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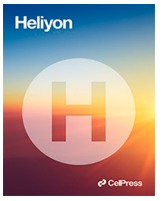

Review article

Research trends and hotspots of polyphyllin in high-incidence cancers: A bibliometric analysis

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ABSTRACT

Background: Polyphyllin, a natural compound derived primarily from the *Paris* genus, manifests its anticancer properties. Extensive research on its therapeutic potential in cancers has been reported. However, there is no systematical analysis of the general aspects of research on polyphyllin by bibliometric analysis. The aim of this study is to visualize emerging trends and hotspots and predict potential research directions in this field.

Methods: In this study, we collected relevant research articles from the Web of Science Core Collection Bibliometrics. Using R-bibliometrix, we analyzed the research status, hotspots, frontiers, and development trends of polyphyllin in high-incidence cancers. To conduct a comprehensive visual analysis, CiteSpace and VOSviewer were used for visual analysis of authors, countries, institutions, keywords, and co-cited references within the published articles.

Results: A total of 257 articles focusing on the research of polyphyllin in high-incidence cancers were retrieved from the WOSCC database, covering the period from 2005 to 2023. The analysis revealed a consistent increasing trend in annual publications during this timeframe. Notably, China emerged as the most productive country, with Tianjin University leading the institutions. The Journal of Ethnopharmacology stood out as the most prominent journal in this field, while Gao WY emerged as the most prolific author. Polyphyllin VI, polyphyllin II, and polyphyllin VII have emerged as the latest research hotspots. Additionally, the investigation of autophagy and its associated mechanisms has gained significant attention as a novel research direction.

Conclusion: This study presents a novel visualization of the research on polyphyllin saponins in the field of highly prevalent cancers using bibliometric analysis. The investigation of polyphyllin D has emerged as a primary focus in this field, with lung cancer, breast cancer, and liver cancer being the key areas of current research. Lastly, polyphyllin saponins show potential application in the field of cancer.

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1. Introduction

Cancer has the high mortality and it is one of the primary causes of death in countries around the world. The incidence of cancer is increasing with the growing global aging population [1]. Over the past decade, significant advancements in early detection, surgical techniques, and targeted therapies have accelerated progress in cancer research, the goal of which is to decrease cancer-related mortality. However, there are still numerous challenges on the way of studying cancers. Even though cancer can be discovered in its early stages or terminal stages, the recovery rate of treatment is not optimistic. Breast cancer, lung cancer, and liver cancer are high incidence according to the AACR cancer progress report in 2023. Breast cancer, a heterogeneous disease, continues showing an upward trend incidence rate in female because of high metastasis, which can cause lung or liver metastases. Liver cancer is hepatocellular carcinoma and always be found when it is in late stages, hardly showing symptoms in the early stages [2]. Therefore, there is still a long and arduous journey in the research of high-incidence cancers.

Polyphyllin, a kind of natural compounds steroidal saponin mainly extracted from genus *Paris*. exerts its anti-tumor effects primarily by suppressing the growth of tumor cells and triggering cell cycle arrest [3–5], promoting apoptosis and autophagy [6–8], as well as inhibiting tumor metastasis [9,10] and enhancing chemotherapy sensitivity [11,12]. Polyphyllin I, polyphyllin II, polyphyllin VI, and polyphyllin VII have been identified as the primary active ingredients with anticancer properties [13]. Additionally, there are other minor active compounds, such as formosanin C showing promising results in inhibiting pulmonary metastasis in mouse models of lung adenocarcinoma [14], Paris saponin H inducing apoptosis, suppressing epithelial-mesenchymal transition (EMT) in liver cancer [15], and polyphyllin E effectively inhibiting cell proliferation, migration, and invasion in ovarian cancer [16].

Bibliometric analysis, a popular and rigorous method, utilizes statistical methods to describe or visualize the relationships between published articles and their associated data [17]. Bibliometrics is a widely utilized method for tracking the evolution and development of knowledge domains. It helps to identify potential research hotspots and trends within various fields of study [18]. Through visual displays of bibliometric analysis, researchers can gain a more intuitive, comprehensive, and systematic understanding of the development within a specific field [19]. Although research on polyphyllin in high-incidence cancers has been rapidly developing, there is still no relevant literature on bibliometric analysis. Therefore, we conducted a comprehensive scientific measurement analysis using the bibliometrix package (version 4.2.0) in RStudio. The retrieved data files were imported into Biblioshiny to obtain key information about publications, which includes time span, annual scientific output, average citations per year, author trends, sources, and author impact. Furthermore, we visualized the research trends and frontier hubs in this field using bibliometric software such as VOSviewer and CiteSpace. The aim of this analysis is to provide an overall understanding of the research status of polyphyllin in high-incidence cancer studies and to provide resources for researchers to delve into the relevant field and identify potential collaborations.

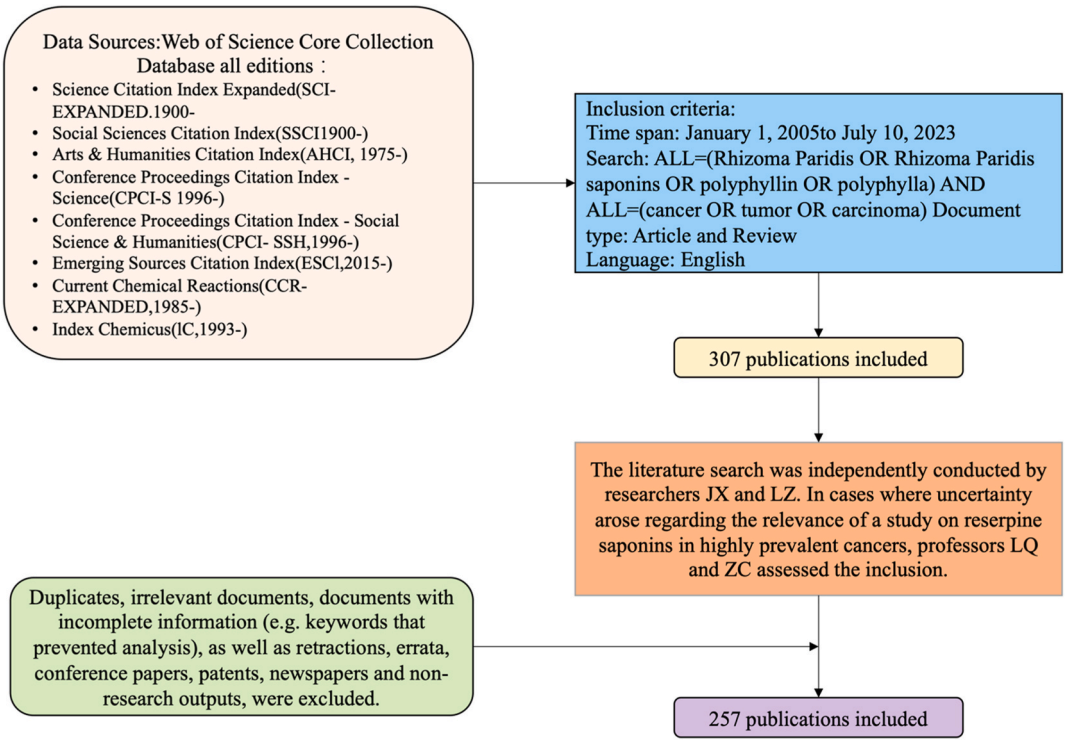

Fig. 1. The process of literature search and analysis.

2. Materials and methods

2.1. Data sources and search strategies

In this study, we utilized the widely recognized and comprehensive database, Web of Science Core Collection (WOSCC), as the source for data collection in our econometric analyses [20]. We retrieved relevant literature from 2005 to July 10, 2023, using the search query ALL= (Rhizoma Paridis OR Rhizoma Paridis saponins OR polyphyllin OR polyphylla) AND ALL= (cancer OR tumor OR carcinoma). We restricted the article type to include only articles and reviews and limited the language to English. The literature search was independently conducted by researchers JX and LZ.

2.2. Inclusion and exclusion criteria

Professors LQ and ZC assessed the inclusion in cases where uncertainty arose regarding the relevance of a study on reserpine saponins in highly prevalent cancers. After excluding duplicates, irrelevant literature, documents with incomplete information such as keywords that hindered analysis, as well as retractions, errata, conference papers, patents, newspapers, and non-research outputs, a total of 257 documents were selected. The literature search was completed on July 10, 2023. The detailed search process is shown in Fig. 1.

2.3. Statistical analysis

CiteSpace, a software developed by Dr. Chaomei Chen, currently is regarded as the vital tool for conducting bibliometric analysis [21]. It possesses the remarkable ability to construct visually captivating networks, calculate intermediary centrality, and detect bursts of activity, thereby unveiling the ever-evolving landscape of emerging trends and identifying the frontiers of research [22]. Additionally, it has the capacity to label pivotal keywords [23]. The visual representation consists of nodes and lines, with the size of each node reflecting the quantity of associated items, while the connections between nodes denote co-occurrences, collaborations, or citations. To evaluate the significance and connectivity of a node within the network, the measure of betweenness centrality is employed. A higher betweenness centrality indicates a greater number of connections that traverse through the node. Notably, circles with a betweenness centrality exceeding 0.1 were distinguished by the color of purple. When it comes to clustering, the parameters of modularity Q and mean silhouette value hold paramount importance. Clusters were deemed dominant and influential when Q exceeding 0.3 and the mean silhouette value exceeding 0.5 [24–26].

VOSviewer is primarily utilized for the analysis of bibliometric network graphs developed by Nees Jan van Eck et al. [27]. It provides visual analysis of the distribution of countries, institutions, authors, collaborations, and keyword collaborations. Clustering is done automatically through similarity matrix and VOS mapping technology, with corresponding labels added according to the content.

The bibliometrix package in R 4.2.2 was employed to automate the transformation and analysis of bibliographic information for selected publications, including the outputs of institutional and periodical, in addition to author impact indicators. Indicators such as the number of publications and citations were utilized to assess the impact factors of the authors. The h-index, a commonly employed metric for evaluating the academic output of researchers [28], indicates a higher scholarly impact with a higher value [29]. G-index, as a derivative index of the h-index, can be used to evaluate the academic impact and accomplishments of scholars [30].

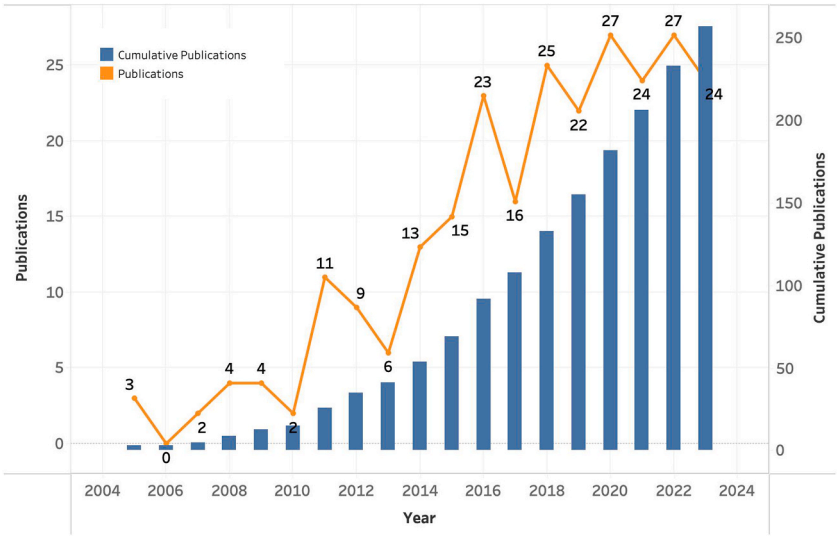

Fig. 2. The annual scientific production and cumulative publications.

3. Results

3.1. Growth and trend of publications

The number of publications related to research on polyphyllin in the field of cancer has steadily increased over the years. In 2005, only three articles were published, accounting for 1.17% of the total. There was a slightly decrease observed between 2011 and 2014, followed by a steady upward trend (Fig. 2). Particularly, the publication in the first seven months of 2023 remained almost the same as that in 2022. This trend indicates a growing interest among scholars in exploring the potential of polyphyllin as a natural product in cancer treatment.

3.2. Author and co-cited author analysis

A total of 257 publications were contributed by 1289 authors, with an average of 7.68 co-authors per article. Table 1 presents the top ten most influential authors in the field of polyphyllin on cancer. Gao WY stands out as the most prolific author, with 33 published articles, accounting for 12.84% of the total. Following closely is Man SL, with 32 papers (12.45%). In terms of citations, Gao WY and Man SL have been cited 625 and 621 times, respectively. Jiang H has published 11 papers and received 450 citations. Based on the H-index ranking, Gao WY and Man SL have the highest scores of 15, followed by Liu Z with an H-index of 13. Four authors have an H-index greater than 10. The M-index, which considers the H-index relative to the number of years since a scientist's first publication, reveals that Man SL has the highest M-index of 1.125, followed by Jiang H with an M-index of 1.1. Considering the M-index, H-index, total citation count, and number of published articles, Gao WY and Man SL emerge as the most prominent authors in this field, with a close collaborative relationship.

The analysis of co-citation among authors is presented in Fig. 3A. Referring to the total link strength, Man SL exhibits the strongest link strength compared to other authors (total link strength = 1762), followed by Xiao X (total link strength = 832) and Liu Z (total link strength = 772).

The visualization analysis of author collaboration is depicted in Fig. 3B. The size of the nodes represents the number of publications, the color of the nodes represents the average publication time of the author, and the thickness of the connections signifies the level of collaboration between authors. A core research group consisting of 16 individuals, represented by Gao WY, Liu Z, and Man SL forms the central research community in this field.

The top authors' collaboration over time is illustrated in Fig. 3C. They first collaborated in 2009, with Gao WY, Man SL, and Liu CX publishing their first joint paper. From 2009 to 2014, the three authors had close collaboration and published 11 papers in total in this field. However, Liu CX had fewer collaborations with the other two authors after that period. From 2011 to 2017, Gao WY and Man SL collaborated with Liu Z and published 18 papers together. Over the past decade, Gao WY and Man SL have maintained a long-term and stable collaboration, with the majority of their publications concentrated in 2011, 2014, and 2016. In 2016, they achieved the highest publication output, with 8 papers.

3.3. Country and organization analysis

A total of 332 institutions from 25 countries and regions have made significant contribution to the research field of polyphyllin on cancer. Table 2 presents the top ten producing and citing countries. The majority of the publications are from China (n = 231), followed by the United States (n = 17) and Japan (n = 6). In terms of citation impact, China ranks first with 4991 citations, followed by the United States (83 citations), Japan (59 citations), and Serbia (40 citations). China also exhibits the highest betweenness centrality (0.89), indicating its pivotal role in the research network. In terms of publication output, citation count, and betweenness centrality, China emerges as the leading country in this field. The visualization of author countries in Fig. 4A reveals that although there is collaboration among countries, not as extensive, with the current research landscape primarily centered in China.

Table 3 displays the top ten institutions in terms of publication count and betweenness centrality. Tianjin University has the highest number of publications (n = 30), followed by Tianjin University of Science & Technology (n = 20) and Chinese Academy of Sciences (n = 18). Chinese Academy of Sciences (0.11) has the highest betweenness centrality, followed by Kunming Medical University (0.08)

Table 1
Top 10 authors distributed by publications.

Rank	Author	Publications	H-index	G-index	PY-start	TGCS	TLCS
1	GAO WY	33	15	24	2009	625	264
2	MAN SL	32	15	24	2009	621	244
3	LIU Z	20	13	18	2011	337	128
4	LIU Y	14	7	13	2014	176	67
5	JIANG H	11	11	11	2014	450	111
6	WANG H	11	9	11	2009	330	144
7	LIU CX	10	8	10	2009	224	107
8	LIU J	10	6	10	2013	128	59
9	ZHANG Y	10	7	10	2016	106	54
10	LI J	9	6	9	2014	122	48

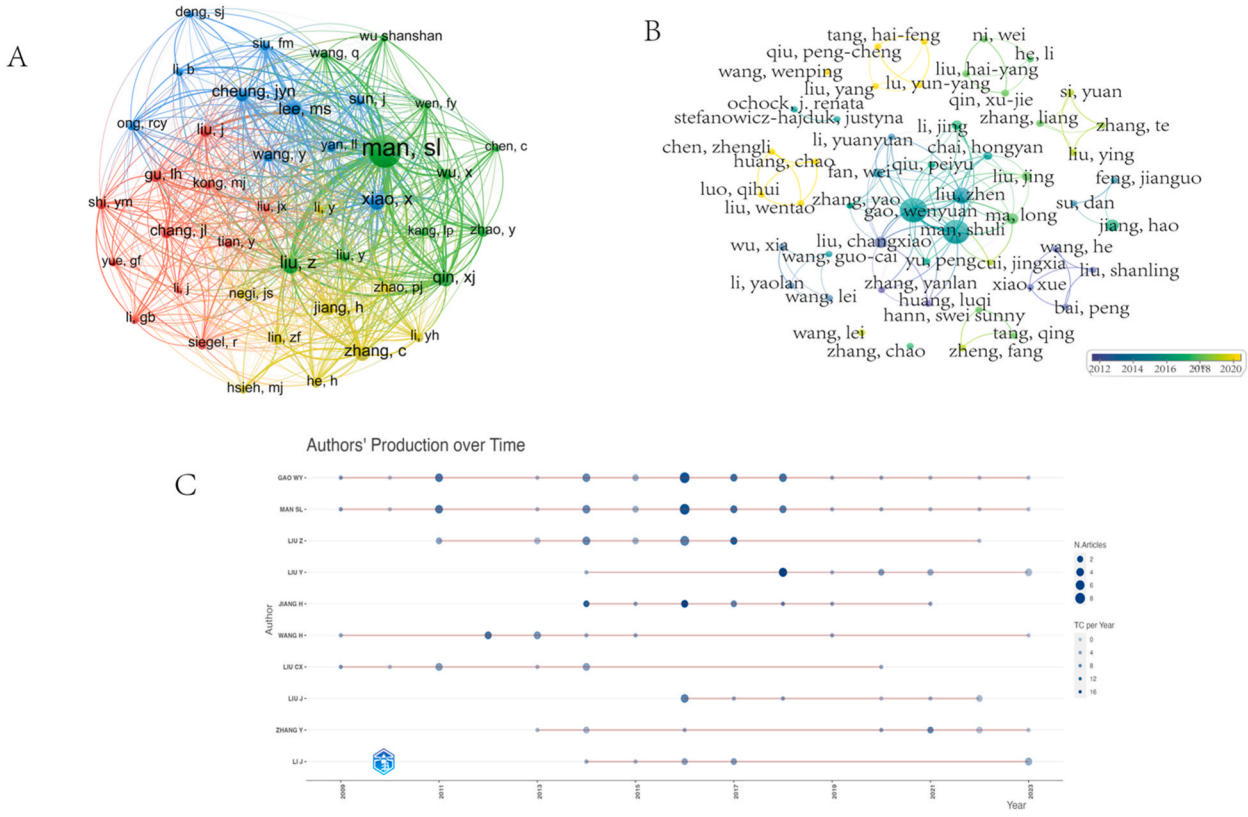

Fig. 3. Visualization analysis by the authors. (A) Visual analysis of co-cited authors. (B) Visual analysis of the number of articles published by the authors. (C) The top 10 authors' production over time.

Table 2
Top 10 countries by publications, citations and centrality.

Rank	Country	Publications	TGCS	Average Article Citations	Rank	Country	Centrality
1	CHINA	231	4991	21.70	1	CHINA	0.89
2	USA	17	83	27.70	2	PAKISTAN	0.22
3	JAPAN	6	59	14.80	3	USA	0.16
4	SERBIA	1	40	40.00	4	NIGERIA	0.12
5	INDIA	5	32	6.40	5	SOUTH KOREA	0.07
6	CANADA	1	31	31.00	6	JAPAN	0.06
7	POLAND	4	31	7.80	7	NEPAL	0.05
8	FRANCE	1	30	30.00	8	FRANCE	0.02
9	NIGERIA	2	22	11.00	9	SWEDEN	0.02
10	KOREA	2	8	4.00	10	VIETNAM	0.01

and Yunnan University of Chinese Medicine (0.08). Fig. 4B provides a visualization of institutions with publication counts more than 5. It is evident that two research networks have formed, with Tianjin University, Tianjin University of Science & Technology, and Chinese Academy of Sciences representing one network. Shanghai University of Traditional Chinese Medicine, with a concentration of publications from 2017 to 2023, shows great potential as an emerging force in the research field.

In the tri-field plot (Fig. 4C), authors are represented on the left side, affiliations are on the right side, and countries are in the middle. The plot illustrates the relationships between countries, authors, and affiliations. China has the highest number of connections with authors (20/20) and affiliations (20/20), followed by the United States (authors = 3/20, affiliations = 7/20). Among the authors with connections to different countries, Wang H, Wang L, and Yang L are associated with the United States, while Gao WY, Man SL, and Liu Z are associated with France.

3.4. Journal and research category analysis

257 manuscripts were published in 152 different journals. According to Table 4, the top ten influential journals in the field of polyphyllin on cancer are as follows: "Journal of Ethnopharmacology" is the most popular journal, contributing 12 publications. It is

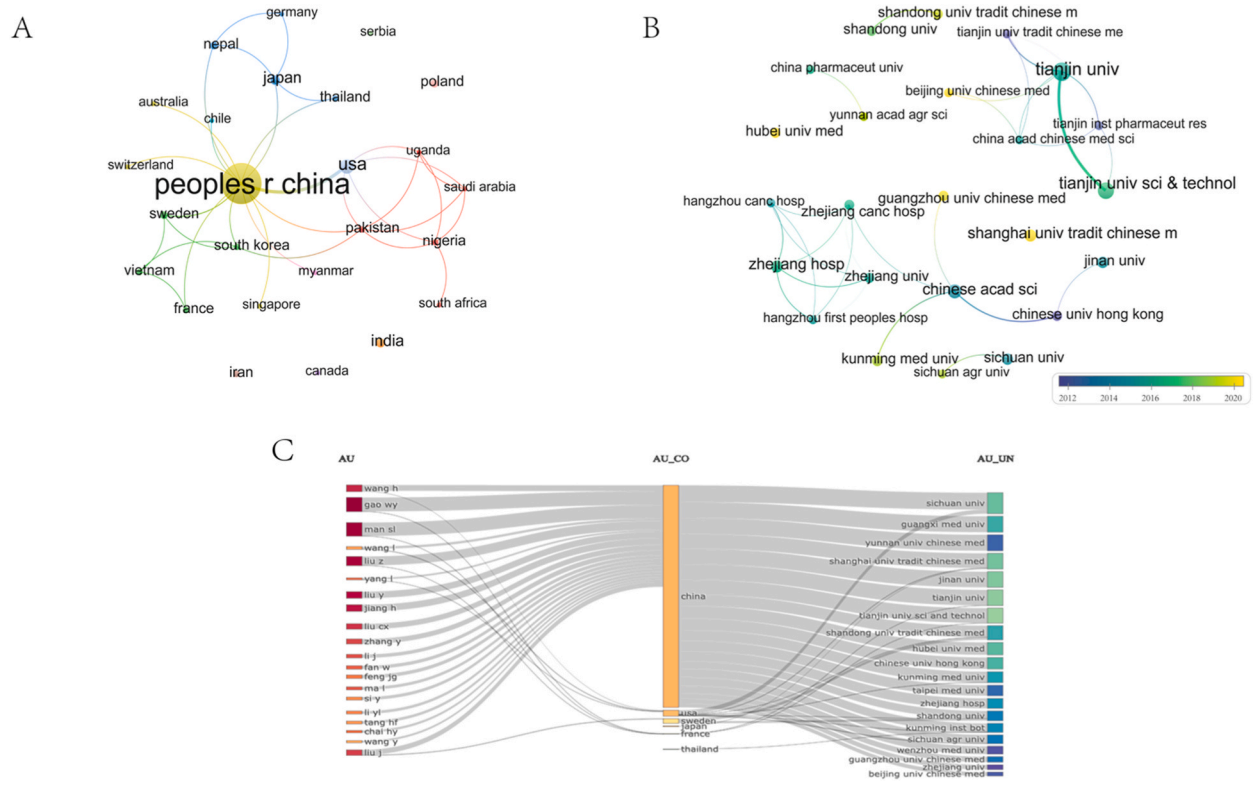

Fig. 4. Network visualization of countries and institutions. The node size represents the number of papers published, and the thickness of the line represents the degree of cooperation. (A) Visual analysis of country cooperation. (B) Visual analysis of institutional cooperation. (C) Three-field plot among countries, authors, and affiliations (left field: authors, middle field: countries, right field: affiliations; number of items each column: 20).

Table 3
Top 10 institutions distributed by publications and centrality.

Rank	Institution	Publications	Institution	Centrality
1	Tianjin Univ	30	Chinese Acad Sci	0.11
2	Tianjin Univ Sci & Technol	20	Kunming Med Univ	0.08
3	Chinese Acad Sci	18	Yunnan Univ Chinese Med	0.08
4	Jinan Univ	10	Soochow Univ	0.07
5	Shanghai Univ Tradit Chinese Med	10	Chinese Univ Hong Kong	0.04
6	Kunming Med Univ	9	Tianjin Univ	0.03
7	Sichuan Univ	9	Jinan Univ	0.03
8	Guangzhou Univ Chinese Med	8	Guangzhou Univ Chinese Med	0.03
9	Chinese Univ Hong Kong	7	Beijing Univ Chinese Med	0.03
10	Zhejiang Hosp	7	Yunnan Acad Agr Sci	0.03

Table 4
Top 10 journals distributed by publications.

Rank	Journal	h-index	g-index	TGCS	Publications	IF	Jif quartile
1	JOURNAL OF ETHNOPHARMACOLOGY	9	12	295	12	5.4	Q2
2	MOLECULES	6	8	189	8	4.6	Q2
3	CHEMICO-BIOLOGICAL INTERACTIONS	6	6	141	6	5.1	Q2
4	FRONTIERS IN PHARMACOLOGY	3	6	39	6	5.6	Q2
5	MOLECULAR MEDICINE REPORTS	5	5	190	5	3.4	Q4
6	STEROIDS	5	5	155	5	2.7	Q3
7	ONCOLOGY LETTERS	4	5	100	5	2.9	Q4
8	PLOS ONE	4	4	130	4	3.7	Q3
9	RSC ADVANCES	4	4	34	4	3.9	Q3
10	ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS	3	3	43	3	3.9	Q3

followed by "Molecules" with 8 publications, "Chemico-Biological Interactions" and "Frontiers in Pharmacology" with 6 publications each. In terms of citation sources, "Journal of Ethnopharmacology" has the highest number of citations, reaching 295. It is followed by "Molecular Medicine Reports" (190 citations) and "Molecules" (189 citations).

According to the visualization in VOSviewer (Fig. 5A), the relationships among the journals in the field of interest are as follows: the size of the nodes represents the publication output of each journal, the color of the nodes represents the average publication time, and the connections between nodes indicate the strength of the relationships between journals. Based on the visualization, "Frontiers in Pharmacology" emerges as the journal with the highest publication output in the past three years. Furthermore, the journals can be categorized into three clusters based on the frequency of co-citations, which often indicate similar research directions (Fig. 5B). The red cluster focuses on biology and medicine, including journals such as Cell, Cell Death & Disease, and Autophagy. The green cluster is dedicated to medicine and chemistry, encompassing journals such as Molecules, Archives of Pharmacal Research, and International Journal of Oncology. Lastly, the blue cluster centers are about biochemistry and molecular biology, featuring journals such as Journal of Ethnopharmacology, Steroids, and Molecular Cancer Therapeutics.

In order to investigate the cross-disciplinary nature of various fields, we employed knowledge flow analysis to study the progression of knowledge citations and the co-citation patterns between citing and cited journals [31]. By overlaying dual maps of journals, we were able to visually observe the distribution of topics, changes in citation trajectories, and shifts in research centers (Fig. 5C) [32]. The results revealed that both the citing journals and the cited articles were primarily concentrated in the fields of molecular biology and immunology, with limited instances of cross-disciplinary citations.

3.5. Cited and co-cited references analysis

Table 5 presents a list of highly cited articles, with the most cited article "Effects of polyphyllin D, a steroidal saponin in *Paris polyphylla*, in growth inhibition of human breast cancer cells and in xenograft" by Lee M in 2005 (66 citations), followed by Cheung JYN (53 citations) and Man SL (37 citations). A visualization network of co-cited references was established using Citespace (Fig. 6A). "Shi YM (2015) ", "Li GB (2017) ", and "Man SL (2011)" were often co-cited. Cluster analysis categorized the majority of relevant terms related to polyphyllin D in high-frequency tumors into 10 main clusters (Table 6). The top 5 clusters were "rhizoma paridis", "cell cycle", "metabonomics", "matrix metalloproteinase", and "cancerous inhibitor of protein phosphatase 2a". Silhouette values (S) indicate the average silhouette value of each cluster. A cluster is considered appropriate if $S > 0.5$, and compelling if $S > 0.7$. In this study, the S

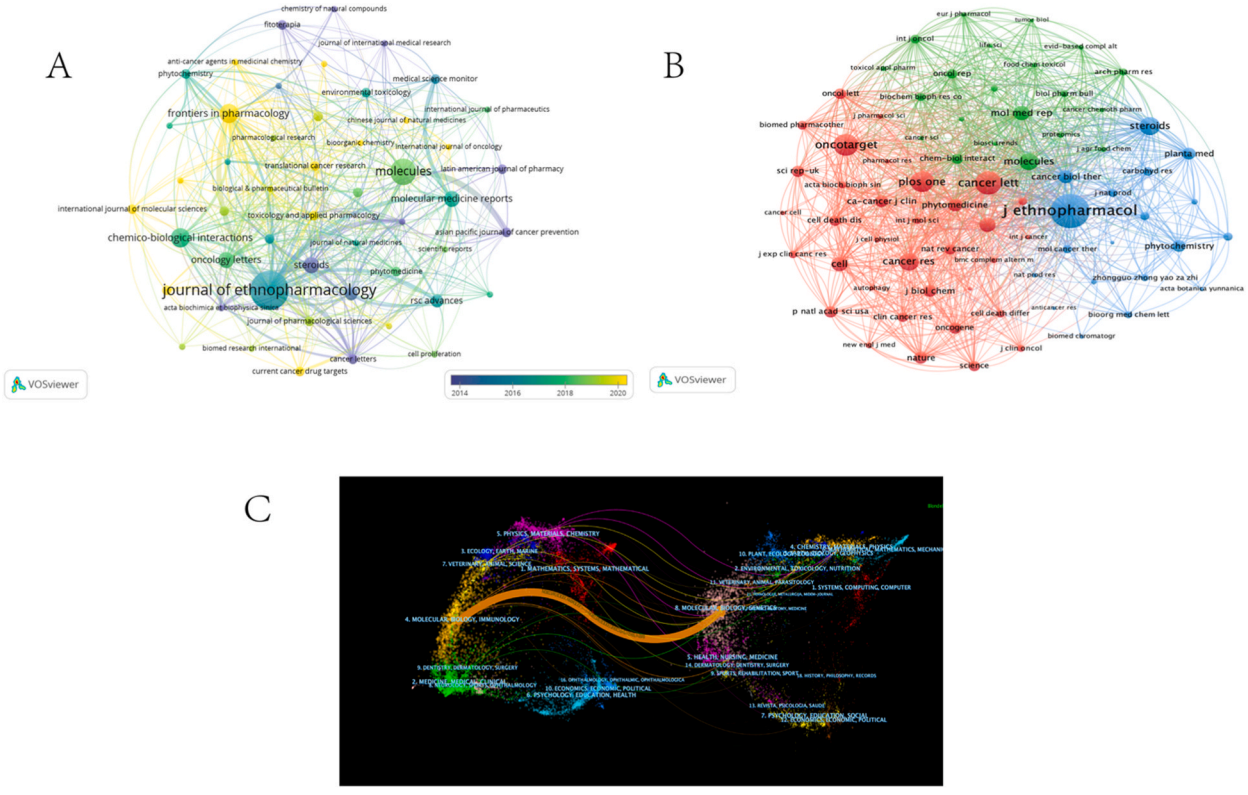

Fig. 5. Analysis of journals and co-cited journals. (A) Analysis of journals published. The node size represents the number of articles published in the journal, and the node color represents the average time of articles published in the journal. (B) Journal co-citation analysis. Node colors represent different domains. (C) Dual map overlay of journals.

Table 5
Top 10 cited literatures.

Rank	Authors	Source	Title	DOI	Year	Local Citations	Global Citations	LC/GC Ratio (%)
1	LEE MS	CANCER BIOL THER	Effects of polyphyllin D, a steroidal saponin in Paris polyphylla, in growth inhibition of human breast cancer cells and in xenograft	10.4161/cbt.November 4, 2136	2005	66	141	46.81
2	CHEUNG JYN	CANCER LETT	Polyphyllin D is a potent apoptosis inducer in drug-resistant HepG2 cells	10.1016/j.canlet.2004.06.042	2005	53	132	40.15
3	MAN SL	ARCH PHARM RES	Paridis saponins inhibiting carcinoma growth and metastasis in vitro and in vivo	10.1007/s12272-011-0105-4	2011	37	68	54.41
4	MAN SL	STEROIDS	Antitumor and antimetastatic activities of Rhizoma Paridis saponins	10.1016/j.steroids.2009.08.004	2009	34	86	39.53
5	SHI YM	PHYTOMEDICINE	Polyphyllin I induced-apoptosis is enhanced by inhibition of autophagy in human hepatocellular carcinoma cells	10.1016/j.phymed.2015.08.014	2015	34	50	68.00
6	ONG RCY	CANCER LETT	Polyphyllin D induces mitochondrial fragmentation and acts directly on the mitochondria to induce apoptosis in drug-resistant HepG2 cells	10.1016/j.canlet.2007.11.005	2008	33	68	48.53
7	XIAO X	MOL CANCER THER	The antitumoral effect of Paris Saponin I associated with the induction of apoptosis through the mitochondrial pathway	10.1158/1535–7163.MCT-08-0939	2009	33	51	64.71
8	LIN ZF	PHYTOTHER RES	Anti-lung Cancer Effects of Polyphyllin VI and VII Potentially Correlate with Apoptosis In Vitro and In Vivo	10.1002/ptr.5430	2015	33	39	84.62
9	SIU FM	PROTEOMICS	Proteomic and transcriptomic study on the action of a cytotoxic saponin (Polyphyllin D): induction of endoplasmic reticulum stress and mitochondria-mediated apoptotic pathways	10.1002/pmic.200700829	2008	31	81	38.27
10	KONG MJ	ACTA BIOCH BIOPH SIN	Effects of polyphyllin I on growth inhibition of human non-small lung cancer cells and in xenograft	10.1093/abbs/gmq091	2010	28	45	62.22

values for the top ten clusters exceed 0.7, indicating that these clusters were considered compelling. In this study, "rhizoma paridis" (Cluster #0) is the largest cluster, comprising 90 articles. Strong citations are mainly concentrated in clusters #0, #1, and #2, suggesting that research in this field may revolve around the cell cycle and metabolomics. A timeline was constructed for the clusters (Fig. 6C), indicating that "polyphyllin VI" and "cytotoxicity" form a recently emerged cluster that has consistently maintained high intensity, suggesting that they may represent the latest research hotspots.

Fig. 6D displays the 25 references that experienced an explosion in citations from 2005 to 2023. Based on the explosion time, Man SL in 2011 and Shi YM in 2015 were particularly prominent, while Zhang YF in 2018 represented a new explosion. Man SL et al. measured migration inhibition through wound healing and MTT assays with non-cytotoxic doses determined, and found that the total extract of polyphyllin was an effective anticancer agent, inducing programmed cell death and inhibiting the migration of mouse lung adenocarcinoma [33]. Shi YM et al. discovered polyphyllin I inducing apoptosis via the caspase-dependent pathway and activating autophagy via the PI3K/AKT/mTOR pathway [34]. Zhang YF et al. found that the mechanism by which polyphyllin I inhibits the growth of SGC7901/DDP cells and invasion achieved by decreasing the expression of CIP2A and subsequently inhibiting the CIP2A/PP2A/Akt signal axis [35]. These findings indicate that research on polyphyllin in high-incidence cancers such as liver cancer, lung cancer, and breast cancer has received widespread attention in recent years.

3.6. Keyword analysis

According to the visual analysis of keywords using VOSviewer (Fig. 7A&B), "polyphyllin I″, "rhizoma paridis saponins", and "apoptosis" are the three most prominent terms. In recent years, "polyphyllin II", "polyphyllin VI", "polyphyllin VII", and "autophagy" have emerged as new research hotspots. Using CiteSpace for intermediary centrality analysis (Fig. 7C), "apoptosis" (0.35) exhibits the highest centrality, followed by "cell cycle arrest" (0.28) and "cell" (0.2). Intermediary centrality represents the connectivity of a node, with higher values indicating more connections to other terms and indicating greater importance of the node. As shown in Table 7, the tumors with the highest intermediary centrality are "breast cancer" (0.18) and "lung cancer" (0.17), while the cell with the highest intermediary centrality is "Hepg2 cell" (0.15).

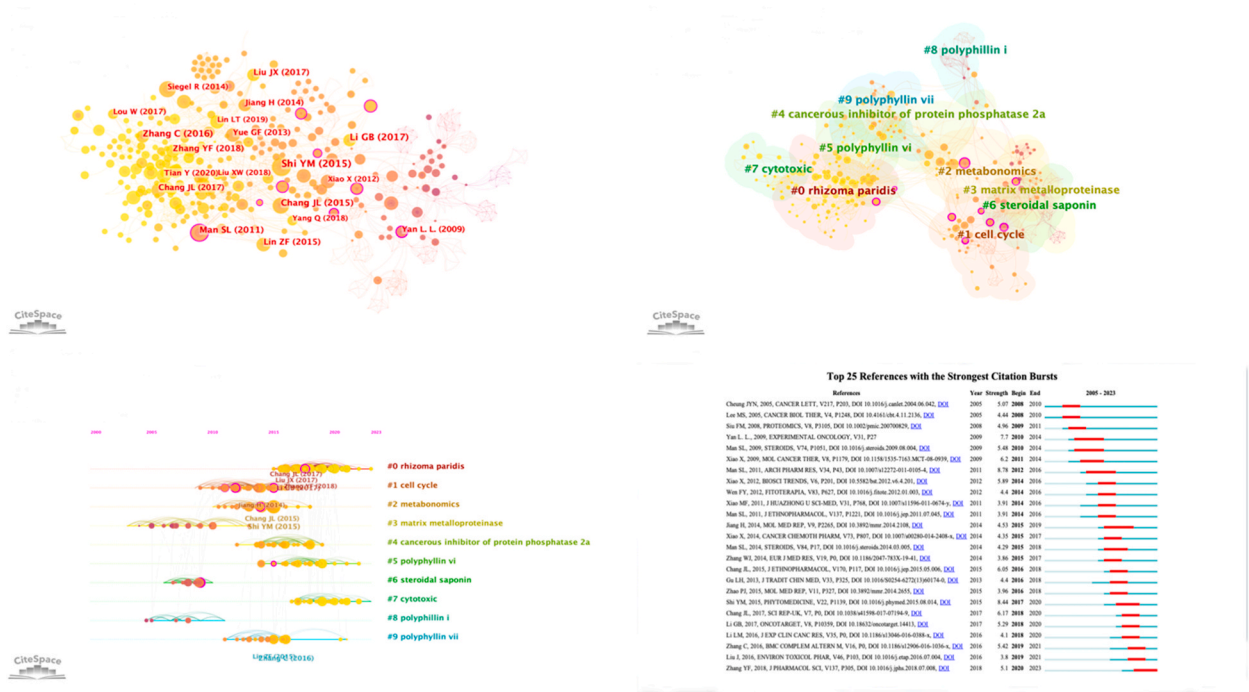

Fig. 6. Analysis of most commonly cited references. (A) Visualization of co-cited references. (B) Cluster analysis of co-cited references. (C) Timeline graph of cluster analysis. (D) Top 25 references with the strongest bursts. The red line segment represents the time when the references emerge. The larger the strength value, the larger its burst strength section.

Table 6
Top 10 largest clusters of co-cited references.

Cluster	Label(LLR)	Size	Silhouette	Average year
0	rhizoma paridis	90	0.861	2018
1	cell cycle	64	0.896	2013
2	metabonomics	46	0.837	2013
3	matrix metalloproteinase	42	0.894	2017
4	cancerous inhibitor of protein phosphatase 2a	37	0.924	2016
5	polyphyllin vi	36	0.893	2017
6	steroidal saponin	31	0.97	2007
7	cytotoxic	21	0.979	2019
8	polyphillin i	20	0.966	2007
9	polyphyllin vii	20	0.903	2014

The detection of burst keywords is to reveal the evolution of topics, predict future directions, and discover potential breakthroughs. As depicted in Fig. 7D, "constituent" and "diosgenyl saponin" exhibit the longest duration of burst, while the latest burst is concentrated in "inhibition", "autophagy" and "mechanism". This signifies that research in this field has gradually progressed from focusing on the constituent structure to diving into the underlying mechanisms. Notably, "polyphyllin VI", "polyphyllin II" and "polyphyllin VII" have emerged as the latest research focal points.

4. Discussion

In this study, we objectively analyzed the literature on the research of polyphyllin in the field of cancer using bibliometric methods. Our results indicate that the number of annual publications in this field has been gradually increasing after 2016, suggesting that polyphyllin is receiving increasing attention in recent years. The number of publications and citations in a research field are considered as important indicators for assessing the academic reputation and scientific research capabilities of a country or an institution [36]. China not only is the country with the highest number of publications, but also has the highest number of citations. In terms of publication output, China is far ahead of the second-ranked country, United States, when it comes to the average number of citations per article, the difference is not significant. As to institutions, the top ten institutions are all from China, but collaboration between institutions is not strong. In terms of international collaboration, only a few authors from China have collaborations with institutions overseas and other countries. This indicates that research in this field is mostly concentrated in China, which may be related to the long

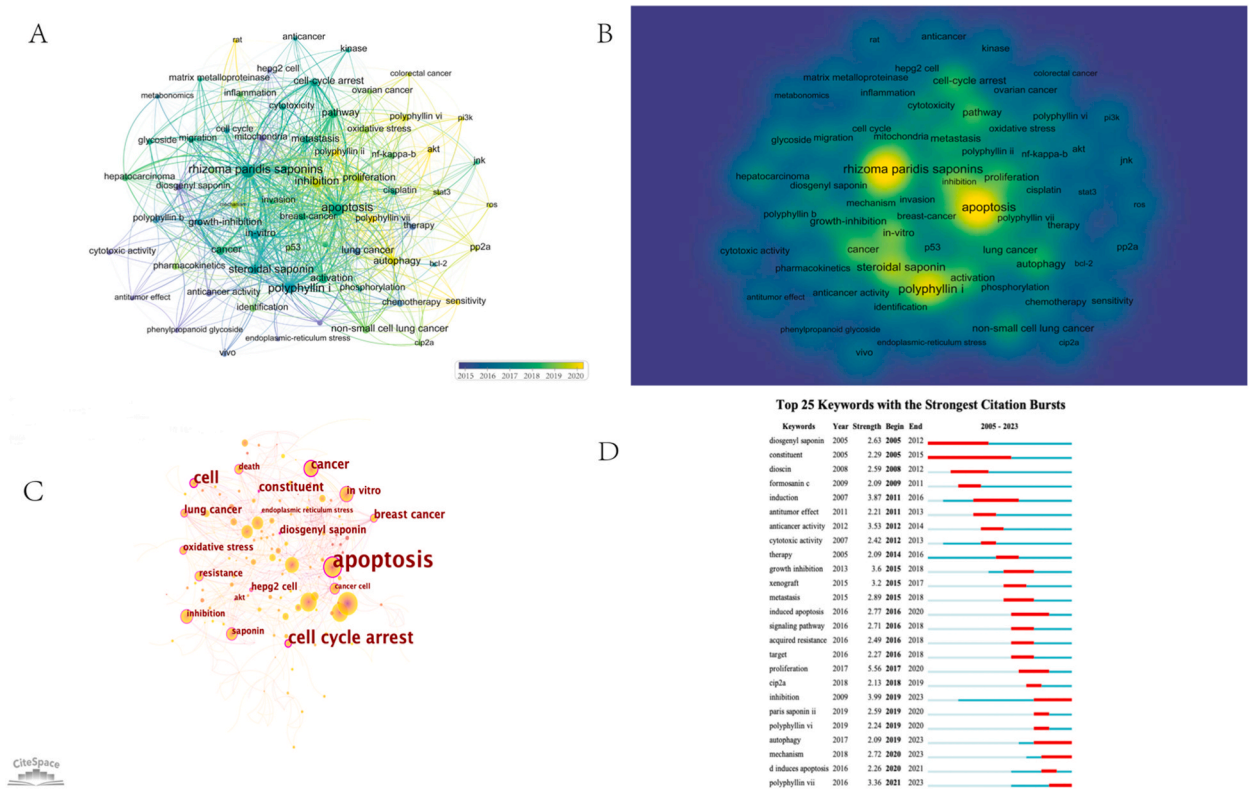

Fig. 7. Keywords visual analysis. (A) Visual analysis of keyword frequency. Node size represents the frequency of keyword occurrence, and color represents the average time of occurrence of the keyword. (B) Key word density stacking. Higher brightness indicates greater connection of the keyword. (C) Keyword visualization according to mediation centrality. Node size represents the size of mediation centrality. (D) Top 25 keywords with the strongest bursts. The red line segment represents the time when the keyword emerges. The larger the strength value, the larger its burst strength section.

Table 7
Top 10 keywords by frequency and centrality.

Rank	Frequency	Keyword	Centrality	Keyword
1	82	polyphyllin i	0.35	apoptosis
2	78	rhizoma paridis saponin	0.28	cell cycle arrest
3	67	apoptosis	0.25	cell
4	55	steroidal saponin	0.2	cancer
5	42	inhibition	0.2	constituent
6	41	growth	0.18	breast cancer
7	35	in vitro	0.17	diosgenyl saponin
8	35	cancer cell	0.17	in vitro
9	35	activation	0.17	lung cancer
10	29	cancer	0.15	hepg2 cell

history of traditional medicine utilization of *Paris polyphylla* and *P. polyphylla* var. *yunnanensis* were used to treat venomous snake bites, carbuncles and sore throat.

We conducted an assessment of the top influential authors in the field of research on polyphyllin in high-incidence cancers, utilizing metrics such as the H-index, G-index, citation frequency, and collaboration network analysis. Our results indicate that Gao WY and Man SL are the top influential authors. They have focused on anti-tumor research in lung cancer and liver cancer, particularly in the field of polyphyllin I and formosanin C. It is reported that polyphyllin exhibited anti-tumor effects by inducing apoptosis, upregulating TIMP-2 expression, and downregulating the levels of MMP-2 and MMP-9, thereby triggering programmed cell death and inhibiting the metastasis of lung adenocarcinoma in vivo [37]. Additionally, it is found that polyphyllin I and formosanin C exhibited synergistic antitumor effects on liver cancer cells [38].

It is worth noting that in our study, there was not a perfect correlation between highly cited articles and high-impact journals. In this study, the majority of high-output journals were classified as Q2 and Q3. "Frontiers in Pharmacology" (IF 5.6) had the highest

impact factor (IF), but its citation count was relatively low. "Journal of Ethnopharmacology" (IF 5.4) was the highest-output journal and also the most frequently cited. Among the top ten high-output journals, only "Journal of Ethnopharmacology" had a G-index higher than 10, indicating that this journal has made a greater contribution in the field and possesses strong persuasiveness and influence.

Emerging academic hubs can be identified through the analysis of co-cited articles and literature clusters, which reflect the core content and hot topics in a specific field. Highly cited papers play a crucial role in promoting core research, while high-intensity bursts indicate the emergence of new and trending areas of academic interest [39]. The three most highly cited articles are as follows:

1. Lee M in 2005 (66 citations) - This study found that the viability of breast cancer cell lines MCF-7 and MDA-MB-231 was inhibited in a dose-dependent manner after polyphyllin D treatment and induced apoptosis in the end. The apoptotic characteristics included DNA fragmentation, a low diploid peak in cell cycle analysis, phosphatidylserine externalization, and delayed loss of membrane integrity. Mechanistic studies revealed that polyphyllin D had the potential to dissipate the mitochondrial membrane, down-regulate anti-apoptotic protein Bcl-2 expression, upregulate pro-apoptotic protein expression of Bax, and activate Caspase-9. It was determined that polyphyllin D induced apoptosis through mitochondrial dysfunction [40].
2. Cheung JYN in 2005 (53 citations) - For the first time, this study demonstrated that polyphyllin D could be as a potential anticancer agent overcoming drug resistance and inducing programmed cell death by triggering mitochondrial dysfunction [41].
3. Man SL in 2011 (37 citations) - This study investigated a mixture isolated from *Paris polyphylla*, with polyphyllin D, formosanin C, dioscin, paris H, paris VII, and pennogenin 3-O-α-L-rhamnopyranosyl 1 → 4)- [β-L-rhamnopyranosyl (1 → 2)]-β-D-glucopyranoside identified as the main components. It was found that the total extract of polyphyllin inhibited the migration of lung adenocarcinoma cells from mouse in vitro and in vivo to varying degrees [33].

In addition, the largest cluster with 90 references is "rhizoma paridis" (Cluster ID 0#). Xiang, Songtao et al. discovered that polyphyllin I could inhibit growth, induce cell cycle arrest and reduce migration and invasion in castration-resistant prostate cancer cells by downregulating EZH2, DNMT1, and HOTAIR [9]. In 2011, Man, Shuli et al. identified the components of the extract of rhizoma paridis. Wound healing assay and migration assay were used to evaluate the migration inhibition with non-cytotoxic doses, which were measured by MTT assay in this study. The results showed that the mixture of components exhibited potent anticancer activity by inducing programmed cell death and inhibiting migration in murine lung adenocarcinoma both in vitro and in vivo [33]. Among all the clusters, the cluster with the highest centrality is "cell cycle" (Cluster ID 1#), covering the most highly cited references. Zhao, Pengjun et al. evaluated the combined effect of Paris saponin I and hyperthermia on various non-small cell lung cancer cell lines. They found that Paris saponin I together with hyperthermia could result in cell death and tumor inhibition, which was realized by the multi processes including G2/M arrest and regulation of Bax, Bcl-2, and caspase-3 expression [42]. Zhang, Wenjie et al. studied the proliferation-inhibitory effect of Paris saponin VII on human cervical cancer using HeLa cells and its molecular mechanism. They found that Paris saponin VII may induce apoptosis by increasing the expression of caspase-3, caspase-9, and Bax, and at the same time decreasing the expression of Bcl-2 via intrinsic apoptotic pathways [43]. Xiao, Meifang et al. investigated the effect of Paris saponin I on the growth and apoptosis of human gastric cancer cells. Paris saponin I treatment caused the disruption of the cell cycle arrested at G2/M and triggering apoptosis [44]. In summary, the research on polyphyllin in high-incidence cancers has received increasing attention based on the analysis of literature clustering and co-citation. In summary, the highly cited literature mainly focuses on the research of polyphyllin D in liver cancer, lung cancer and breast cancer, with a strong association with apoptosis induced by mitochondrial dysfunction.

Based on the joint analysis of keyword frequency and occurrence, the research on polyphyllin glycosides in highly prevalent cancers has attracted widespread attention.

1) Research on polyphyllin glycosides in lung cancer: Siu, Fung-Ming investigated the mechanism of effect of polyphyllin D on human non-small cell lung cancer cell line (NCL-H460). Proteomic and transcriptomic analysis revealed that increased expression of C/EBP homologous transcription factor (chop) and caspase-4 activation taken place in the early stages of polyphyllin D treatment. While, it is found that prolonged PD treatment could induce tumor suppressor p53, disrupt mitochondrial membrane and activate the expression of caspase-9 and caspase-3 [45]. Lai, Lei et al. found that polyphyllin I could reverse the resistance of osimertinib in osimertinib-resistant non-small cell lung cancer both in vitro and in vivo. The mechanism could be associated with down-regulating the PI3K/Akt signaling pathway and elevating the protein expression of apoptosis-related genes [46]. Zheng, Ruzhen et al. also discovered that polyphyllin II increased sensitization of drug-resistant of PC-9/ZD cells to gefitinib via inhibiting the PI3K/Akt/mTOR signaling pathway [47]. He, Hao et al. also found that polyphyllin VII could result in apoptotic cell death in A549 human lung cancer cells by inhibiting the PI3K/Akt and NF-κB pathway [48].
2) Research on polyphyllin glycosides in breast cancer: In 2005, Lee, Mei-Sze et al. treated MCF-7 and MDA-MB-231 cells with polyphyllin D and found that it had the potential to dissipate the mitochondrial membrane, downregulate the expression of Bcl-2, upregulate the expression of Bax, and activate Caspase-9 to induce apoptosis [40]. Yang, Qin et al. evaluated the effects of polyphyllin VII on bone destruction induced by metastatic breast cancer in vivo and its potential mechanisms. They found that polyphyllin VII alleviated osteolytic damage induced in MDA-MB-231 cells in vivo through inhibiting osteoclast differentiation by suppressing the c-Fos/NFATc1 signaling pathway [49]. Nguyen Thi Duyen et al. found that Paris saponin II could induce cell cycle arrest at the G1/S phase and activate apoptosis related pathways by increasing the expression of p53, p21, p27, and Bax proteins, and suppressing the expression of cyclin D1 and retinoblastoma protein significantly in MCF-7 cells [50]. Zhou, Yulu et al. discovered that polyphyllin III induced iron deficiency in MDA-MB-231 breast cancer cells regulated by ACSL4, exerting its

anticancer effects. They also observed that upregulation of xCT mediated by KLF4 played a negative feedback role during iron deficiency progression, which may contribute to the phenomenon of drug resistance in cancer treatment [51].

3) Research on polyphyllin glycosides in liver cancer: Li, Yuanyuan et al. conducted a study on the potential anti-cancer properties of Formosanin C (FC), a compound derived from Rhizoma Paridis. Their findings revealed that FC exhibits inhibitory effects on the growth of liver cancer cells (HepG2) through inducing apoptosis and arresting the cell cycle in the S phase. Furthermore significant alterations in the exometabolome of FC-treated cells were observed by metabolic profiling, further supporting its potential as a promising anti-cancer drug [52]. Man, Shuli et al. discovered that Rhizoma Paridis Saponins (RPS) possess potent anti-lung cancer and anti-hepatocarcinoma properties. Metabolic profiling in H22 hepatocarcinoma mice revealed that RPS inhibited ketone transformation and ATP production, while promoting lipid accumulation. In normal mice, RPS increased glucose and valine levels, indicating enhanced energy metabolism. In H22 cancer mice, RPS suppressed fatty acid oxidation, gluconeogenesis, and tumor growth by altering metabolic profiles [53]. Liu, Jing et al. investigated the anti-tumor effects of Rhizoma Paridis saponin (RPS) in a rat model of diethyl nitrosamine (DEN)-induced hepatoma. After 20 weeks of RPS treatment, they conducted various tests and found that RPS alleviated liver injury by reducing malondialdehyde (MDA) and nitric oxide (NO) levels, increasing superoxide dismutases (SOD) production, and up-regulating GST-α/μ/π expression in DEN-induced rats. These findings suggest that RPS has potential as a potential agent against chemically induced liver cancer [54].

5. Conclusions

In summary, research on polyphyllin in the field of highly prevalent cancers is currently in a developmental stage, with a noticeable increase in the number of retrieved articles. The majority of the research output originates from China, with only a few articles involving international collaboration. The Chinese Academy of Sciences and Tianjin University play significant roles in the advancement of this field. Gao WY and Man SL have published the highest number of articles and have made substantial contributions in this area. Components such as polyphyllin VI, polyphyllin II, and polyphyllin VII exhibit promising research prospects, and the investigation of related mechanisms such as autophagy may emerge as future research focal points. Overall, our research provides a comprehensive visualization of the relevant literature on polyphyllin in highly prevalent cancers, highlighting key aspects of this topic and offering guidance and references for further exploration of diseases and drugs.

6. Limitation

This study visualized the relationship between polyphyllin and highly prevalent cancers, using bibliometrics to understand trends and hotspots. However, this study has limitations. For instance, due to the current limitations of scientific measurement software, it is a challenge to analyze data from multiple databases simultaneously. Therefore, this study solely relied on the WOSCC database. Additionally, this study only included articles and reviews, excluding abstracts, conference papers, or books. Hence, future research can be conducted using more comprehensive databases for a more comprehensive and accurate analysis.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Ethics statement

Review and/or approval by an ethics committee was not needed for this study because this study was an analysis based on the literature and did not involve human or animal studies.

CRediT authorship contribution statement

Xin Jiang: Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Zhen Liu:** Supervision, Resources, Investigation. **Runlan Wan:** Funding acquisition. **Renming Cai:** Visualization. **Jiaxin Yang:** Project administration. **Linfeng Li:** Validation. **Huiling Hu:** Visualization. **Lilan Ou:** Software. **Chun Zhang:** Writing – review & editing, Funding acquisition, Conceptualization. **Qiuyu Liu:** Writing – review & editing, Visualization, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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