-tumor activity.[1] With its unique chemical structure, cinobufagin exhibits a variety of pharmacological effects, including the inhibition of tumor cell growth, induction of apoptosis, anti-angiogenesis, reversal of multidrug resistance, and modulation of the immune system.[2] These properties have highlighted the significant potential of cinobufagin for use in cancer therapy. However, while the anti-tumor effects of cinobufagin have been widely recognized, its research progress, trends, and hotspots have not been systematically analyzed using bibliometric methods. Bibliometrics[3] is a field that applies mathematical and statistical techniques to quantitatively analyze literature data by examining various elements in the literature, such as authors, keywords, and citations.[4] Bibliometrics, through quantitative analysis and visualization, reveals the knowledge structure, research dynamics, collaborative networks, and emerging research hotspots within a field.[5,6]

Given that no comprehensive bibliometric study has focused on the application of cinobufagin in tumor therapy, this study intends to systematically analyze the global literature in this field through bibliometrics and visualization methods. Specifically, this study aims to (i) analyze the annual publication trends and geographical distribution characteristics, (ii) identify high-impact authors, institutions, and journals, (iii) construct a co-author and co-citation network map, and (iv) reveal research hotspots and emerging topics through keyword and reference analysis.[7] This study provides a valuable reference for comprehensively understanding the research status in this field, identifying knowledge gaps, and guiding future basic and clinical research.

## 2. Research methodology

### 2.1. Research tools

CiteSpace (v.6.2) and VOSviewer (v.1.6.20) are two widely used visualization tools in the field of bibliometrics, each with its own strengths and limitations. In some cases, these tools can be used together to leverage their complementary features.[8] CiteSpace offers various visualization outputs, including clustering, timeline, and time-zone views, illustrating the distribution of research topics and their evolution over time. VOSviewer provides powerful network analysis functions, such as centrality analysis, clustering analysis, and module detection.[9] While CiteSpace's automatic clustering and multiple visualization options facilitate in-depth analysis of literature data, VOSviewer excels at handling large datasets and visualizing complex network structures.[10] When used in combination, these tools offer a more comprehensive and detailed bibliometric analysis, particularly for interdisciplinary or large-scale literature reviews.[11]

### 2.2. Data sources

The study flowchart is presented in Figure 1. The Web of Science (WoS) database was selected as the data source for this study due to its inclusion of high-quality journal articles, conference papers, book chapters, and other significant literature resources.[12] Moreover, the data is highly authoritative.[13] Most international journals require submissions in English when submitting papers, as English-language literature is more widely disseminated globally, making research results more universal and comparable. Selecting English publications facilitates comparison with international studies and enhances the academic value and influence of the research.[14] Furthermore, bibliometric tools offer stronger support for English literature, providing more effective data cleaning, standardized field specifications, and improved visualization.

Cinobufagin is a regional drug in China and has not been included in key Chinese databases such as China National Knowledge Infrastructure or Wanfang.[15] This is because certain search results may contain non-academic content, such as journal introductions and news, which affects the accuracy of the analysis. Hence, to ensure the comprehensiveness and accuracy of the selected literature, the indices chosen for this study were the Science Citation Index (SCI) and the Emerging Science Citation Index (ESCI), with the indexing period spanning from the inception of the database until September 3, 2024. The search query used was: "(TS= [cinobufagin] AND TS= ["Tumor*" OR "Cancer*" OR "Neoplasms*" OR "Malignant Neoplasm*" OR "Malignancy*" OR "Neoplasm, Malignant" OR "Neoplasms, Malignant"])." A total of 179 publications were retrieved. After excluding conference abstracts or errata papers, unpublished articles, duplicate publications, and irrelevant publications, 172 publications were included for bibliometric and visualization analysis.

### 2.3. Bibliometrics and visualization analysis

The retrieved literature with complete records and references was exported in plain text format and saved as "download.txt." Four folders were created: "data," "input," "output," and "project." The "download.txt" file was placed in the "input" folder. The steps for using CiteSpace and

VOSviewer were strictly followed during the visual knowledge map construction.

For CiteSpace, the CiteSpace 6.2 advanced edition was installed. The "Data-Import/Export" option was selected from the software's home page, followed by "WoS." The data were imported from the "input" folder, and the export folder was set to "output." The "Remove duplication" option was selected, followed by "WoS" to remove duplicates. After returning to the main interface, the "New" option was selected, and the years of choice (from database construction to September 2024) were chosen. The slicing years were set to "1 year," and "Keyword" was selected for analysis. Finally, the "WoS" option was chosen to import the data from the "input" folder, and the export folder was set to "output." Then, either "Keyword" or "Reference" was selected for analysis, and "GO" was clicked to perform the visual analysis. The data can be displayed as a timeline graph, time area graph, or other visualization types. Key concepts in CiteSpace include emergence detection, centrality analysis, and heterogeneous networks, which can visually represent dynamic research changes, hot topics, and academic frontiers. In knowledge graphs, nodes represent authors, institutions, countries, or keywords. The size of the nodes reflects the frequency of occurrence or citation, while the node's color indicates the time of its occurrence or the year of its citation.[16]

The VOSviewer software was installed from the official website. After installation, the "File>Create" option was chosen, and the"Create a map based on bibliography" option was selected. Next, the "Read data from bibliographic database files" was clicked, followed by "Next" and "Web of Science." The "input" folder within the "Web of Science" directory was chosen. Subsequently, the "downlowd.txt" file in the "input " folder was clicked, and co-cited authors, journals, countries, and citations were selected for visual analysis. For the co-cited author analysis, at least three documents per author and 39 authors were chosen, while for the co-cited journal analysis, the minimum number of documents per author was set to 2, with 30 authors selected. For the co-cited country analysis, the minimum number of documents per country was 1, with 23 countries selected. For the institutional co-citation analysis, the minimum number of documents per organization was 3, with 37 organizations chosen. Key concepts in VOSviewer include distance-based visualization, co-occurrence clustering, and multilevel network analysis. In the co-occurrence network, nodes represent entities, and connecting lines represent co-occurrence relationships. The thickness of the lines reflects the strength of co-occurrence, and the distance between nodes indicates the similarity of their relationships. Shorter distances indicate closer relationships, which helps to identify research topic clusters and the evolution of knowledge structures. Different colored clusters correspond to distinct research topics or domains.[17]

## 3. Results

### 3.1. Annual trend of publications

A total of 172 articles were retrieved, with the earliest publication dating back to 2003. During the indexing period (2003–2024), an average of 8.1 articles were published annually. In 2011, the number of publications was generally higher than in previous years (Figure 2). Although there were occasional fluctuations, the overall trend was on the rise. In 2023, 19 papers were published, indicating that researchers have gradually realized the advantages of cinobufagin in treating tumors. The growing number of related publications indicates increasing attention to this research field in recent years.

### 3.2. Global distribution and collaboration networks

Most of the publications were authored by researchers from East Asia, West Asia, Europe, North America, and Oceania. China ($n$ = 157) had the largest number of publications, followed by the United States ($n$ = 7), Japan ($n$ = 7), South Korea ($n$ = 6), and Brazil ($n$ = 2). Close collaboration was observed among research groups from North America, Europe, and East Asia (Figure 3). Among the top 10 countries in terms of publication volume, Japan ranked first for the average number of citations ($n$ = 75.71), followed by Brazil ($n$ = 38.5), the United States ($n$ = 37.43), and China ($n$ = 24.29) (Table 1).

**Table 1. Top 10 countries in the cited literature**

| Country | Publications | Citations | Average citations |
|---|---|---|---|
| People's Republic of China | 157 | 3,813 | 24.29 |
| Japan | 7 | 530 | 75.71 |
| United States of America | 7 | 262 | 37.43 |
| South Korea | 6 | 16 | 2.67 |
| Australia | 2 | 47 | 23.50 |
| Brazil | 2 | 77 | 38.50 |
| Canada | 2 | 13 | 6.50 |
| Poland | 2 | 26 | 13.00 |
| England | 1 | 5 | 5.00 |
| Uzbekistan | 1 | 10 | 10.00 |

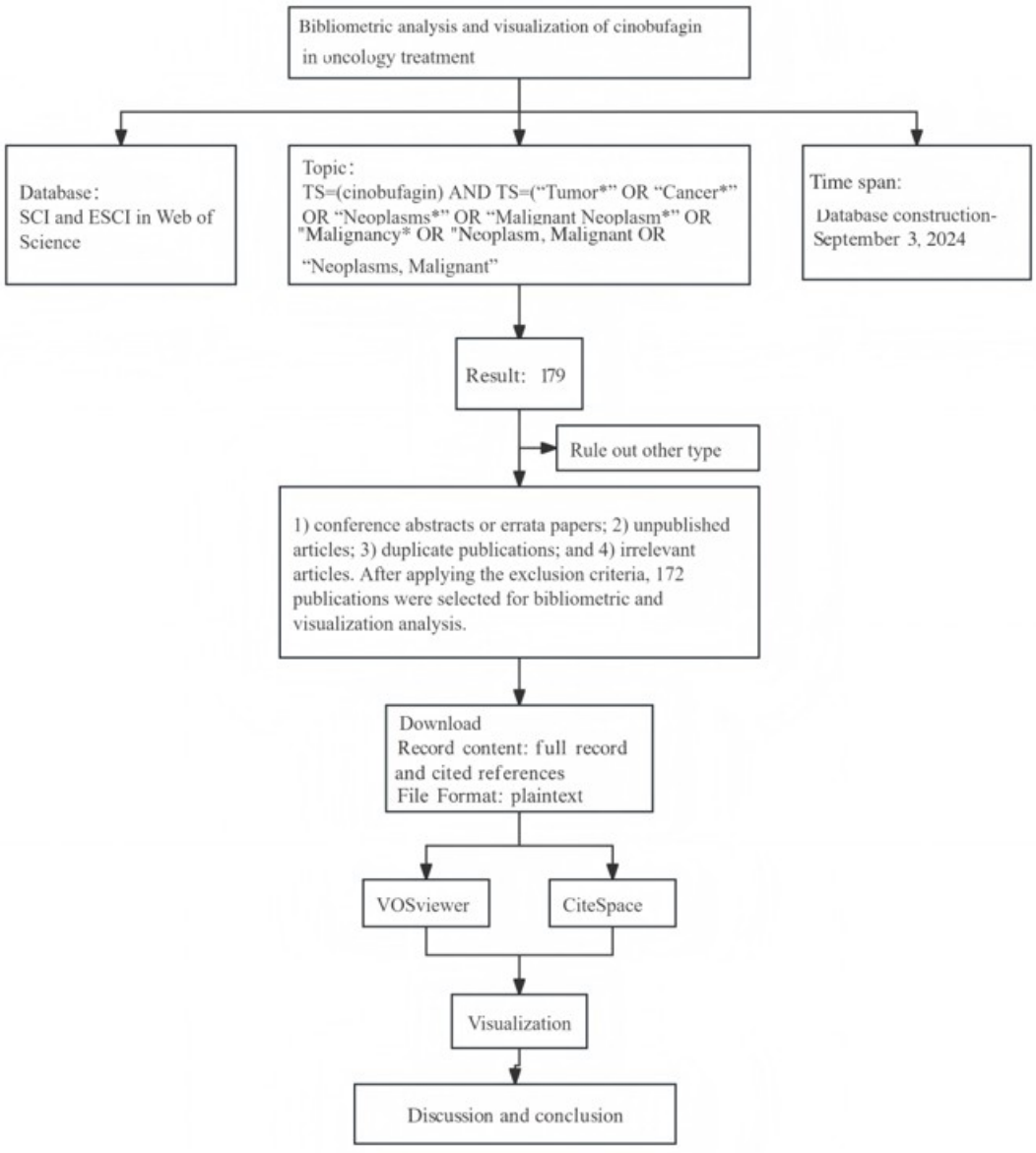



**Figure 1.** Flow chart of the study
Abbreviations: ESCI: Emerging Sources Citation Index; SCI: Science Citation Index.

### 3.3. Leading institutions and institutional collaboration network

A total of 251 institutions contributed to the 172 published articles. The institution with the highest number of publications was Shanghai University of Traditional Chinese Medicine ($n$ = 16), followed by Shanghai Jiao Tong University ($n$ = 10), Peking University ($n$ = 10), Dalian Medical University ($n$ = 10), Shandong University ($n$ = 6), Binzhou Medical University ($n$ = 6), Jilin University ($n$ = 6), Sun Yat-sen University ($n$ = 6), the Chinese Academy of Sciences ($n$ = 6), Zhejiang University ($n$ = 5), and Shenyang Pharmaceutical University ($n$ = 5). Among the top 10 institutions in terms of publication volume, Shandong University ranked first for the average number of citations ($n$ = 68.5), followed by Peking University ($n$ = 34.6), Shenyang Pharmaceutical University ($n$ = 26.60), and Shanghai University of Traditional Chinese Medicine ($n$ = 24.44) (Table 2). Figure 4 illustrates the network co-occurrence relationship between co-cited institutions.

### 3.4. Authors and co-authorship networks

A total of 1,187 authors have contributed to publications in

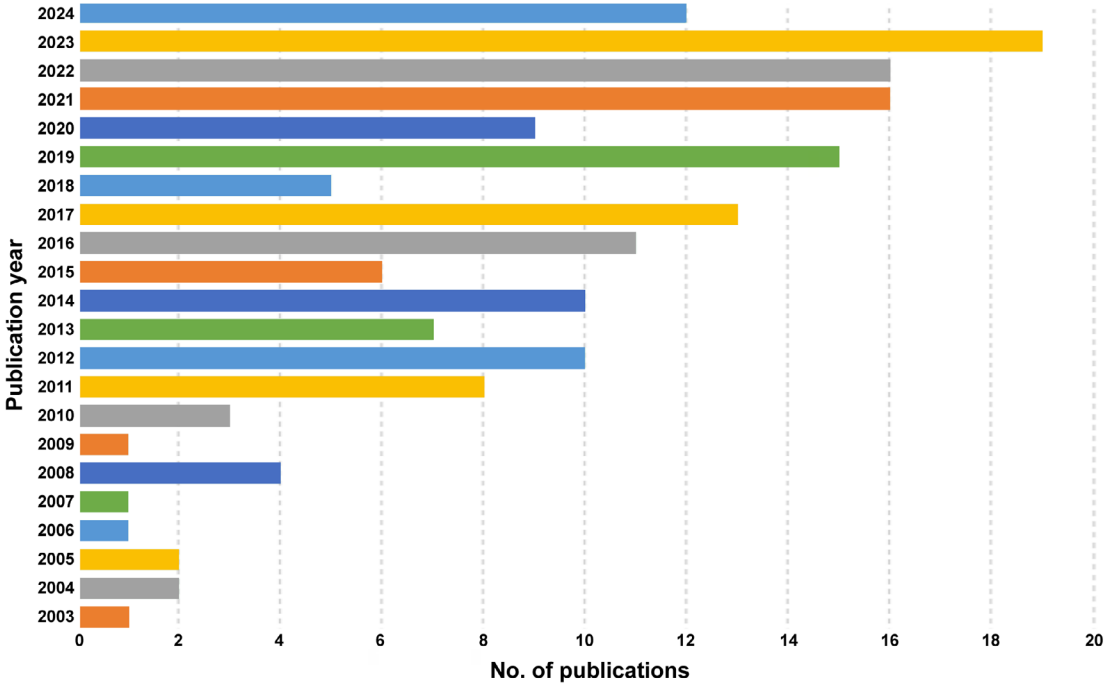



**Figure 2.** Distribution of articles by year of publication. The vertical axis refers to the year of publication; the horizontal axis is the number of publications in the specified year.

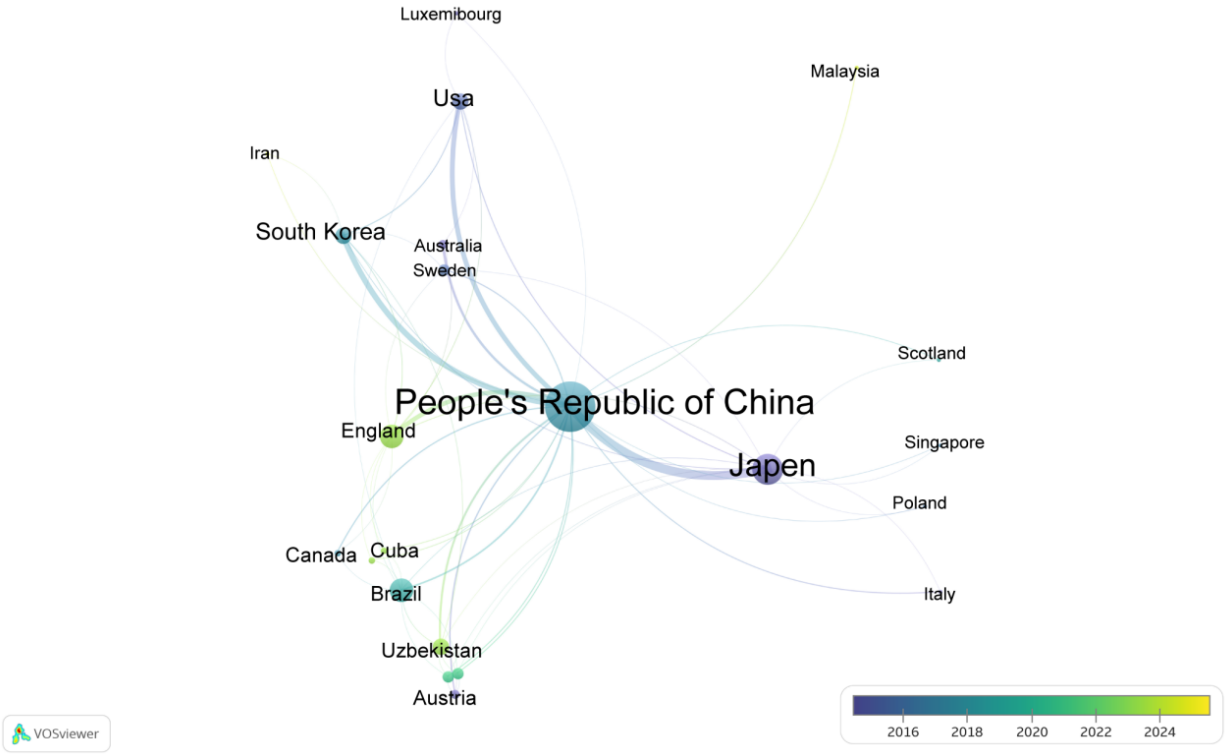



**Figure 3.** The global cooperation network diagram. The figure was generated in VOSviewer v.1.6.20, with the minimum citation threshold set at 1.

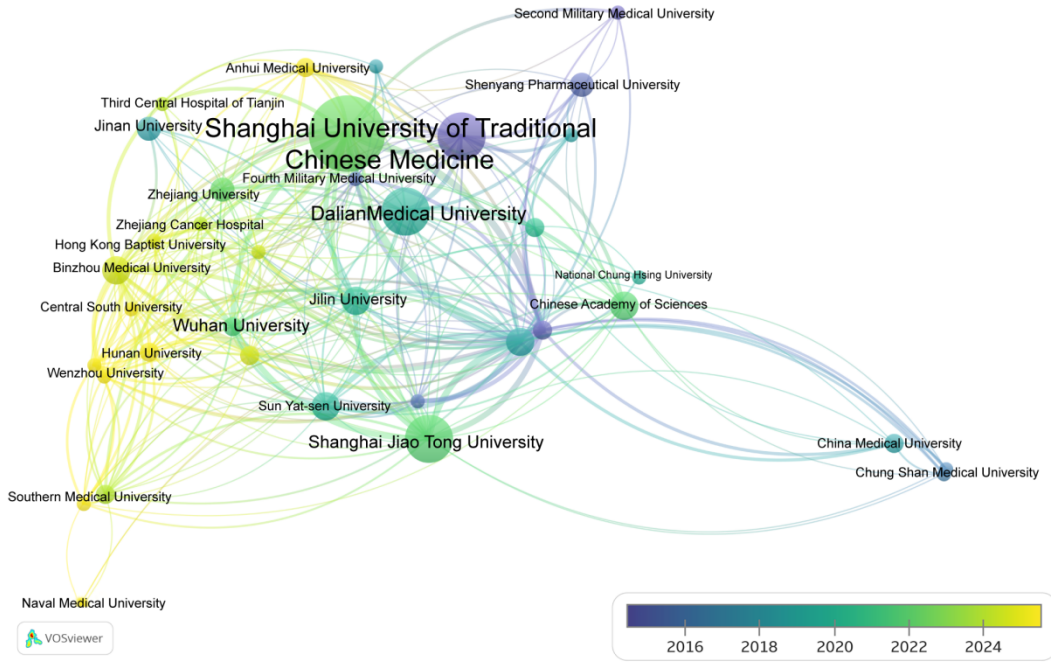



**Figure 4.** The network co-occurrence relationship between co-citation institutions. The figure was generated in VOSviewer v.1.6.20, with the minimum citation threshold set at three.

**Table 2. The top 10 leading institutions cited in the literature**

| Organization | Publications | Citations | Average citations |
|---|---|---|---|
| Shanghai University of Traditional Chinese Medicine | 16 | 391 | 24.44 |
| Shanghai Jiao Tong University | 10 | 161 | 16.10 |
| Peking University | 10 | 346 | 34.60 |
| Dalian Medical University | 10 | 117 | 11.70 |
| Shandong University | 6 | 411 | 68.50 |
| Binzhou Medical University | 6 | 136 | 22.67 |
| Jilin University | 6 | 114 | 19.00 |
| Sun Yat Sen University | 6 | 144 | 24.00 |
| Chinese Academy of Sciences | 6 | 93 | 15.50 |
| Zhejiang University | 5 | 40 | 8.00 |
| Shenyang Pharmaceutical University | 5 | 133 | 26.60 |

this field. Ten authors have published four relevant articles, and 29 have published three. Among the top 10 authors in terms of publication volume, the highest-ranked authors based on the average number of citations were Inagaki Yoshinori, Kokudo Norihiro, and Tang Wei ($n$ = 102.5), followed by Gao Bo ($n$ = 55.5), Yin Peihao ($n$ = 39), and Guo De-an ($n$ = 17.25) (Table 3). Figure 5 illustrates the network of co-occurrence relationships among co-cited authors.

### 3.5. Most influential journals based on citations

A total of 118 journals included articles in this area. The journal with the most articles was *Journal of Ethnopharmacology* ($n$ = 7), followed by *Oncology Reports*

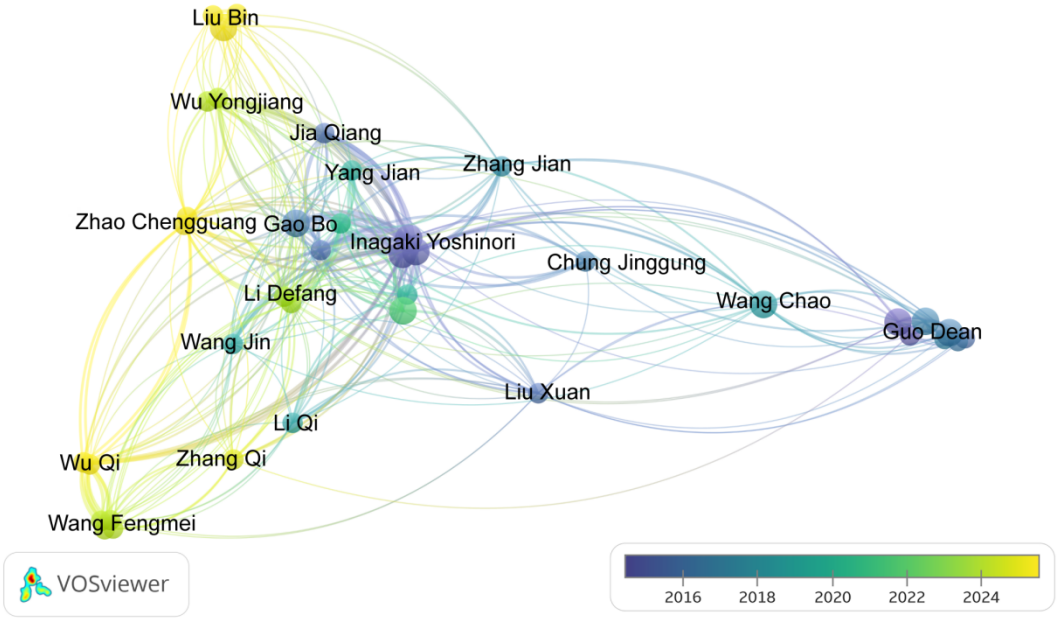



**Figure 5.** The network co-occurrence relationship between co-citation authors. The figure was generated in VOSviewer v.1.6.20, with the minimum citation threshold set at 1.

*and Frontiers in Pharmacology* ($n$ = 5), *Oncotarget*, *Evidence-Based Complementary and Alternative Medicine*, and *RSC Advances* ($n$ = 4), and *Cancer Science*, *Frontiers in Oncology*, and *International Journal of Molecular Sciences* ($n$ = 3) (Table 4). Among the top 10 co-cited journals, the highest average number of citations was in *Cancer Science* ($n$ = 105.33), followed by *Oncology Reports* ($n$ = 41.40), *International Journal of Molecular Sciences* ($n$ = 36.67), *Oncotarget* ($n$ = 29.25), and *Journal of Ethnopharmacology* ($n$ = 28.43). Figure 6 shows the network co-occurrence between co-cited journals.

**Table 3. Top 10 authors of the cited papers**

| Author | Publications | Citations | Average citations |
|---|---|---|---|
| Inagaki Yoshinori | 4 | 410 | 102.5 |
| Kokudo Norihiro | 4 | 410 | 102.5 |
| Tang Wei | 4 | 410 | 102.5 |
| Gao Bo | 4 | 222 | 55.5 |
| Yin Peihao | 4 | 156 | 39 |
| Wang Chao | 4 | 61 | 15.25 |
| Guo De-an | 4 | 69 | 17.25 |
| Liu Bin | 4 | 45 | 11.25 |
| Ma Xiaochi | 4 | 35 | 8.75 |
| Ye M | 4 | 189 | 47.25 |

**Table 4. Top 10 journals of the cited papers**

| Source | Publications | Citations | Average citations |
|---|---|---|---|
| *Journal of Ethnopharmacology* | 7 | 199 | 28.43 |
| *Oncology Reports* | 5 | 207 | 41.40 |
| *Frontiers In Pharmacology* | 5 | 22 | 4.40 |
| *Oncotarget* | 4 | 117 | 29.25 |
| *Evidence-Based Complementary and Alternative Medicine* | 4 | 103 | 25.75 |
| *RSC Advances* | 4 | 37 | 9.25 |
| *Cancer Science* | 3 | 316 | 105.33 |
| *Frontiers in Oncology* | 3 | 81 | 27.00 |
| *International Journal of Molecular Sciences* | 3 | 110 | 36.67 |
| *Drug Design, Development and Therapy* | 3 | 53 | 17.67 |

### 3.6. Co-citation and reference clustering analysis

Among the 172 papers, 15 documents were cited more

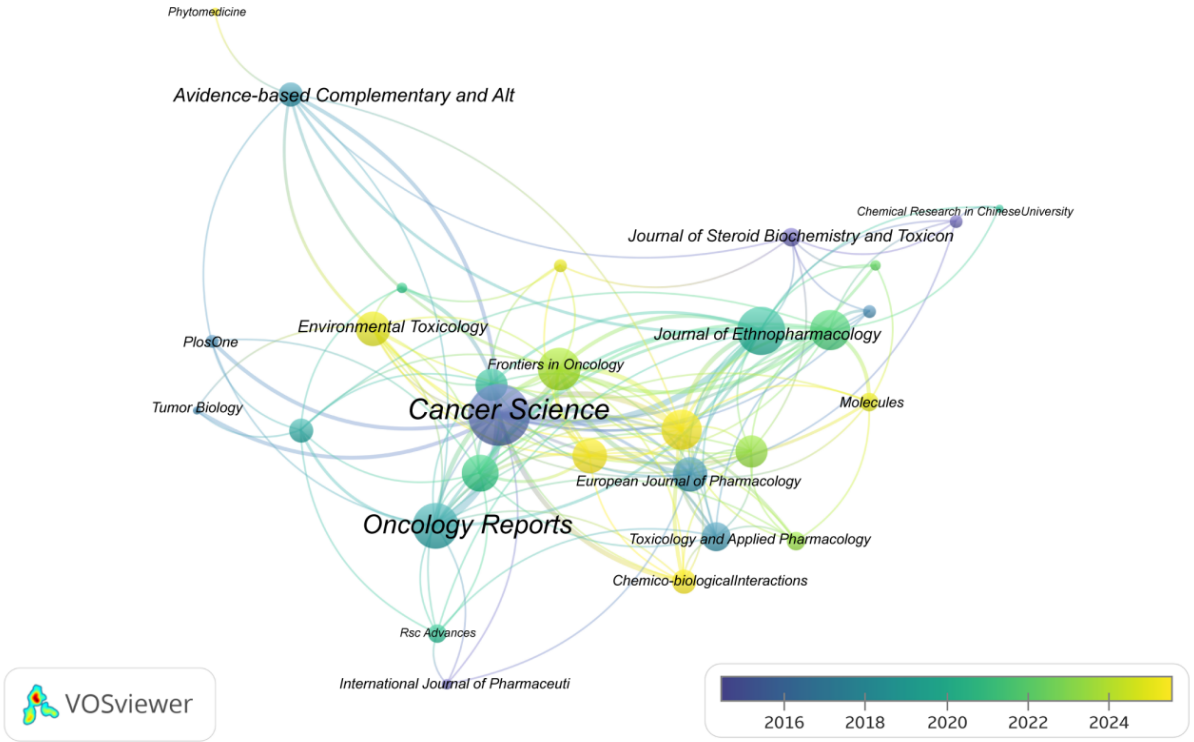



**Figure 6.** The network co-occurrence relationship between co-cited journals. The figure was generated in VOSviewer v.1.6.20, with the minimum citation threshold set at 2.

than 10 times, with the highest number of citations being 19 (Table 5). Figure 7 presents a co-occurrence graph of co-cited references, highlighting the authors of the most cited references and their publication dates. Most of these highly cited articles were published in recent years (Figure 7A. The top 10 keyword clusters with the largest distribution were: anti-tumor effect, cinobufagin, cardiac glycosides, traditional Chinese medicine, comparative pharmacokinetics, cell cycle blockade, synergistic anti-tumor effect, advanced cholangiocarcinoma, EGFR-mutated lung cancer, and androgens (Figure 7B). Figure 7C shows a timeline plot of co-cited references over time within this clustering. The earliest burst intensity in the co-cited literature occurred in 2004 ($n$ = 4.22), while the most recent burst was in 2022 ($n$ = 3.16), and the highest burst intensity was 6.78 in 2017 (Figure 7D).

### 3.7. Keywords and research hotspot evolution

The top 10 keywords identified were cinobufagin (59 times), hepatocellular carcinoma (39 times), toadstool toxin (37 times), apoptosis (33 times), malignant tumors and cells (both 31 times), toadstool dienoglycolides (26 times), activation (22 times), expression (20 times), and cultivation (16 times) (Table 6; Figure 8A). Cluster analysis of the keywords yielded a Q value of 0.4692 and an S value of 0.7905. The top 10 keyword clusters identified were toadstool essence, cell cycle, hepatocellular carcinoma, huperzine toxin base, cell cycle blockade, bioconstituent activity, peripheral opioid receptor, Bcl-2, cycle blockade, and gemcitabine (Figure 8B). Figure 8C illustrates the timeline of keyword occurrence, highlighting ongoing research topics such as wahoo toxin, malignancy, and mechanisms. Figure 8D aggregates the nodes within the same time period, showing that, over time, emerging research themes include traditional Chinese medicine, tumor survival, lung cancer, and colon cancer. Keyword bursts, identified by their high intensity of occurrence, include biotransformation, artemisinin, cultivation, high-performance liquid chromatography, human leukemia cells, inhibition, human liver cancer, cancer cells, cinobufagin toxin base, prostate cancer, induced apoptosis, chemotherapy, lung cancer, cell cycle arrest, survival rate, hepatocellular carcinoma, colorectal cancer, and apoptosis. The keyword with the highest burst intensity was human leukemia cells (burst intensity of 4.41), with the most significant burst occurring in 2011 ($n$ = 4). Research on the role of apoptosis in the mechanism of cinobufagin's anti-tumor effects began in 2003 and has continued through to a peak in research activity from 2022 to 2024 (Figure 8E).

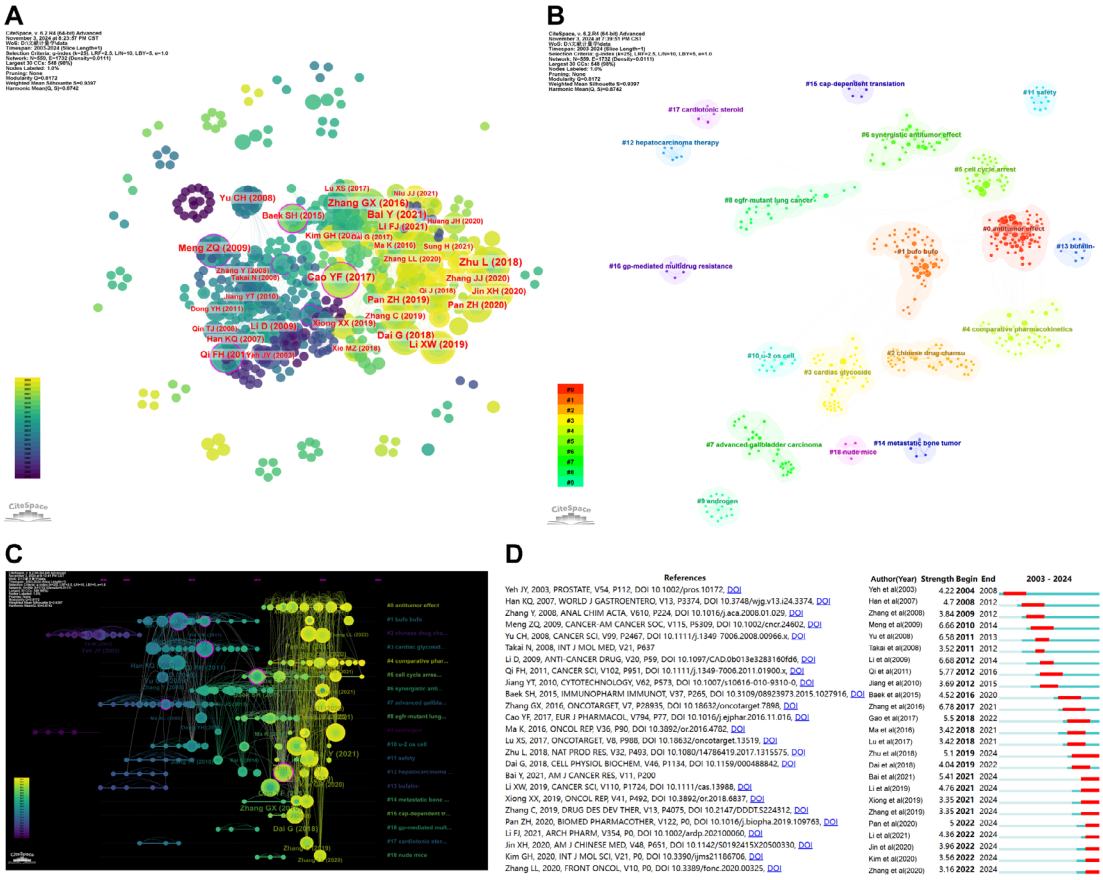


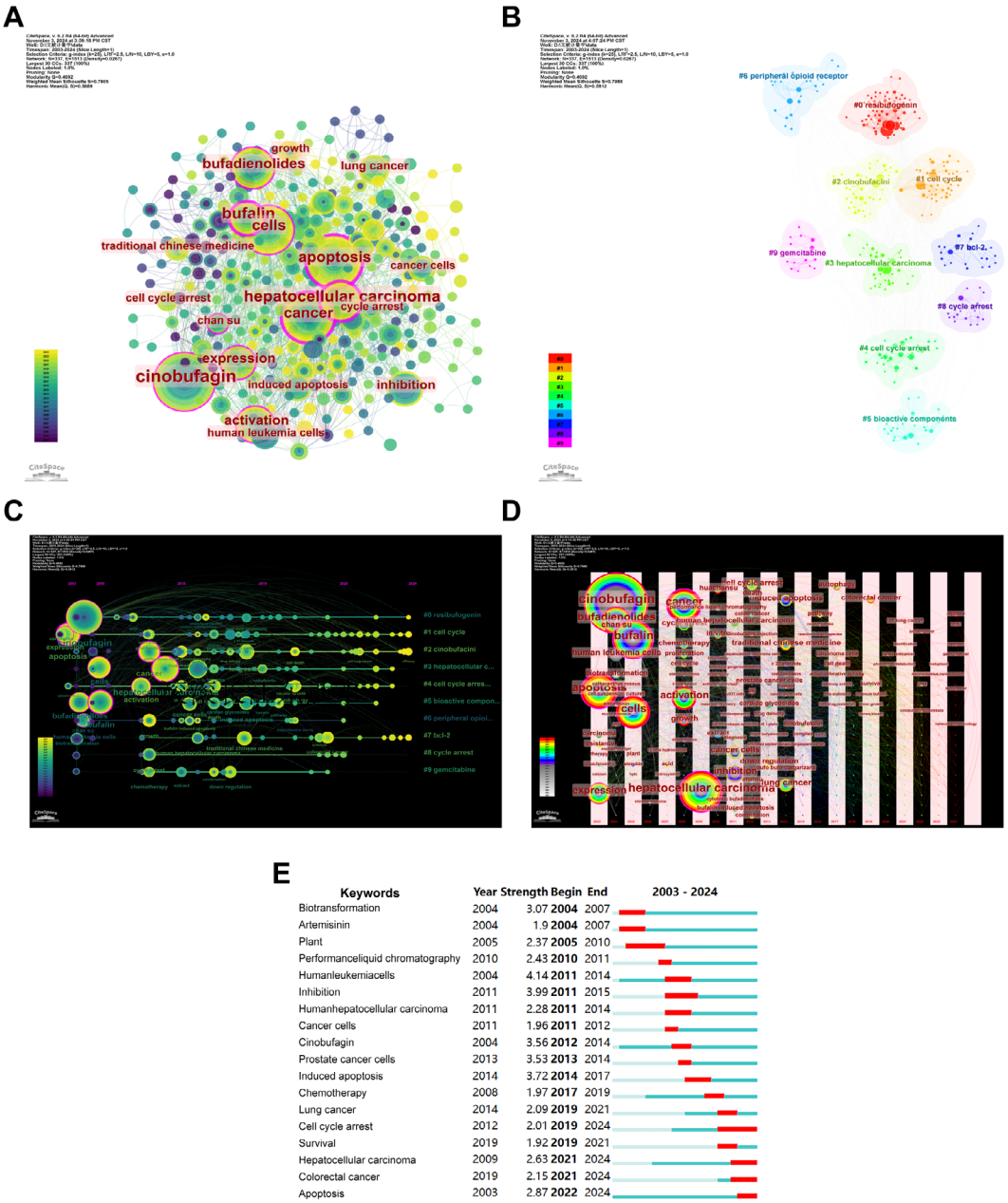

**Figure 7.** Multi-dimensional analysis of co-cited literature networks. (A) The network relationship diagram between co-cited literature. (B) The clustering graph of co-citation literature. (C) The relationship between co-cited literature and time. (D) The burst time and intensity of the co-cited literature. The figures were produced using CiteSpace v.6.2, with time slicing set to one year.

**Table 5. Top 10 citations of co-cited literature**

| Cited references | Count | Centrality | Year |
|---|---|---|---|
| Zhu *et al.*[18] | 19 | 0.03 | 2018 |
| Bai *et al.*[19] | 17 | 0.07 | 2021 |
| Zhang *et al.*[20] | 16 | 0.05 | 2016 |
| Cao *et al.*[21] | 16 | 0.36 | 2017 |
| Li *et al.*[22] | 15 | 0.02 | 2019 |
| Dai *et al.*[23] | 15 | 0.05 | 2018 |
| Meng *et al.*[24] | 14 | 0.15 | 2009 |
| Pan *et al.*[25] | 13 | 0.02 | 2019 |
| Li *et al.*[26] | 12 | 0.02 | 2009 |
| Yu *et al.*[27] | 12 | 0.02 | 2008 |

**Table 6. Top 10 keywords in the cited literature**

| Keywords | Count | Centrality | Year |
|---|---|---|---|
| Cinobufagin | 59 | 0.18 | 2004 |
| Hepatocellular carcinoma | 39 | 0.22 | 2009 |
| Bufalin | 37 | 0.27 | 2005 |
| Apoptosis | 33 | 0.25 | 2003 |
| Cancer | 31 | 0.24 | 2008 |
| Cells | 31 | 0.17 | 2005 |
| Bufadienolides | 26 | 0.18 | 2004 |
| Activation | 22 | 0.13 | 2008 |
| Expression | 20 | 0.16 | 2003 |
| Inhibition | 16 | 0.03 | 2011 |




| Keywords | Year | Strength | Begin | End | 2003 - 2024 |
|---|---|---|---|---|---|
| Biotransformation | 2004 | 3.07 | 2004 | 2007 | |
| Artemisinin | 2004 | 1.9 | 2004 | 2007 | |
| Plant | 2005 | 2.37 | 2005 | 2010 | |
| Performanceliquid chromatography | 2010 | 2.43 | 2010 | 2011 | |
| Humanleukemiacells | 2004 | 4.14 | 2011 | 2014 | |
| Inhibition | 2011 | 3.99 | 2011 | 2015 | |
| Humanhepatocellular carcinoma | 2011 | 2.28 | 2011 | 2014 | |
| Cancer cells | 2011 | 1.96 | 2011 | 2012 | |
| Cinobufagin | 2004 | 3.56 | 2012 | 2014 | |
| Prostate cancer cells | 2013 | 3.53 | 2013 | 2014 | |
| Induced apoptosis | 2014 | 3.72 | 2014 | 2017 | |
| Chemotherapy | 2008 | 1.97 | 2017 | 2019 | |
| Lung cancer | 2014 | 2.09 | 2019 | 2021 | |
| Cell cycle arrest | 2012 | 2.01 | 2019 | 2024 | |
| Survival | 2019 | 1.92 | 2019 | 2021 | |
| Hepatocellular carcinoma | 2009 | 2.63 | 2021 | 2024 | |
| Colorectal cancer | 2019 | 2.15 | 2021 | 2024 | |
| Apoptosis | 2003 | 2.87 | 2022 | 2024 | |

**Figure 8.** CiteSpace visual analysis of bibliometric data on cinobufagin and its anti-tumour mechanisms. (A) The co-occurrence relationship of keywords. (B) The clustering graph of keywords. (C) The graph of keywords evolving with time. (D) The graph of keywords evolving with time and region. (E) Top 18 keywords with the strongest citation bursts. The figures were produced using CiteSpace v.6.2, with time slicing set to one year.

## 4. Discussion

In international pharmacology and natural product research, cinobufagin and its main active ingredient bufalin, also known as bufotoxin, have become one of the most studied natural products[28] in recent years. The name is derived from its chemical nature and biological origin—steroid compounds in toad venom glands and skin gland secretions. Bufalin is a typical bufadienolide cardiac steroid with an unsaturated lactone ring and a steroid nucleus in its chemical structure. Its high affinity binding with sodium–potassium adenosine triphosphatase (NKA) endows it with cardiac glycoside-like activity, and provides key target support for its anti-tumor effect.[29] From the perspective of natural sources, cinobufagin is mainly extracted from *Bufo gargarizans* and other toad species. The *Bufo gargarizans* species is distributed in eastern, central, and southwestern

China. In addition, natural populations of this species also exist in Southeast Asian countries, such as Vietnam, Laos, and Thailand. Bufadienolide-extractable toads can also be found in North America and parts of Europe, although the species differ. This wide geographical distribution facilitates the acquisition of raw materials for cinobufotalin and promotes the development of transnational pharmacological research.[29] Notably, China has maintained an international leading position in resource utilization, pharmacological research, and formulation development of cinobufotalin, a dominance closely related to the regional abundance of resources and the long-standing application of traditional Chinese medicine. The international research on bufalin is gradually showing a multidisciplinary trend, involving pharmacology, molecular biology, chemistry, medicinal chemistry, drug delivery systems, biomaterials, and nanotechnology.[30] In addition, the application of cinobufotalin in tumor therapy has also attracted wide attention. The research content covers its biological activity, pharmacological characteristics, and anti-tumor mechanisms. With the development of big data and visualization technology, bibliometric analysis provides an effective tool for systematically summarizing the knowledge structure, hotspot evolution, and international cooperation network in bufalin research.[31] Through the retrieval and analysis of WoS, we can quantify the annual publication trend of bufalin-related research, the contribution of major countries and institutions, core authors, highly cited literature, and the clustering distribution of research topics.[32] This type of analysis identifies research frontiers and provides direction and guidance for subsequent basic and clinical research.[23]

CiteSpace and VOSviewer are highly consistent in hot spot identification and knowledge base characterization, but they have different emphases on temporal evolution, key nodes, transformative identification, macro structure, cooperative network, and readable visualization. After unified preprocessing and parameter sensitivity control, VOSviewer was mainly used to identify the relevant dominant authors, journals, institutions, and national frontiers. In terms of evolution, the timeline of CiteSpace showed that there have been evident burst clusters since 2003. Combined with the results of VOSviewer, the keywords showed a gradient migration from the main components of cinobufotalin to its anti-tumor mechanism. Co-citation analysis revealed that studies on the effects of bufalin and cinobufagin on the proliferation of androgen-dependent and -independent prostate cancer cells constitute the knowledge base in this field. Burst literature highlighted that cinobufagin suppresses tumor growth by inducing intrinsic apoptosis through the protein kinase B signaling pathway in human non-small cell lung cancer cells, suggesting potential structural changes that bridge different research clusters. These findings indicate that future studies could further integrate the anti-tumor mechanism of traditional Chinese medicine.

To systematically assess the research progress in this field, this study employed a scientometric methodology to conduct an in-depth analysis of the literature on cinobufagin in oncology treatment. By searching the WoS database, 172 relevant articles were retrieved from September 2003 to 2024. The citation records and full-text information of these articles were used to construct a map of the research trends, thereby elucidating the research hotspots and their evolutionary trajectories.

Between 2003 and 2010, research on the use of cinobufagin in tumor therapy was relatively limited. The technical level and scientific research resources at that time posed certain challenges for early tumor detection and treatment. Additionally, there was a limited understanding of the potential advantages of traditional Chinese medicine in oncology.[33] Although toad venom has been used in Chinese medicine for thousands of years, cinobufagin was developed as a modern proprietary Chinese medicine, primarily for drug safety and efficacy, and has since emerged as an alternative to traditional toad venom. However, the clinical understanding of the efficacy and mechanisms of cinobufagin remains incomplete, and early studies were mainly focused on identifying its active ingredients and conducting basic experimental research.[34] Since 2011, however, there has been an increase in literature related to cinobufagin, with a particularly rapid growth in recent years. This reflects the growing recognition of the efficacy of traditional Chinese medicine in oncology, which aligns with China's strong advocacy for developing traditional Chinese medicine.[35] In this context, China has published the largest number of studies in this field. The research institution with the highest number of publications was Shanghai University of Traditional Chinese Medicine, which also ranked first among the co-cited institutions. This indicates that research on cinobufagin, a component of traditional Chinese medicine, has garnered significant attention within traditional Chinese medicine institutions. Following China, Japan and the United States were tied for second place. This result reflects the comprehensive national capabilities and scientific research strength of these two countries, which are highly proactive in scientific research and have made globally impactful contributions. The most cited journal in this field is the *Journal of Ethnopharmacology*, a leading medical publication primarily focused on medical toxicology and pharmacology. The most cited article was published in *Cancer Science*, a journal founded in 1907 and sponsored

by the Japan Anti-Cancer Society, which primarily covers basic, translational, and clinical cancer research. The preeminent articles in this field have appeared in *Cancer Science*, suggesting that research on cinobufagin has evolved from pharmacological studies to clinical applications. In terms of influential researchers, Inagaki Yoshinori, Kokudo Norihiro, and Tang Wei, all from the Graduate School of Medicine at the University of Tokyo, are prominent leaders in this field. These researchers, who focused on the mechanisms of cinobufagin in the treatment of liver cancer, were co-authors on all four of their publications, indicating a collaborative research team.[36] Despite China contributing 157 papers to this field, the most highly cited article was authored by researchers from Japan, highlighting Japan's in-depth exploration and significant influence in this area.

Moreover, through cluster analysis of co-citations and keywords, this study identified 23 co-citation clusters, revealing significant modularity results (Q = 0.8172) and high-profile scores (S = 0.9397), suggesting the formation of a structured academic network in this field. The Q value ranges between 0 and 1, reflecting the clustering structure's significance. The higher the Q value, the more reasonable the clustering results; the higher the discrimination between different clusters, the stronger the keyword correlation within the same cluster. The clustering results are statistically significant when the Q value is greater than 0.3, and the clustering effect is ideal when the Q value is greater than 0.5. The S value ranges between −1 and 1, with higher values corresponding to a better clustering effect. A high S value reflects strong similarity among samples within a cluster and clear differences between clusters. When $S \geq 0.7$, the clustering results are considered highly reliable, the similarity of samples in the cluster is high, and the difference between clusters is evident. The Q value is often interpreted together with S to jointly evaluate the clustering quality. When $S \geq 0.7$, the results are more robust, and the combination of Q and S ensures the reliability and stability of the analysis outcomes.[37] Additionally, keyword cluster analysis generated nine clusters with strong structural integrity (Q = 0.4692) and a high contour score (S = 0.7988), further validating the reliability of the analysis. The top five keywords with high frequency and centrality were "cinobufagin toxin base," "hepatocellular carcinoma," "toad toxin," "apoptosis," and "gene expression," with "cinobufagin" ranking first in both citation frequency and centrality. The outbreak intensity of these five keywords has remained high from the early research stage to the present. Outbreak intensity generally refers to the significant increase in the frequency of a keyword in a specific period, which is often used to measure the level of attention or popularity of a topic.[38]In academic research, it indicates evolving hotspots in specific fields, such as the emergence of new technologies or theories in a certain discipline.[39] The higher the value, the higher the intensity of the outbreak. As a novel proprietary Chinese medicine, cinobufagin's primary anti-tumor active ingredients are cinobufagin and toadstool compounds, both of which are pivotal in pharmacological research. The exploration of the anti-tumor mechanisms of cinobufagin is equally important. Keyword analysis highlighted a strong research focus on mechanisms related to hepatocellular carcinoma, with particular attention to cell apoptosis and gene expression.[17]

We identified five major research directions of cinobufagin research in tumor therapy. First is the biological activity of cinobufagin and its molecular mechanisms of action, particularly in the induction of apoptosis, inhibition of cell proliferation, cell cycle arrest, and regulation of signaling pathways. Additionally, beyond cinobufagin and toadstool compounds, more than 40 compounds and derivatives with anticancer properties have been identified. Future research should isolate these additional anti-tumor components and evaluate their medicinal potential.[40] Thirdly, the combined application of cinobufagin and traditional chemotherapeutic agents can be assessed to explore their synergistic effects in enhancing efficacy, reducing drug resistance, and mitigating the side effects of chemotherapy. The fourth direction is the role of traditional Chinese medicine in improving survival rates in cancer patients, especially in the clinical application of adjuvant therapy and enhancing quality of life, and lastly, the safety and potential side effects of cinobufagin. While studies suggest that cinobufagin may be beneficial in cancer treatment, there are concerns regarding its potential hepatorenal toxicity, cardiotoxicity, and central nervous system toxicity.[41] According to these five main research directions, this study will further explore the anti-tumor mechanism of cinobufotalin and its potential toxicities and side effects.

Cinobufotalin and its main active components exert multi-target and multi-pathway synergistic effects *in vivo*, constituting the basis of their anti-tumor activity. One of the classical molecular targets is NKA.[42] The binding of bufadienolide, the main component of bufadienolide, to NKA not only disrupts cellular ion homeostasis but also activates and inhibits downstream kinase cascades (such as Src, epidermal growth factor receptor, phosphoinositide 3-kinase/protein kinase B), functioning as a signal complex to regulate cell proliferation and survival through signal transduction.[43] Bufalin and cinobufagin can induce mitochondrial-dependent[44] endogenous apoptosis in tumor cells, which is characterized by decreased

mitochondrial membrane potential, increased reactive oxygen species production, up-regulation of Bax and down-regulation of Bcl-2, and activation of caspase-9/3.[45] At the same time, they can amplify apoptotic signals by inhibiting survival pathways such as phosphoinositide 3-kinase/protein kinase B. In addition, cinobufotalin compounds often induce cell cycle arrest, G0/G1 or G2/M arrest in different cell lines, accompanied by changes in cyclin/cyclin-dependent kinase expression, thereby inhibiting cell proliferation.[46] In terms of tumor metastasis and invasion—including down-regulating epithelial–mesenchymal transition-related molecules, inhibiting matrix metalloproteinase expression, and blocking pro-invasive pathways such as signal transducer and activator of transcription 3, Notch, or nuclear factor kappa B—the migration, matrix degradation, and metastasis of tumor cells are inhibited.[47] Metabolomics and spatial omics studies further suggest that bufadienolide can interfere with tumor metabolic reprogramming, such as changes in lipid metabolism distribution and metabolic pathways, which may provide a metabolic basis for its compound anti-tumor effect *in vivo*.[48] Studies have also shown that cinobufotalin can regulate the tumor microenvironment by affecting the polarization of tumor-associated macrophages and exerting sensitization or synergistic effects with chemotherapy drugs, contributing to its anti-tumor role.[49]

Another major research focus on cinobufacini is the study of its toxicity and side effects. Cinobufotalin and its source *Venenum bufonis* are mainly rich in bufadienolide cardiac glycoside steroids, such as bufalin, cinobufagin, resibufogenin, and cinobufotalin.[50] These components exert anti-tumor activity but also represent the main source of toxicity. Among the adverse effects, cardiotoxicity is the most critical, as cinobufacini-induced cardiac damage often results in patient death, not from tumor progression but from heart-related complications.[51] Bufadienolide compounds are similar to digoxin in structure. By inhibiting the NAK activity of cardiomyocytes, bufadienolide compounds change the balance of $Na^+$ and $Ca^{2+}$ in cardiomyocytes, resulting in intracellular $Ca^{2+}$ overload, which in turn changes the electrophysiological stability of cardiomyocytes and induces arrhythmia and conduction block.[52] This is highly similar to the toxic mechanism of cardiac glycosides and has been strongly verified *in vitro* and *in vivo* models. The clinical and drug safety reassessment study reported adverse cardiovascular events associated with toad molting injections, suggesting the risk of electrophysiological changes, bradycardia, ventricular or atrial arrhythmia, and severe cardiogenic events in a dose-dependent manner.[53] Clinical manifestations include myocardial ischemia, arrhythmia, myocarditis, thromboembolism, and blood pressure changes. Currently, strategies to prevent and manage the cardiotoxicity of cinobufotalin injection remain in the exploratory stage, and the use of anti-tumor agents to mitigate this toxicity remains a critical challenge requiring further attention. Based on evidence and reports, patients using such formulations are recommended to conduct baseline and follow-up electrocardiograms, strict dose control, and be aware of potential drug interactions, especially with other drugs that affect the heart or electrolytes in the body. In terms of neurotoxicity in the central nervous system, *in vitro* electrophysiological studies have shown that bufadienolides, such as resibufogenin and cinobufagin, can affect the excitability of the central nervous system through the NAK inhibition mechanism, which is characterized by increased neuronal discharge. The clinical manifestations of central nervous system toxicity are mostly disturbance of consciousness, convulsions, and respiratory depression.[54] Although a few studies support neuroexcitability changes, strict clinical epidemiological evidence is limited, as existing evidence is mostly case or small-scale adverse reaction analysis. To reduce the toxicity and side effects of cinobufotalin, this study proposes the following suggestions:

(i) Carefully design the dosage regimen according to the dose and response relationship, with appropriate dose escalation and toxicity evaluation.
(ii) Exercise caution in patients with previous cardiovascular disease or those taking QT-prolonging drugs, in accordance with cinobufacini prescribing information.
(iii) Implement baseline and dynamic electrocardiogram and electrolyte monitoring.
(iv) Incorporate central nervous system assessments in early clinical studies, such as a history collection of neurological symptoms, electroencephalography, and respiratory function monitoring when necessary.
(v) Improve the administration strategy to reduce exposure of heart and brain tissues and target organs to toxicity.

Attention should be paid to relevant toxicity monitoring indicators and interventions, such as correcting electrolyte imbalances, discontinuing the drug if necessary, and providing symptomatic support. These precautions are critical in the management of adverse drug reactions. In addition, cinobufacini at high doses or short intervals may cause allergic reactions, manifested as rash and itching. Most allergic reactions are temporary; they can be relieved after the drug is completely metabolized. The drug can be discontinued, and anti-allergy treatment can be performed if necessary. Future research directions can also consider

improving the safety and side effects of the drugs.[55]

The results of these scientometric analyses provide a comprehensive overview of the current state of research on cinobufagin in tumor therapy and highlight potential application pathways and research opportunities for clinical practice. At present, while preliminary progress has been made in specific cancer types, such as hepatocellular carcinoma and colon cancer, the efficacy and underlying mechanisms of action in other cancer types remain subjects of ongoing investigation.[56] Future studies should focus on strengthening the evaluation of cinobufagin's efficacy across a broader range of cancers. Additionally, integrating multidisciplinary approaches, such as molecular biology and metabolomics, will be essential for further exploring its mechanisms, particularly concerning the relationship between abnormal lipid metabolism and the tumor microenvironment.[57] This approach will help elucidate the anti-tumor potential of cinobufagin.

## 5. Limitations

This study possesses several limitations. The literature was obtained from the WoS database, while ignoring a large number of Chinese research articles, which may lead to language bias and missing data related to traditional Chinese medicine.[58] As a traditional Chinese patent medicine, bufalin has a long research history in China, with a wealth of literature available in the Chinese language. Including these sources would offer a more comprehensive understanding of its therapeutic efficacy and underlying mechanisms. Furthermore, bibliometric analyses, which rely on citation counts and the strength of associations, may fail to capture innovative research that has not yet gained widespread recognition. While these limitations may affect the comprehensiveness of the study, they do not diminish the potential value of bufalin as an emerging therapeutic agent in oncology.

## 6. Conclusion

Currently, research on cinobufagin in cancer therapy remains in its early stages. Research trends are gradually shifting from isolated efficacy assessments to a broader exploration of the mechanisms underlying tumorigenesis and development, primarily focusing on improving patient survival rates. Due to its diverse pharmacological properties, cinobufagin demonstrates considerable research potential. Through high-quality clinical studies and more extensive documentation, cinobufagin is expected to offer innovative therapeutic strategies for cancer treatment, ultimately providing significant survival benefits to patients.

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## Conflict of interest

The authors report no conflicts of interest in this work.

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## Ethics approval and consent to participate

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