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ORIGINAL RESEARCH

Research Hotspots of Traditional Chinese Medicine for Liver Cancer in the Future Directions: A Bibliometric Analysis

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Background: Traditional Chinese medicine (TCM) demonstrates growing potential in liver cancer management, yet a comprehensive overview mapping the intellectual landscape and evolving trends of this field is lacking. This study aims to fill this gap by conducting a systematic bibliometric analysis of TCM for liver cancer research over the past decade.

Methods: We performed a bibliometric analysis of publications related to TCM and liver cancer retrieved from major databases including China National Knowledge Infrastructure (CNKI), Wanfang, VIP, and Web of Science. The search timeframe spanned from February 14, 2015, to the search date (February 14, 2025). The literature was analyzed using scientific mapping tools, such as CiteSpace, Origin 2024, R, and VOSviewer, to identify publication trends, collaborative networks, research hotspots, and frontier topics.

Results: The analysis reveals a steadily growing and globally engaged field, with China being the dominant contributor. While core research teams are emerging, international and cross-regional collaborations remain limited. A clear thematic divergence exists: international literature primarily focuses on exploring the pharmacological mechanisms of TCM compounds, whereas Chinese-language studies place greater emphasis on clinical applications, medication rules, data mining, and TCM syndrome differentiation. Key emerging research frontiers include mechanisms of action, omics technologies, bioinformatics technology, network pharmacology and molecular docking, TCM syndrome research, TCM theory innovation and exploration, TCM nanodelivery, data mining, and deep learning.

Conclusion: This bibliometric review provides a comprehensive landscape of TCM research for liver cancer, highlighting its dynamic growth and the complementary nature of mechanistic and clinical research streams. The findings underscore the necessity for enhanced international collaboration to bridge existing gaps and foster integrated, innovative approaches for advancing TCM in oncology.

Keywords: traditional Chinese medicine, Chinese herbal medicine, liver cancer, bibliometrics, visual analysis, mechanisms

Introduction

As a highly prevalent neoplastic disease, hepatic malignancies demonstrate escalating incidence rates worldwide, constituting a growing concern in contemporary oncology research.[1] Epidemiological reports from 2022 indicate that hepatic malignancies occupy the sixth position in global cancer prevalence, documenting approximately 865,000 new incident cases.[2] Within this disease spectrum, hepatocellular carcinoma (HCC) emerges as the predominant histological subtype, comprising 75–85% of total diagnoses.[3] In 2020, China contributed to 45% of global HCC cases and 47% of global HCC deaths.[4] In 2022, China reported 4,824,700 new cancer cases, including 367,700 liver cancer cases (ranking 4th), and 2,574,200 cancer deaths, including 316,500 liver cancer deaths (ranking 2nd).[5] Surgical resection and liver transplantation constitute the cornerstone of management for individuals with early-stage liver cancer.[6] However, high postoperative recurrence rates and donor scarcity significantly diminish treatment efficacy.[7] Multi-kinase inhibitors, such

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as sorafenib and regorafenib, have been approved for the treatment of unresectable or advanced hepatocellular carcinoma. However, most patients will eventually experience disease progression and develop treatment-emergent adverse events.[8] Other treatments like interventional therapy, ablation, radiotherapy, chemotherapy, and immunotherapy often yield unsatisfactory efficacy and are accompanied by severe side effects, resulting in generally low patient compliance.[9] Effective alternative therapeutics with lower economic burdens and reduced toxicity warrant immediate development.

Traditional Chinese medicine (TCM) offers a historically grounded, multi-targeted framework for liver cancer therapy, increasingly validated through contemporary oncology research. Extensive experience accumulated through long-term clinical practice has formed a unique TCM theoretical system. Syndrome differentiation and treatment, as the core practice of TCM's holistic framework, constitutes the foundation for developing therapeutic strategies against liver cancer. Primary liver cancer constitutes a systemic disorder, whose pathogenesis entails endogenous toxin accumulation, vital qi deficiency, and qi stagnation, culminating in a disruption of yin-yang equilibrium. Given that disease arises from imbalances, TCM intervention seeks to restore yin-yang equilibrium and qi-blood harmony, thereby promoting systemic health. The TCM approach to liver cancer integrates holistic patient management with syndrome-specific interventions. Key TCM modalities—yin-nourishing (correcting fluid-metabolic imbalance), heat-clearing/detoxification (anti-inflammation), blood-activating/stasis-resolving (microcirculation improvement), mass-softening (tissue remodeling), and liver-soothing/qi-regulating (neuroendocrine modulation)—synergistically enhance patient survival.[10] TCM demonstrates efficacy in alleviating clinical symptoms, enhancing quality of life, and delaying disease progression in liver cancer patients. These benefits are primarily mediated through multitargeted biological actions, including inhibit cellular proliferation, inducing apoptosis, causing cell cycle arrest, inducing autophagy, inhibiting epithelial–mesenchymal transition (EMT), suppressing metastasis, regulating immune function, modulate the tumor microenvironment (TME), regulate metabolic reprogramming, and inhibiting angiogenesis. Collectively, these mechanisms synergistically prevent tumor recurrence and metastasis, embodying the TCM principle of "Fuzheng Quxie" that harmonizes systemic homeostasis with targeted oncogenic inhibition.[11]

The field of bibliometrics originated in the early decades of the 20th century and subsequently attained recognition as a distinct academic discipline in 1969.[12] To this day, it has become an indispensable and widely used tool in the field of literature analysis.[13] Bibliometric analysis systematically explores the distribution, trends, and characteristics of existing literature in a specific field through quantitative methods.[14] Such analysis can extract multidimensional information, covering key elements such as authors, keywords, journal sources, countries, research institutions, and citation relationships. Consequently, bibliometric evaluation offers profound and significant perspectives concerning the developmental trajectory of particular academic domains.[15] Ninkov et al emphasized the importance of using visualization methods in bibliometrics for co-citation analysis, which helps effectively interpret data and enhance the comprehensiveness of results.[16] In the medical field, the application of bibliometrics holds a critical position, as this field adopted this method relatively early.[17] Hence, employing bibliometrics as an analytical approach enables the creation of an all-encompassing knowledge framework pertaining to the domain of TCM in the context of liver cancer. Furthermore, this method can, to a certain degree, anticipate forthcoming trends and pinpoint pivotal areas of emphasis within this specialized field.

This study employed bibliometric analysis integrated with scientific visualization techniques to systematically map the scholarly literature on TCM interventions for liver cancer. VOSviewer, CiteSpace, and R software were used to examine the number of articles, citation counts, and research trends based on countries, authors, and keywords. The primary datasets utilized in this investigation were extracted from the Web of Science Core Collection (WOSCC), along with the CNKI, Wanfang, and VIP repositories, which collectively served as the foundational sources for data acquisition. The study aimed to:① quantify publication outputs and identify leading countries, institutions, authors, and journals; ②visualize collaborative networks and uncover research hotspots through keyword co-occurrence and clustering analyses; ③ trace the evolution of research themes using timeline and burst detection analyses;④forecast emerging frontiers and future directions. ⑤to compare the thematic structures between Chinese- and English-language literature so as to identify cross-lingual research niches suitable for international cooperation. The findings are expected to provide a valuable reference for researchers to understand the current landscape, identify potential collaborators, and stimulate innovative research aligned with TCM principles for liver cancer management.

Methods

Data Collection

For the purpose of this research, the Chinese-language scholarly materials were obtained from databases including CNKI, Wanfang, and VIP. In contrast, the English-language literature was predominantly retrieved from the Web of Science (WOS) database. First, medical subject headings were searched from the US National Library of Medicine/MeSH database. The search strategy is implemented by combining subject terms with free terms to cover a wide range of literature relevant to the research direction. Subsequently, the following search strategies were formulated: the Chinese search query was SU=("traditional Chinese medicine" + "TCM" + "Chinese herb" + "Chinese herbal medicine" + "herb" + "Chinese herbal" + "Chinese patent medicine" + "formula" + "Han prescription" + "integrated traditional Chinese and western medicine" + "acupuncture") and SU=("liver malignancy" + "hepatocellular carcinoma" + "liver cancer" + "adult liver cancer" + "intrahepatic cholangiocarcinoma" + "combined hepatocellular-cholangiocarcinoma" + "primary liver cancer"), and the English search query was TS=(traditional Chinese medicine or TCM or herb or herbal or Chinese herb or Chinese herbal medicine or Chinese patent medicine or Chinese traditional patent medicine or formula or han prescription or integrated traditional Chinese and western medicine or acupuncture or moxibustion) and (Carcinoma, Hepatocellular or Cancer of Liver or Hepatocellular Cancer* or Hepatic Cancer* or Liver Cancer or Liver Cancers or Cancer of the Liver or Hepatocellular Carcinomas or Liver Cell Carcinoma, Adult or Adult Liver Cancer* or Liver Cell Carcinoma* or Hepatoma* or intrahepatic cholangiocarcinoma or Combined Hepatocellular-Cholangiocarcinoma or primary carcinoma of liver or Primary Liver Cancer). The search timeframe spanned from February 14, 2015, to the search date (February 14, 2025). On February 14, 2025, all document extraction and export were uniformly completed to minimize potential bias from database updates.

The inclusion criteria for this study are as follows:①Articles in the field of traditional Chinese medicine (TCM) for liver cancer; ② Original research papers and review literature; ③ Literature with complete bibliographic information exportable; ④ Studies not directly targeting liver cancer or TCM must explicitly focus on at least one of the following aspects: potential pathogenic pathways, clinical efficacy, or molecular signaling mechanisms involved in TCM treatment of liver cancer; ⑤ Research articles published between February 14, 2015, and February 14, 2025. The exclusion criteria are: ① Literature types such as conference abstracts, letters, editorial materials, books, achievements, newspapers, patents, and retracted articles; ② Unpublished manuscripts, duplicate literature, non-English and non-Chinese documents; ③ Articles irrelevant to the research theme; ④Articles not available in full text; ⑤Literature with missing critical information such as publication date, authors, or keywords.

For different expressions of the same institution, such as "Hebei University of Chinese Medicine" and "Hebei Chinese Medicine University", we standardize them to the latest name, such as "Hebei University of Chinese Medicine". To ensure accuracy in keyword analysis, we merged synonyms and near-synonyms based on a predefined replacement list. For example, terms like "primary liver cancer" were unified as "liver cancer"; "traditional Chinese medicine treatment" and "Chinese medicine" were standardized to "traditional Chinese medicine"; "integrated Chinese and Western medicine therapy", and "integration of traditional Chinese and Western medicine" were consolidated as "integrated Chinese and Western medicine". Similar processing was applied to English keywords such as standardizing "hepatocellular-carcinoma" to "hepatocellular carcinoma", "nf-kappa b" to NF-κB", and "liver-cancer" to "liver cancer". In country analysis, "China" and "taiwan" were integrated into "China". This standardization process combined script-assisted automation with manual verification to minimize errors.

The Chinese-language scholarly resources were exported utilizing the Refworks format, whereas the English-language literature was exported in the form of plain text. Import the Refworks-formatted files exported separately from CNKI, Wanfang, and VIP into the "Data Extraction Module" of the COOC (version 14.6) software, and then merge them to generate a comprehensive dataset. Utilize the "Data Cleaning Module" in COOC software to detect and delete duplicates based on document titles, authors, and publication years. This software employs a hierarchical detection strategy, encompassing relationship detection, precise DOI matching, standardized title comparison, and author information analysis, thereby efficiently identifying and removing duplicate entries to ensure the uniqueness of each document in the final analysis set. To achieve integrated analysis of Chinese and English literature data, translation and format

conversion of Chinese literature information are required. This process is collaboratively accomplished using COOC software in conjunction with other tools. To ensure accuracy, multiple methods are employed: initial translation is performed using machine translation tools; for specialized terminology, manual proofreading and correction are conducted; finally, back-translation is used, where another researcher not involved in the initial translation verifies the accuracy of key entries. After translation and verification, the standardized Excel spreadsheet is re-imported into COOC software. Using the format conversion function of COOC, the data is converted into Refworks format for subsequent bibliometric analysis.

Two researchers independently examined the titles, abstracts, and keywords of the literature to exclude studies unrelated to the research topic based on the inclusion and exclusion criteria. When discrepancies arose during the screening process, a third researcher was consulted.

Data Analysis

This study utilized CiteSpace (version 6.3.R6), VOSviewer (version 1.6.20), Excel2019 (version 16.0), Origin 2024 (version 10.1), R (version 4.5.0) and Literature Metrology Online Analysis Platform (https://bibliometric.com/app) to construct knowledge graphs, with each tool demonstrating its unique advantages and capabilities. Excel 19 was used to create statistical tables and publication trend charts.

CiteSpace generated timeline graphs, journal dual-map overlays, and keyword burst detection graphs, clearly illustrating the evolution of knowledge within specific clusters, the historical span of literature, and field development trends.[18] The configurations for the CiteSpace parameters were established as specified below: time slicing from February 2015 to February 2025, year per slice as 1 year, k=25, top N per slice as 50, When the node type was institution, journal, or country, Pruning selected Minimum spanning tree and Pruning the merged network, whereas for keyword nodes, Pruning selected Pathfinder, Pruning sliced networks, and Pruning the merged network. The values of all other parameters were maintained at their default settings.

VOSviewer provided diverse visualizations of keywords, collaborating institutions, and authors, producing intuitive graphical representations, including network graphs, timeline views, and density distribution maps.[19] It employed a visual clustering approach to present these relationships, thereby facilitating the swift identification of global collaboration trends and research communities. With this tool, intricate collaborative networks within the academic sphere could be effectively visualized and analyzed. The parameter settings for VOSviewer are as follows: For the "type of data" option, select "bibliographic data". When the data source involves English-language literature, choose "bibliographic data files"; for Chinese-language literature, select "reference manager files". In the "type of analysis" section, for authors and institutions, choose "Co-authorship"; for keywords, select "Co-occurrence"; for journals, opt for "Citation". For "cited references" and "cited publications", select "Co-citation". The threshold is described in detail in the results section. The viewing of connection numbers is as follows: in the map menu, select the "save map" option to save the file as a CSV file. The row labeled "weight<Links>" in the file represents the connection numbers.

Additionally, the bibliometrix, shiny, sf, map, and DT package in R software was employed to comprehensively and deeply analyze the research status of a specific field, capturing research hotspots from multiple perspectives. It was used to generate country collaboration maps, institutional geographic distribution heatmaps, and the H-index values of contributing authors in the field of TCM and liver cancer.[20]

Use the Literature Metrology Online Analysis Platform (https://bibliometric.com/app) to draw an Inter-Country /Region Collaboration Chord Diagram. Set the parameters as follows: upload the "tab-delimited" file containing the basic data records, select the option for cooperation relationship analysis, and choose the analysis of inter-country relationships.

Origin 2024 was used to create author-keyword biclustering analysis visualization matrix and keyword co-occurrence distribution heatmaps. The specific steps for drawing author-keyword biclustering analysis visualization matrices are as follows. This figure is generated using the "Cluster Plot" function in Origin. The input data is an author-keyword co-occurrence matrix. For the clustering method, hierarchical clustering is selected, with Euclidean distance employed as the similarity metric. The color scheme is also set to a gradient ranging from blue (indicating high association) to red (indicating low association). The rows (authors) and columns (keywords) of the matrix are reordered based on the

clustering results to visually display the clustering patterns of research communities and topics. The specific steps for drawing keyword co-occurrence distribution heatmaps are as follows, use CiteSpace to count the annual occurrence frequencies of high-frequency keywords. The data is organized in a matrix format, where rows represent keywords and columns represent years (from 2015 to 2024). In Origin, select "Plot" > "Heatmap" > "Color Fill" to create a heatmap. The color mapping is set to a continuous gradient, transitioning from blue (indicating high-frequency co-occurrence) to red (indicating low-frequency co-occurrence). The axis labels have been customized to ensure that the years and keywords are clearly legible.

Results

Publication Statistics and Trends

The total number of retrieved documents is 11,230, including 7,736 literature on the Chinese language and 3,494 literature on the English language. After screening based on inclusion/exclusion criteria, deduplication, and reading titles and abstracts, 4,490 documents were finally included, among which 3,073 were Chinese and 1,417 were English. The literature screening process is shown in Figure 1. As seen in Figure 2, English publications show an increasing trend year by year, while Chinese publications remain stable at around 300.

Author Analysis

In accordance with Price's Law, an assessment was conducted to determine the publication output attributable to the core authors, resulting in N1≈4 (Chinese) and N2≈4 (English). Therefore, the VOSviewer software was used to visualize Chinese and English authors who published four or more articles, as shown in Figures 3 and 4.

Figure 3 shows that 194 core authors of English literature formed 33 clusters, with each cluster containing 1–22 authors. Within the realm of English-language literature focusing on TCM and liver cancer, multiple research teams were formed with Yibin Feng, Wei Wang, Yu Zhang, Jing Li, Jing Wang, etc. as the core. Among them, Yibin Feng, Wei Wang, Yu Zhang, Jing Li, Xin Li; Jing Wang, Changquan Ling, Zhiyun Yang, Yan Chen, and Yu Sun, formed the research teams with more collaboration, while cooperation between other teams was relatively loose. In terms of researcher collaboration, Yibin Feng (16 connections), Rui Hu (16 connections), Jing Li (16 connections), and Wei Zhang (16 connections) had the most extensive connections with other researchers, followed by Jialing Sun (14 connections), Jing Wang (14 connections), Ning Wang (14 connections), and Yan Chen (13 connections).

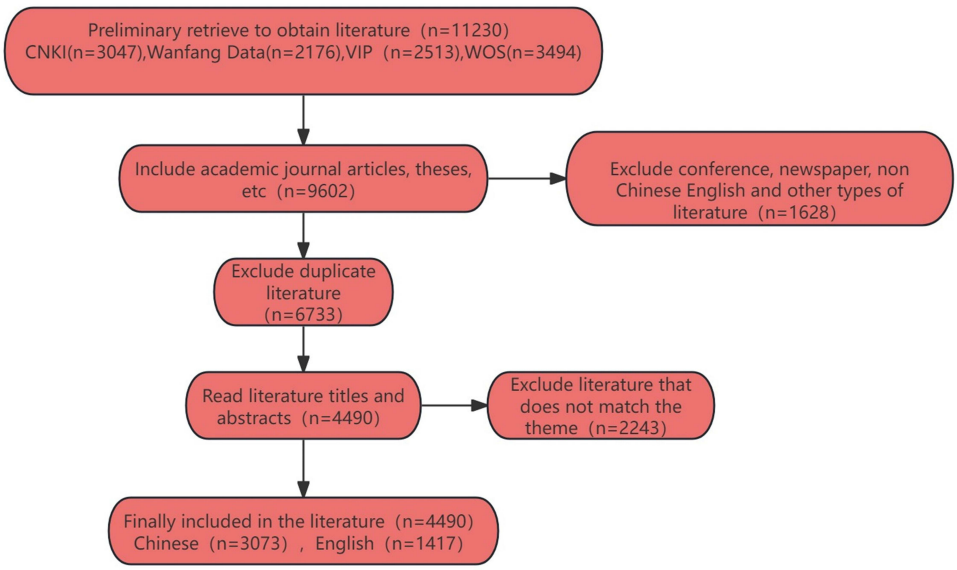

Figure 1 Literature screening flowchart.

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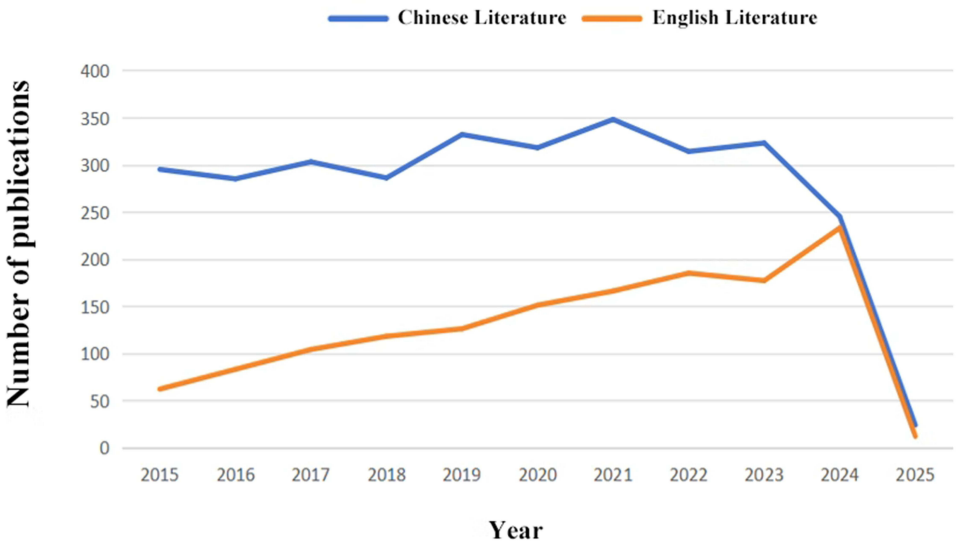

Figure 2 Publication volume trend from 2014 to 2025 year.

Figure 4 shows that 301 core authors of the Chinese literature formed 65 clusters, with each cluster containing 1–17 authors. In the field of TCM and liver cancer in Chinese literature, multiple research teams have been formed with Zhai Xiaofeng, Lv Jianlin, Chen Chuang, Chen Xinju, and Wu Xiaoxiong as the core. Among them, Lv Jianlin, Shao Mingyi, and Chen Xinju formed research teams with more collaboration, while Zeng Puhua and Deng Xin collaborated more closely. Cooperation between other teams was relatively weak. In terms of researcher collaboration, Chen Xiaoqi (17 connections) had the most extensive connections with other researchers, followed by Wang Xianbo (12 connections), Zhang Xin (11 connections), and Zeng Puhua (10 connections). It is evident that Chinese literature authors are not as closely collaborative as English literature authors, and domestic cooperation in the field of TCM and liver cancer requires strengthening.

Table 1 shows that the included 1,417 English articles included 8,525 authors, among the top ten authors ranked by their publication counts, three hail from Hong Kong. Yibin Feng had the most publications (23 articles) and the highest citation count (1,221 times), underscoring their prominent role and considerable sway within the global sphere of TCM and liver cancer studies. As shown in Figure 5, the top three English literature authors by H-index are Ning Wang, Yibin Feng, and Horyue Tan suggesting their substantial international influence in this field. Table 1 shows that the included 3,073 Chinese articles included 6,201 authors, with two of the top ten authors by publication count from Shenzhen and 2 from Guangxi. Among them, Zhai Xiaofeng had the most publications (22 articles), while Lin Lizhu had the highest citation count (234 times) among the top 10, indicating this author's significant domestic influence.

Cluster analysis of researchers' keywords revealed the research status of different researchers in the same field. As shown in Figure 6, the English literature identified five clusters based on author clustering: Cluster A includes Yibin Feng, and Yang Liu (two scholars); Cluster B includes Wei Wang, Yu Zhang, etc. (three scholars); Cluster C includes Yue Tan Hor, Wei Zhang, etc. (four scholars); Cluster D mainly includes Jing Li, Yuexia Li, etc. (four scholars); and Cluster E includes Jing Wang and Changquan Ling (two scholars). As shown in Figure 7, Chinese literature identified six clusters: Cluster A includes Zhai Xiaofeng, Chen Xinju, etc. (five scholars); Cluster B includes Wu Xiaoxiong, Zhao Wenxia, etc. (five scholars); Cluster C includes Zeng Puhua, Chen Xiaoqi, etc. (three scholars); Cluster D mainly includes Chen Chuang and Yang Yuanlei (two scholars); Cluster E includes Zhang Nan (one scholar); and Cluster F includes Han Tao (one scholar). Because of similar research directions, scholars within the same cluster have potential collaboration foundations.

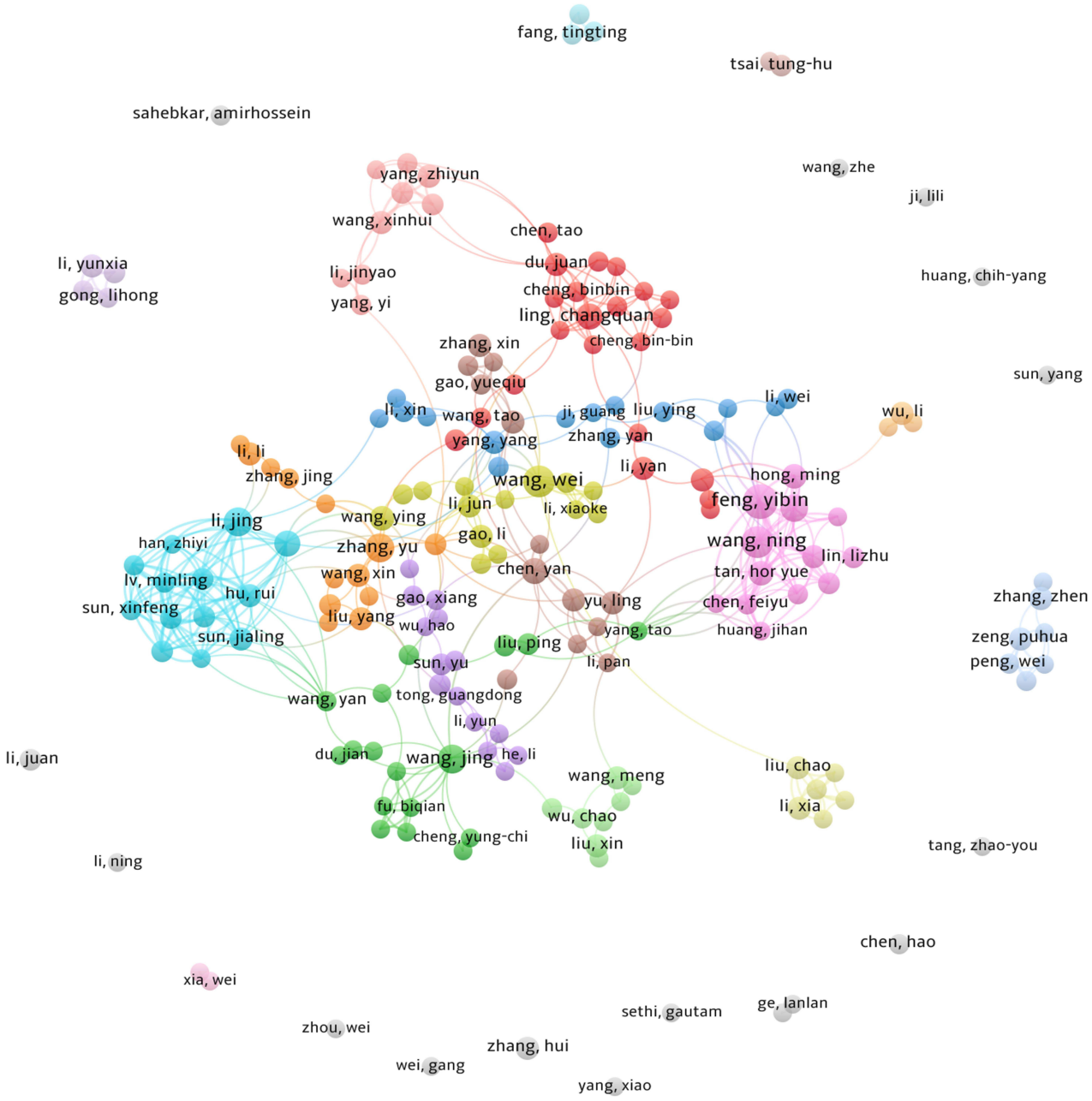

Figure 3 English literature author collaboration network.

Institutional and Countries/Regions Analysis

Therefore, VOSviewer software was used to visualize Chinese and English institutions with 5 or more publications, as shown in Figures 8 and 9.

Figure 8 reveals that Chinese domestic collaborations mainly occur between universities and their affiliated hospitals, as well as among different institutions within the same region. In Chinese literature, Beijing University of Chinese Medicine (12 connections) had the most extensive collaborations, followed by Guangxi University of Chinese Medicine (9 connections), Guangzhou University of Chinese Medicine (8 connections), and Hunan University of Chinese Medicine (5 connections).

Figure 9 shows that internationally, the field of traditional Chinese medicine and liver cancer has attracted attention not only from Chinese domestic institutions but also from other countries. Collaborations are frequent between TCM

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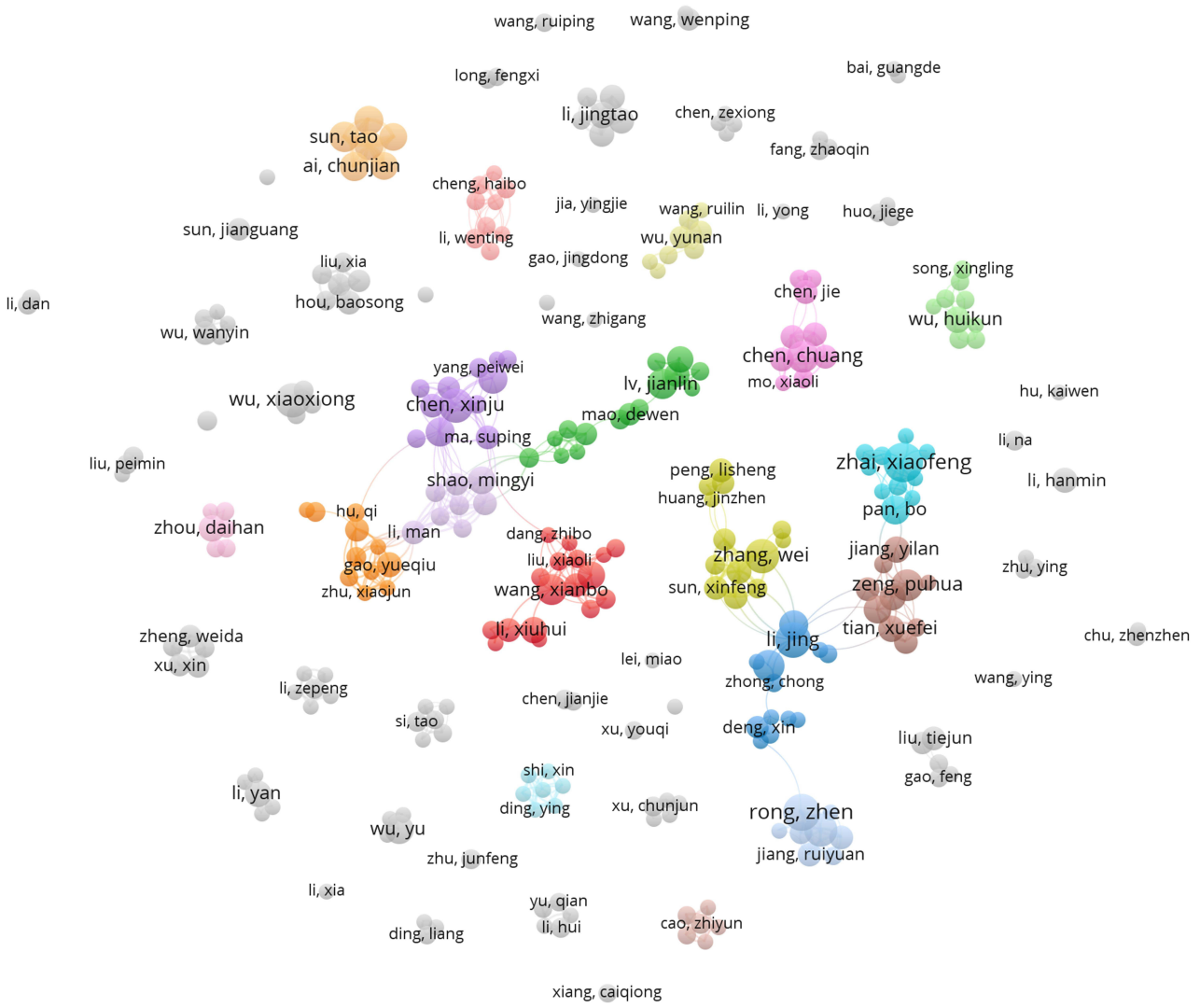

Figure 4 Chinese literature author collaboration network.

universities and Chinese domestic medical universities, with participation from comprehensive universities such as Zhengzhou University, Fudan University, Shanghai Jiao Tong University, and the University of Hong Kong. Additionally, institutions from Taiwan Province, like Kaohsiung Medical University and Chang Gung University, collaborate closely with China Medical University and Yale University (America). Outside China collaborations are prominent among Yeungnam University (Korea), Alexandria University (Egypt), King Saud University (Saudi Arabia), Mazandaran University of Medical Sciences (Iran), and Cairo University (Egypt). In English literature, Guangzhou University of Chinese Medicine (China) (37 connections) has the most extensive collaborations, followed by Shanghai University of Traditional Chinese Medicine (China) (31 connections), the University of Hong Kong (China) (28 connections), and the Chinese Academy of Sciences (China) (25 connections).

There are 1,662 institutions publishing Chinese literature, with Guangxi University of Chinese Medicine (169 publications), Guangzhou University of Chinese Medicine (138 publications), and Beijing University of Chinese Medicine (109 publications) exceeding 100 publications, as shown in Table 2. For English literature, there are 1,558 institutions, fewer than Chinese literature, but collaborations among them are more frequent. Institutions with over 40 publications include Shanghai University of Traditional Chinese Medicine (China) (89 publications), Guangzhou

Table 1 Top 10 Authors by Publication Count

No.	Chinese Literature Author	Number of Publications (articles)	Institution of Chinese Literature Authors	Citation Frequency (times)	Average Citation Frequency per Article (times)	No.	English Literature Author	Number of Publications (articles)	Institution of English Literature Authors	Citation Frequency (times)	Average Citation Frequency per Article (times)
1	Zhai, Xiaofeng	22	The First Affiliated Hospital of Naval Medical University	229	10.4	1	Feng, Yibin	23	The University of Hong Kong	1221	53.1
2	Rong, Zhen	20	Shenzhen Bao'an Pure Chinese Medicine Hospital	162	8.1	2	Wang, Ning	19	The University of Hong Kong	1117	58.8
3	Wu, Xiaoxiong	17	Shanghai Seventh People's Hospital	81	4.8	3	Wang, Wei	19	Beijing University of Chinese Medicine	367	19.3
4	Chen, Xinju	17	The First Affiliated Hospital of Henan University of Chinese Medicine	112	6.6	4	Li, Jing	14	Shanghai University of Traditional Chinese Medicine	156	11.1
5	Mo, Chunmei	16	Shenzhen Bao'an Pure Chinese Medicine Hospital	143	8.9	5	Wang, Jing	13	Southwest Medical University	220	16.9
6	Zeng, Puhua	15	Affiliated Hospital of Hunan Academy of Traditional Chinese Medicine	195	13.0	6	Zhang, Yu	13	Nantong University	125	9.6
7	Lin, Lizhu	14	The First Affiliated Hospital of Guangzhou University of Chinese Medicine	234	16.7	7	Li, Sha	12	The University of Hong Kong	706	58.8
8	Chen, Chuang	14	Affiliated Tumor Hospital of Guangxi Medical University	187	13.4	8	Ling, Changquan	11	Naval Medical University	152	13.8
9	Lv, Jianlin	13	The First Affiliated Hospital of Guangxi University of Chinese Medicine	63	4.8	9	Zhang, Wei	11	Hangzhou Medical College	93	8.5
10	Sun, Tao	13	Cangzhou Infectious Disease Hospital	119	9.2	10	Chen, Yan	10	Sun Yat-sen University	169	16.9

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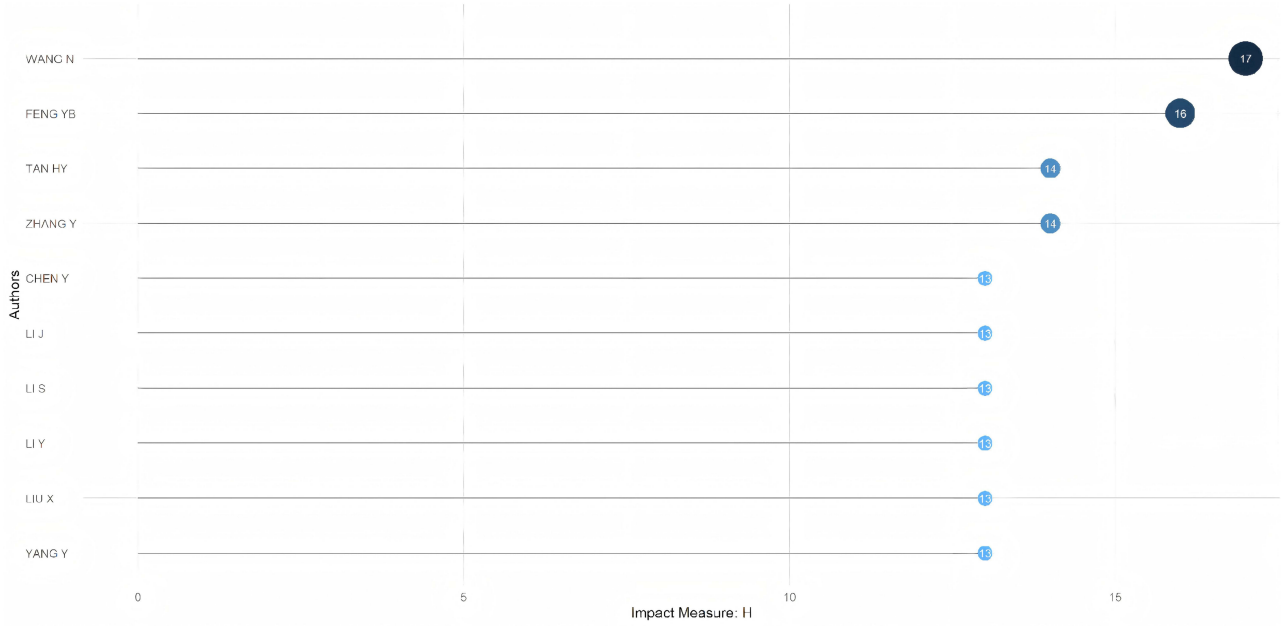

Figure 5 English literature author H-index.

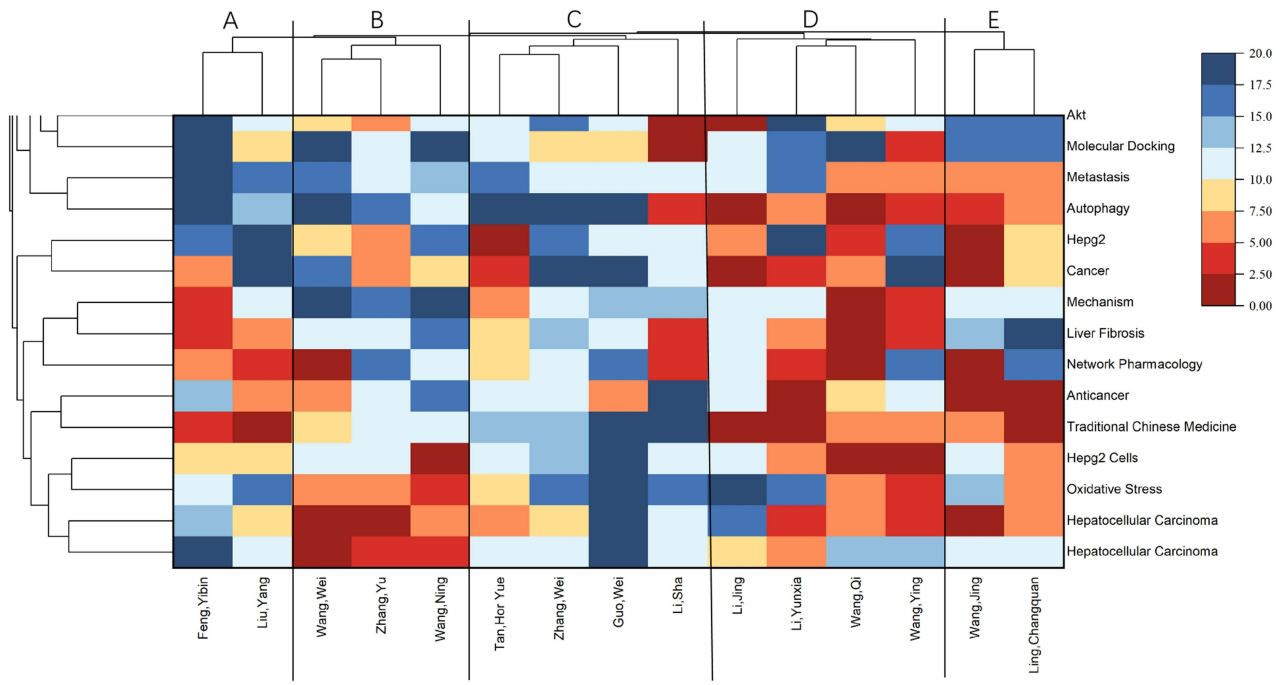

Figure 6 English literature high-yield author-keyword biclustering analysis visualization matrix. The matrix identifies six distinct research clusters (**A-E**) based on author-keyword co-occurrence.

University of Chinese Medicine (China) (67 publications), Beijing University of Chinese Medicine (China) (51 publications), and Nanjing University of Chinese Medicine (China) (42 publications).

Table 2 presents the centrality analysis of Chinese and English institutions using CiteSpace. In Chinese literature, Henan Province Hospital of Traditional Chinese Medicine has the highest centrality (0.13), while in English literature,

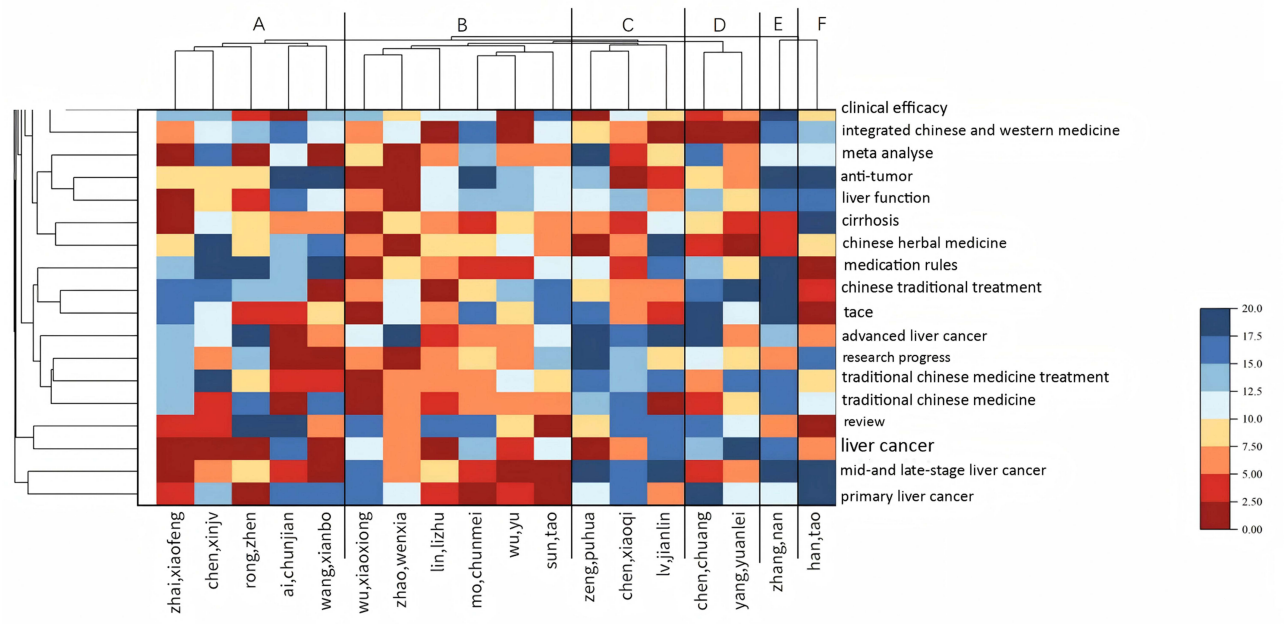

Figure 7 Chinese literature high-yield author-keyword biclustering analysis visualization matrix. The matrix identifies six distinct research clusters (**A**–**F**) based on author-keyword co-occurrence.

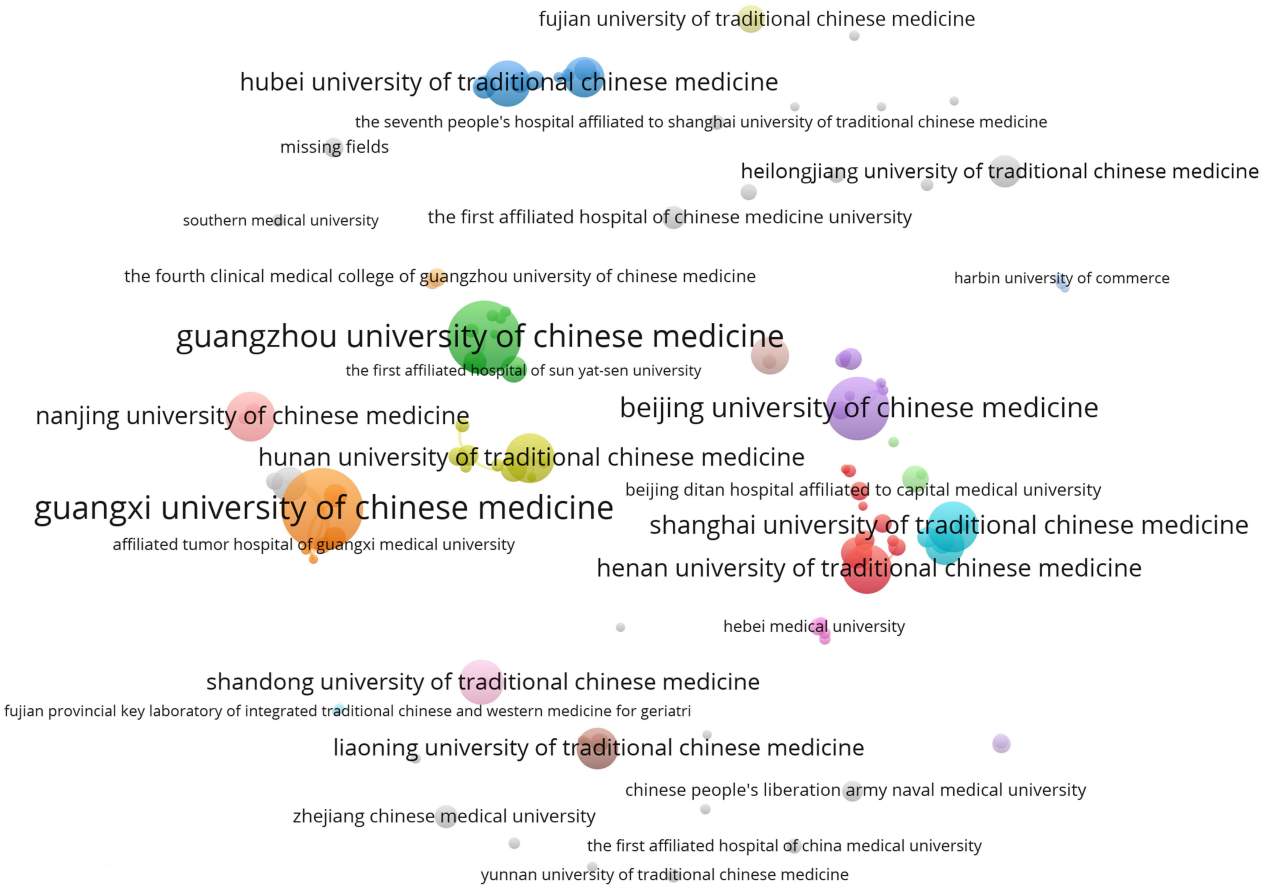

Figure 8 Chinese literature institution collaboration network.

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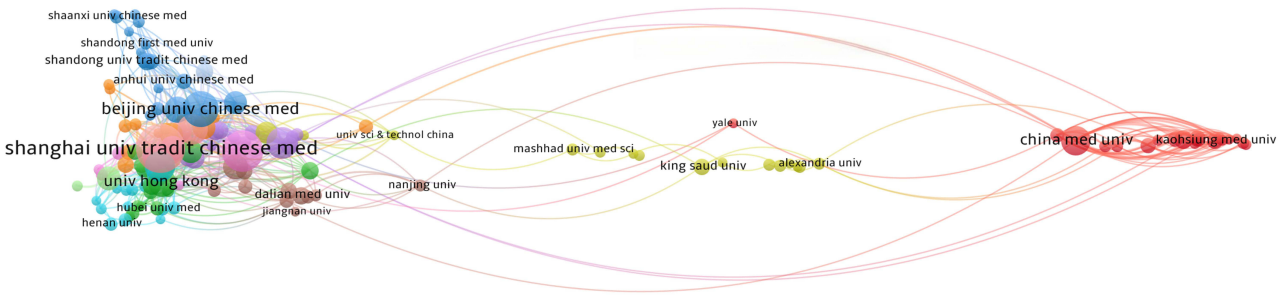

Figure 9 English literature institution collaboration network.

the University of Macau (China) has the highest centrality (0.63), indicating their greater importance in the collaboration network.

In the field of TCM and liver cancer research, researchers from 34 provinces, municipalities, and autonomous regions in China participated. As shown in Table 3 and Figure 10, the top three provinces in terms of Chinese literature publication volume are Guangxi, Beijing, and Shanghai. Figure 11 displays the geographical distribution and collaboration network of research institutions, revealing that institutions in Shandong, Hunan, Guangxi, Beijing, and Shanghai collaborate more frequently with external partners. In terms of research timeline, Anhui, Tianjin, Hebei, Liaoning, and Hong Kong started earlier in TCM and liver cancer research, while Inner Mongolia, Guizhou, Ningxia, Jiangsu, and Qinghai began later. Globally, researchers from 66 countries/regions participated in TCM and liver cancer research. Table 3 shows that China leads in both publication volume and citation frequency, followed by the United States, highlighting their significant influence in this field. In English literature, China has the broadest international connections (40 connections), followed by India (25 connections), the US (23 connections), and Italy (17 connections). According to CiteSpace centrality analysis, Italy, Singapore, and the USA rank top three, indicating their importance in the global collaboration network. Figures 12 and 13 demonstrate frequent collaborations among China, the USA, India, Egypt, South Korea, Japan, Singapore, Europe, and the Middle East. Figure 14 shows that in single-country and multinational collaboration publications, the top four countries are China, South Korea, India, and Egypt, while the USA, Iran, and Saudi Arabia tie for fifth. China and South Korea lead in co-authorship among domestic researchers, while China and India top international co-authorship. Although China collaborates most internationally, its MCP Ratio (0.074) is low compared to Egypt (0.609), which has the highest among the top 20.

Journal and Co-Cited Journal Analysis

There are 399 English journals publishing TCM-based liver cancer research. Using VOSviewer, journals with ≥5 articles were visualized (Figure 15). *Journal of Ethnopharmacology, Evidence-based Complementary and Alternative Medicine, Frontiers in Pharmacology, Biomedicine & Pharmacotherapy* show active citation relationships. *Current Pharmaceutical Design* and *Heliyon* are at the forefront of TCM and liver cancer research. As shown in Table 4, journals with over 100 publications are *Journal of Ethnopharmacology* and *Frontiers in Pharmacology*. Among all journals, *Frontiers in Pharmacology* has the highest citations (1,714), reflecting its high-quality content and broad impact in this field. Among the top 10 journals, *Biomedicine & Pharmacotherapy* has the highest impact factor of 6.9. Additionally, by combining information from VOSviewer software and the Journal Citation Reports, we found that the top 10 journals in terms of publication volume are primarily concentrated in JCR's Q1 (60%) and Q2 (30%), indicating these journals hold significant influence in this field. Figure 16 shows the journal dual-map overlay, where each node represents a journal. The left side of Figure 16 displays citing journals, while the right side shows cited journals. The connecting lines represent citation paths, and the ellipses indicate the number of authors.[21] The orange and yellow colors represent two main citation paths. The yellow path indicates that literature published in Molecular/Biology/Genetics journals is primarily cited by Veterinary/Animal/Science journals, while the orange path shows that literature published in Environmental/Toxicology/Nutrition and Molecular/Biology/Genetics journals is mainly cited by Molecular/Biology/

Table 2 Top 10 Institutions by Publication Count

No.	Publications		Centrality		No.	Publications		Centrality	
	Chinese Literature Institutions	Publications (count)	Chinese Literature Institutions	Centrality		English Literature Institutions	Publications (count)	English Literature Institutions	Centrality
1	Guangxi University of Chinese Medicine	169	Henan Provincial Hospital of Traditional Chinese Medicine	0.13	1	Shanghai University of Traditional Chinese Medicine	89	University of Macau	0.68
2	Guangzhou University of Chinese Medicine	138	Beijing University of Chinese Medicine	0.12	2	Guangzhou University of Chinese Medicine	67	Zhejiang University	0.6
3	Beijing University of Chinese Medicine	109	Beijing Ditan Hospital, Capital Medical University	0.12	3	Beijing University of Chinese Medicine	51	Chinese Academy of Sciences	0.53
4	Hunan University of Chinese Medicine	90	First Clinical Medical College, Henan University of Chinese Medicine	0.12	4	Nanjing University of Chinese Medicine	42	Arid Agriculture University	0.52
5	Hubei University of Chinese Medicine	78	Beijing You'an Hospital, Capital Medical University	0.11	5	Chengdu University of Traditional Chinese Medicine	38	University of Science & Technology of China	0.52
6	Shanghai University of Traditional Chinese Medicine	74	Hepatobiliary Diseases Branch of the Chinese Society of Traditional Chinese Medicine	0.11	6	Fudan University	38	Egyptian Knowledge Bank (EKB)	0.52
7	Nanjing University of Traditional Chinese Medicine	71	Dongzhimen Hospital	0.07	7	China Medical University	37	Shanghai Institute of Materia Medica	0.51
8	Henan University of Traditional Chinese Medicine	67	Tumor Hospital of Sun Yat-sen University	0.07	8	The University of Hong Kong	34	Abdul Wali Khan University	0.5
9	Shandong University of Traditional Chinese Medicine	61	Sun Yat-sen University Cancer Center	0.07	9	Southern Medical University	30	COMSATS University Islamabad (CUI)	0.5
10	Liaoning University of Traditional Chinese Medicine	53	Guangxi University of Chinese Medicine	0.06	10	Capital Medical University	29	Anhui University of Chinese Medicine	0.48

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Table 3 Top 10 Countries/Provinces by Publication Volume and Top 10 Countries by Centrality

No.	Publications		No.	Publications				Centrality	
	Province	Publications (papers)		Country	Publications (papers)	Citation Count (times)	Average Citations per Paper (times)	Country	Centrality
1	Guangxi	250	1	China	1163	19,752	16.98	Italy	1.07
2	Beijing	196	2	USA	65	1840	28.31	Singapore	0.92
3	Shanghai	195	3	South Korea	63	974	15.46	United States	0.86
4	Henan	187	4	India	59	1319	22.36	Estonia	0.86
5	Hubei	130	5	Saudi Arabia	45	1026	22.80	Croatia	0.83
6	Hunan	121	6	Egypt	33	1028	31.15	Poland	0.83
7	Shandong	101	7	Japan	21	709	33.76	Sri Lanka	0.64
8	Shaanxi	79	8	Pakistan	20	901	45.05	France	0.61
9	Hebei	76	9	Iran	19	687	36.16	Japan	0.61
10	Liaoning	70	10	Germany	15	691	46.07	Bangladesh	0.49

Immunology journals. This demonstrates the close relationship between TCM and liver cancer research with molecular biology, immunology, nutrition, genetics, and veterinary medicine.

There are 419 Chinese-language journals publishing TCM-related liver cancer research. As shown in Table 4, the top five journals by publication volume are the *Chinese Journal of Integrated Traditional and Western Medicine on Liver Diseases* (128 articles), *Journal of Oncology in Chinese Medicine* (55 articles), *Clinical Journal of Chinese Medicine* (46 articles), *Guiding Journal of Traditional Chinese Medicine and Pharmacology* (44 articles), and *Chinese Archives of Traditional Chinese Medicine* (43 articles). The top 10 journals account for 499 articles, representing 16.2% of the total.

The purpose of co-citation analysis is to identify frequently cited publications in the field. Using VOSviewer software, we visualized 100 co-cited journals with citation counts of 173 or higher. Figure 17 displays the resulting co-citation map, where the journal co-citation network is divided into four clusters, corresponding to the four colors in Figure 17. The red cluster focuses on the mechanisms of HCC occurrence, the green cluster emphasizes the study of TCM in HCC prevention and treatment at the cellular level, the blue cluster centers on clinical and mechanistic research of TCM in HCC prevention and treatment, while the yellow cluster highlights pharmacological and efficacy studies of TCM compounds or monomers for HCC prevention and treatment. As shown in Table 5, the top 3 most cited journals are *Journal Of Ethnopharmacology, Hepatology, Biomedicine & Pharmacotherapy*. All three journals are in the JCR Q1 category and are well-known in the fields of traditional medicine research or hepatocellular carcinoma.

Keyword Analysis

Keywords summarize the core essence of articles, and analyzing keyword co-occurrence can reveal research hotspots in scientific fields. Using VOSviewer software, we generated keyword co-occurrence network visualizations for 1,417 English articles and 3,073 Chinese articles, visualizing 210 English keywords with frequency ≥10 and 162 Chinese keywords with frequency ≥9, as shown in Figures 18 and 19. In this study, although the number of Chinese articles was 2.1 times that of English articles, the number of Chinese keywords with frequency >9 was fewer than English keywords with frequency >10. Despite the larger quantity of Chinese literature, their research topics appeared more concentrated compared to English literature.

Figure 18 shows that recent research hotspots in English literature include ferroptosis, molecular docking, bioinformatics, molecular mechanism, bioavailability, luteolin, network pharmacology, antibacterial, prognosis, drug discovery, gut microbiota, glycolysis, and lipid metabolism. Figure 19 shows that Chinese literature's recent hotspots include molecular docking, cancer-related fatigue, data mining, medication rules, Huaier granules, gut microbiota, tumor markers, network pharmacology, TME, classical Chinese medicine formulas, bioinformatics, TCM syndrome scores, transcriptomics, immunotherapy, TCM monomers, immunomodulation, liver cancer stem cells, retrospective studies, embolism syndrome, quercetin, and lenvatinib. There is some overlap in research directions between Chinese and English literature, with both increasingly integrating modern technologies (eg, network pharmacology, data mining,

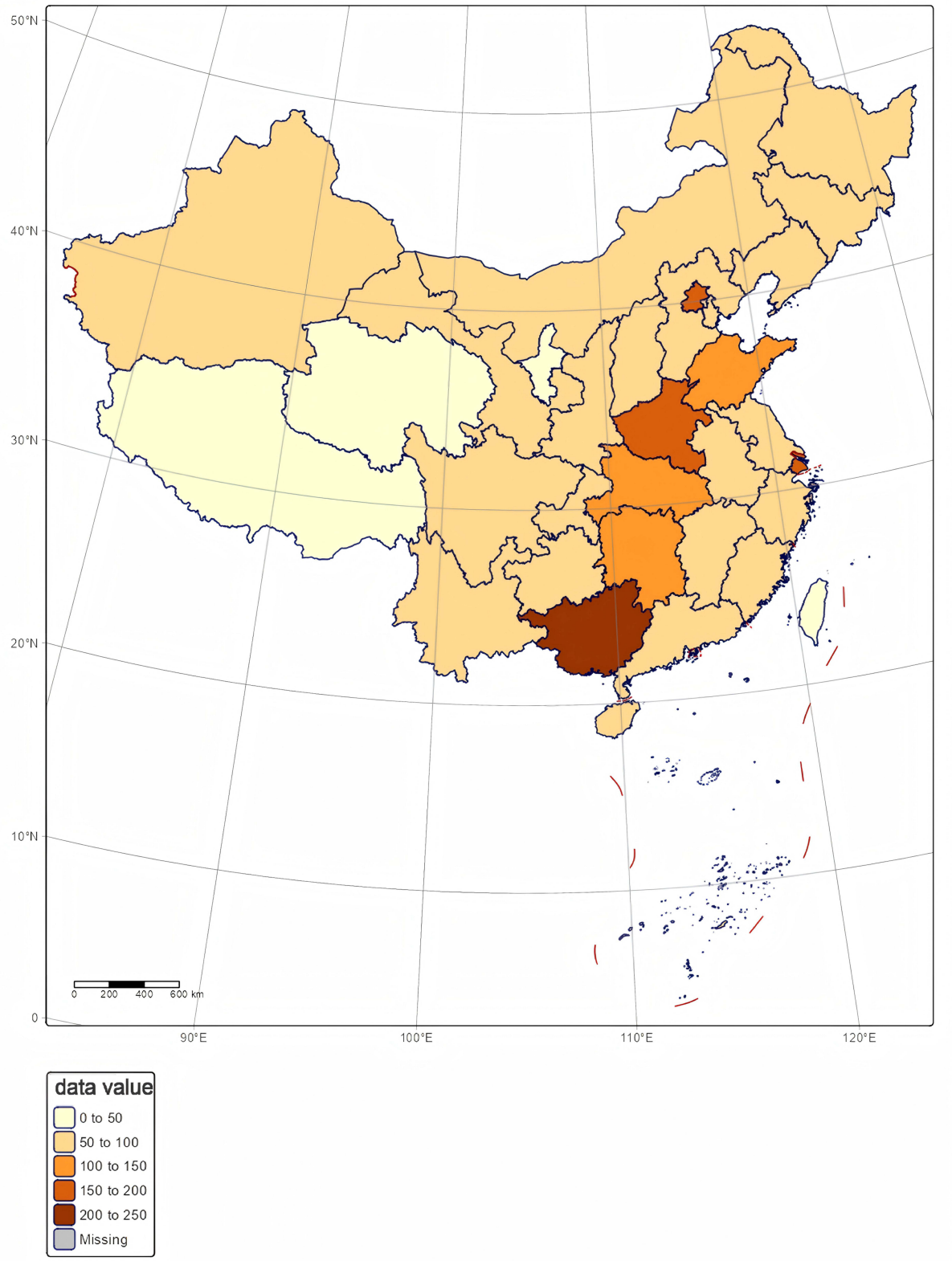

Figure 10 Research institution geographic distribution heatmap.

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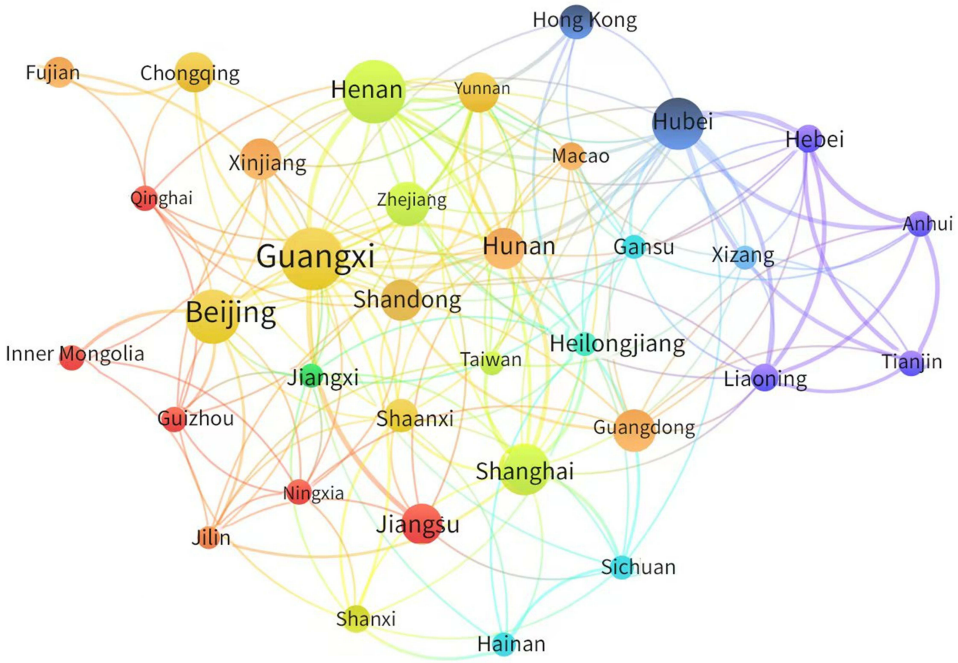

Figure 11 Research institution geographic distribution and collaboration network.

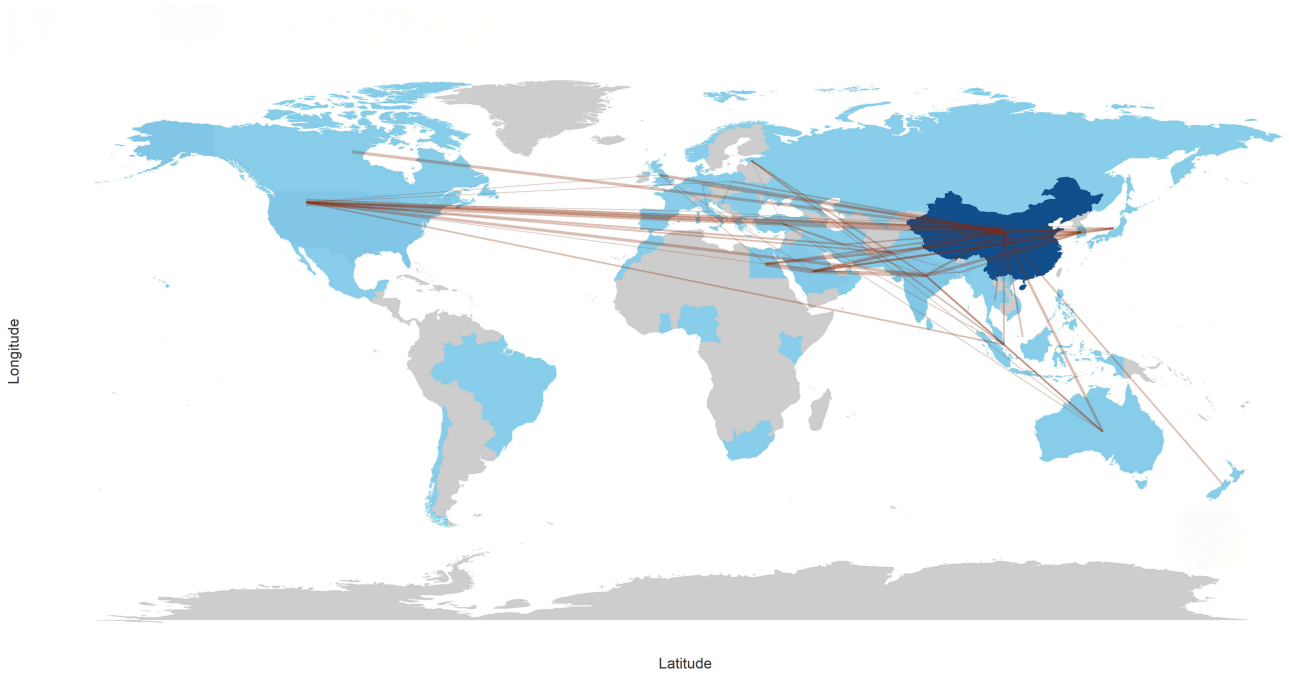

Figure 12 Country/region collaboration network.

molecular docking, transcriptomics, bioinformatics) to explore disease mechanisms and treatments. However, Chinese literature has recently focused more on immunotherapy, TCM syndromes, data mining, medication rules, and classical formulas, emphasizing TCM theories and clinical research on liver cancer, while English literature predominantly centers on experimental studies of molecular mechanisms and pharmacological effects of TCM against liver cancer.

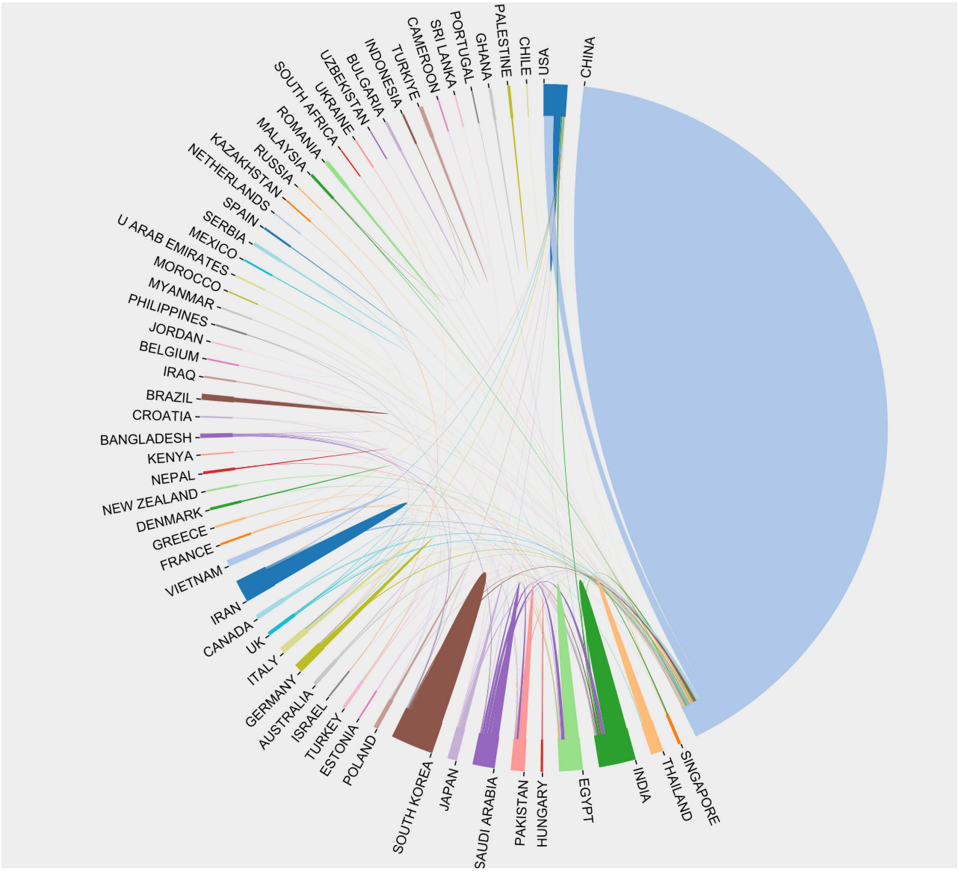

Figure 13 Inter-country/region collaboration chord diagram.

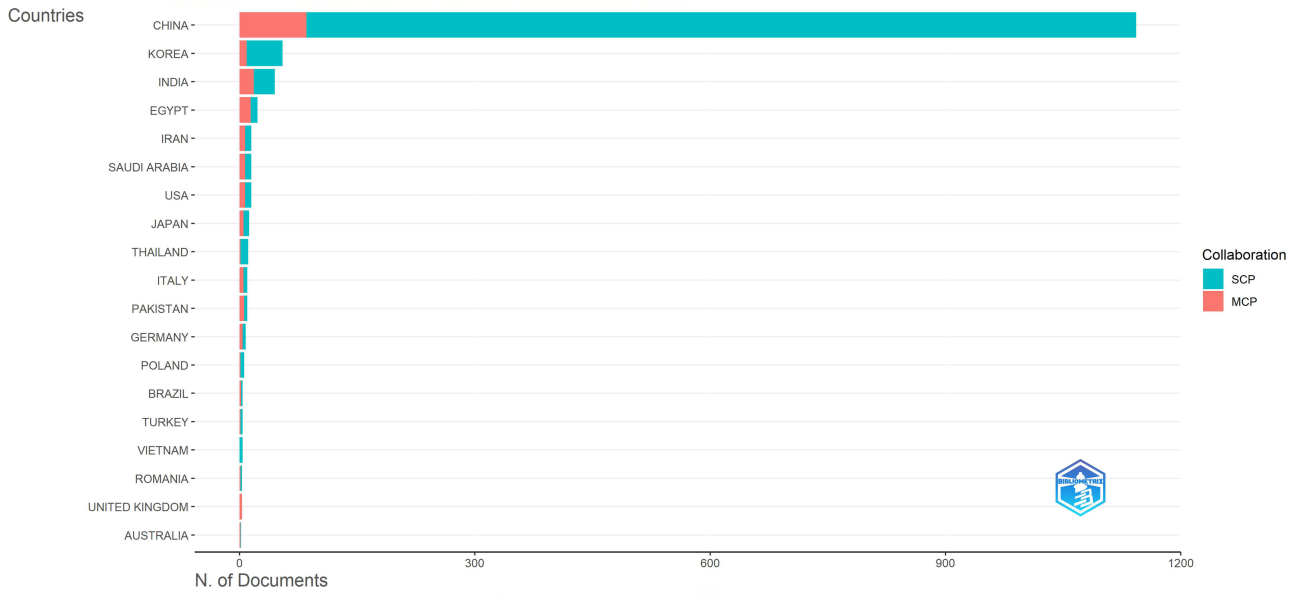

Figure 14 Single vs multi-country collaboration publication statistics. SCP: single country publications, MCP: multiple country publications.

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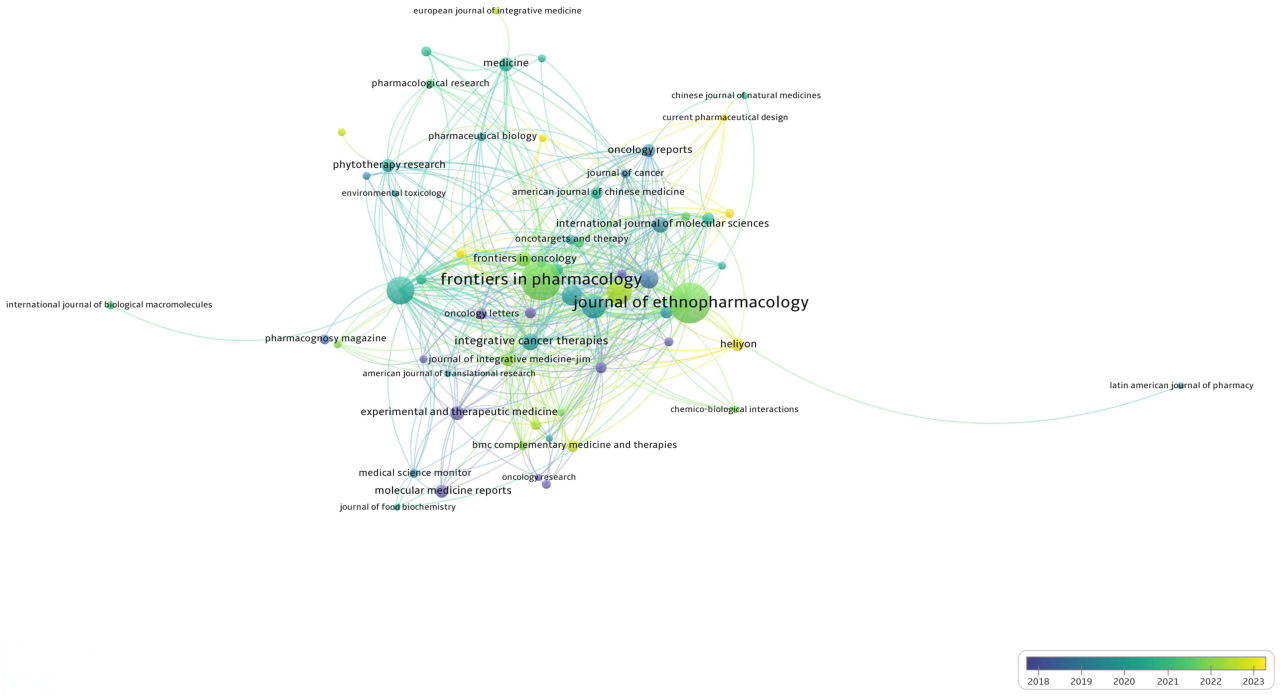

Figure 15 English literature journal distribution and collaboration network.

This study analyzed the top 30 high-frequency keywords in Chinese and English literature. As shown in Table 6 and Figures 18, apart from "hepatocellular carcinoma," "traditional Chinese medicine," and "liver cancer," high-frequency English keywords include apoptosis, pathway, expression, activation, in-vitro, growth, proliferation, NF-κB, inhibition, mechanism, network pharmacology, invasion, migration, cell cycle arrest, and autophagy. Analysis of high-frequency keyword-related literature reveals that English studies focus on pharmacological effects and mechanisms of TCM against liver cancer, often using network pharmacology and in vitro experiments to explore TCM's regulation of apoptosis,

Table 4 Top 10 Journals by Publication Volume

No.	Chinese Journal	Publications (articles)	Impact Factor	No.	English Journal	Publications (articles)	Citations/ times	IF	JCR
1	*Chinese Journal of Integrated Traditional and Western Medicine on Liver Diseases*	128	1.398	1	*Journal of Ethnopharmacology*	107	1289	4.8	Q1
2	*Journal of Traditional Chinese Medicine Oncology*	55	1.893	2	*Frontiers In Pharmacology*	104	1714	4.4	Q1
3	*Clinical Journal of Chinese Medicine*	46	0.784	3	*Evidence-based Complementary And Alternative Medicine*	54	529	NA	NA
4	*Guiding Journal of Traditional Chinese Medicine and Pharmacy*	44	2.267	4	*Phytomedicine*	45	1027	6.7	Q1
5	*Chinese Archives of Traditional Chinese Medicine*	43	4.167	5	*Biomedicine & Pharmacotherapy*	43	1305	6.9	Q1
6	*Journal of Clinical Hepatol*	40	1.836	6	*Molecules*	30	607	4.2	Q2
7	*Chinese Medicine Modern Distance Education of China*	39	0.703	7	*Scientific Reports*	27	771	3.8	Q1
8	*Liaoning Journal of Traditional Chinese Medicine*	38	2.167	8	*Integrative Cancer Therapies*	23	231	2.9	Q2
9	*Journal of Sichuan of Traditional Chinese Medicine*	33	1.367	9	*International Journal of Molecular Sciences*	21	821	4.9	Q1
10	*Hebei journal of traditional Chinese medicine*	33	1.418	10	*Frontiers In Oncology*	18	316	3.5	Q2

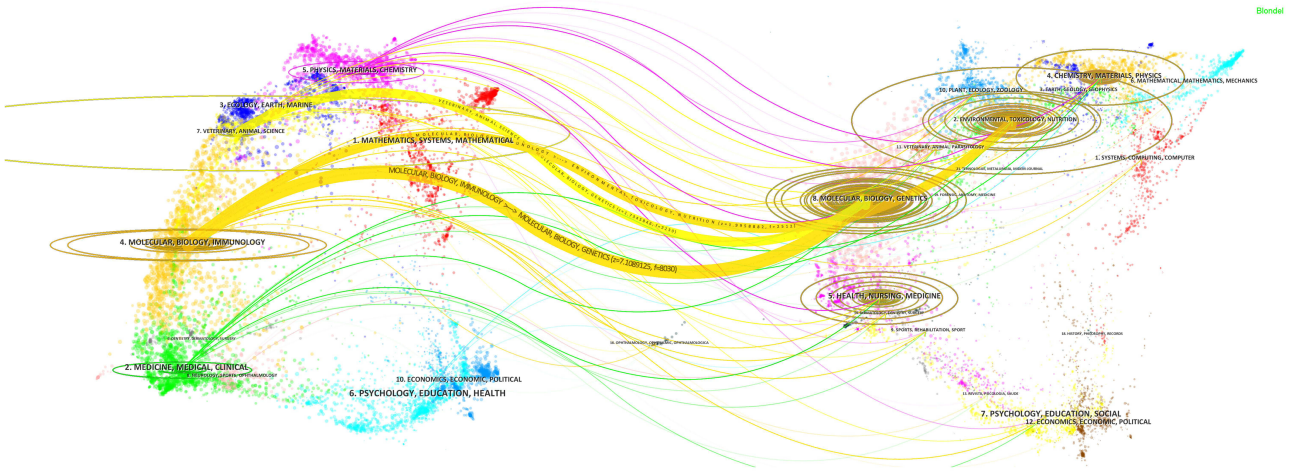

Figure 16 English literature journal dual-map overlay.

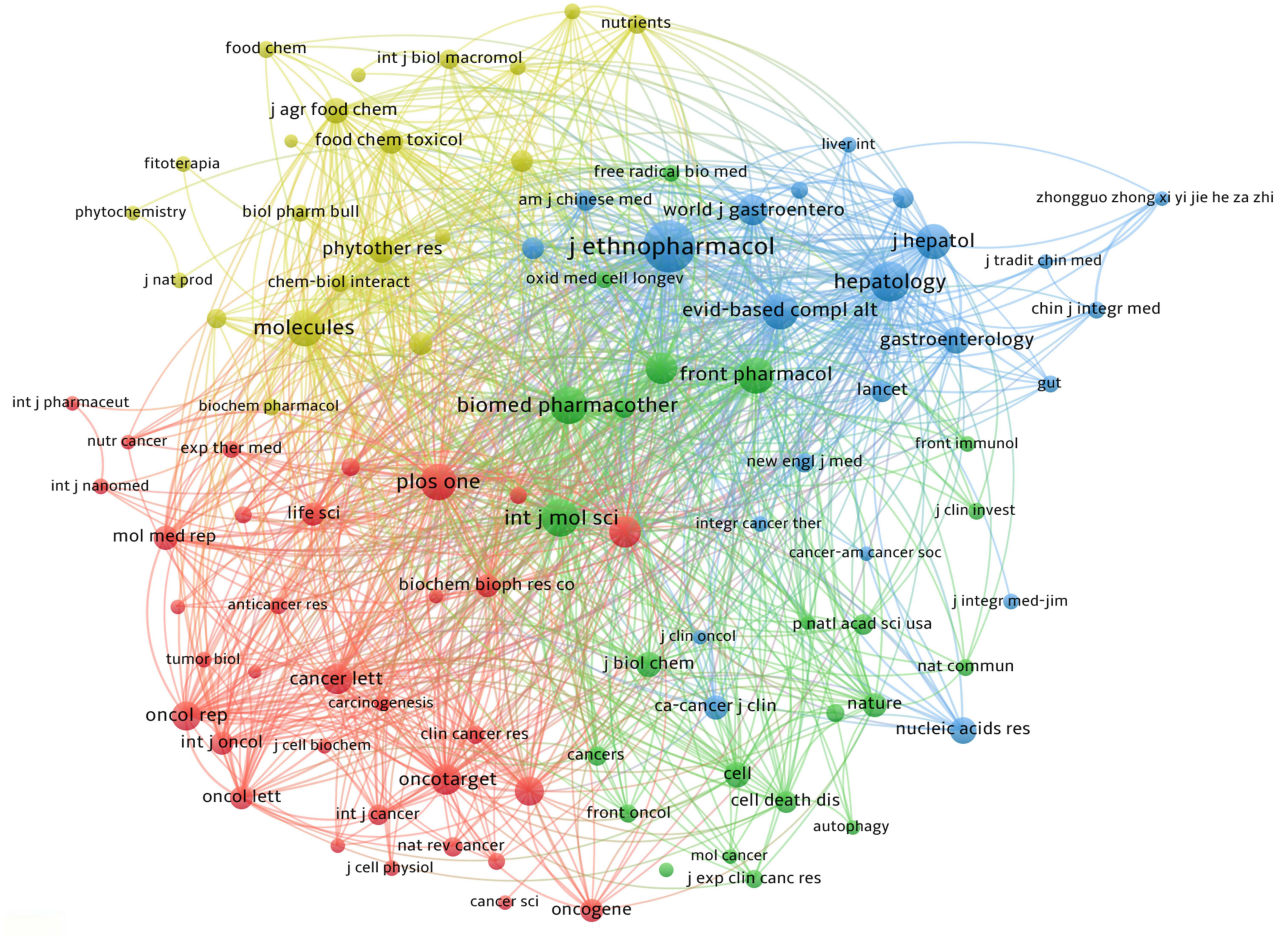

Figure 17 English literature co-cited journal visualization.

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Table 5 Top 10 Co-Cited Journals by Citation Frequency

Ranking	English Literature Journals	Citation Count/Times	Ranking	English Literature Journals	Citation Count/times
1	*Journal Of Ethnopharmacology*	1842	6	*Molecules*	965
2	*Hepatology*	1151	7	*Frontiers in Pharmacology*	964
3	*Biomedicine & Pharmacotherapy*	1055	8	*Evidence-based Complementary And Alternative Medicine*	956
4	*International Journal of Molecular Sciences*	1022	9	*Journal Of Hepatology*	901
5	*Plos One*	974	10	*Phytomedicine*	769

proliferation, invasion, signaling pathways, cell cycle arrest, and autophagy. Based on keyword linkage counts, apart from "hepatocellular carcinoma," "traditional Chinese medicine," and "liver cancer," apoptosis (206 links), pathway (182), in-vitro (176), activation (172), expression (168), mechanism (161), growth (160), proliferation (157), inhibition (154), NF-κB (154), oxidative stress (146), metastasis (137), network pharmacology (133), cell cycle arrest (131), inflammation (130), and autophagy (125) have broad connections and strong influence. CiteSpace statistics show centrality >0.1 for keywords like cell cycle arrest (0.19), induced apoptosis (0.17), anticancer activity (0.16), cancer therapy (0.16), molecular docking (0.15), cell death (0.15), fibrosis (0.15), carbon tetrachloride (0.15), molecular mechanisms (0.15), angiogenesis (0.13), antioxidant (0.12), liver fibrosis (0.11), hepatic stellate cells (0.11), gene

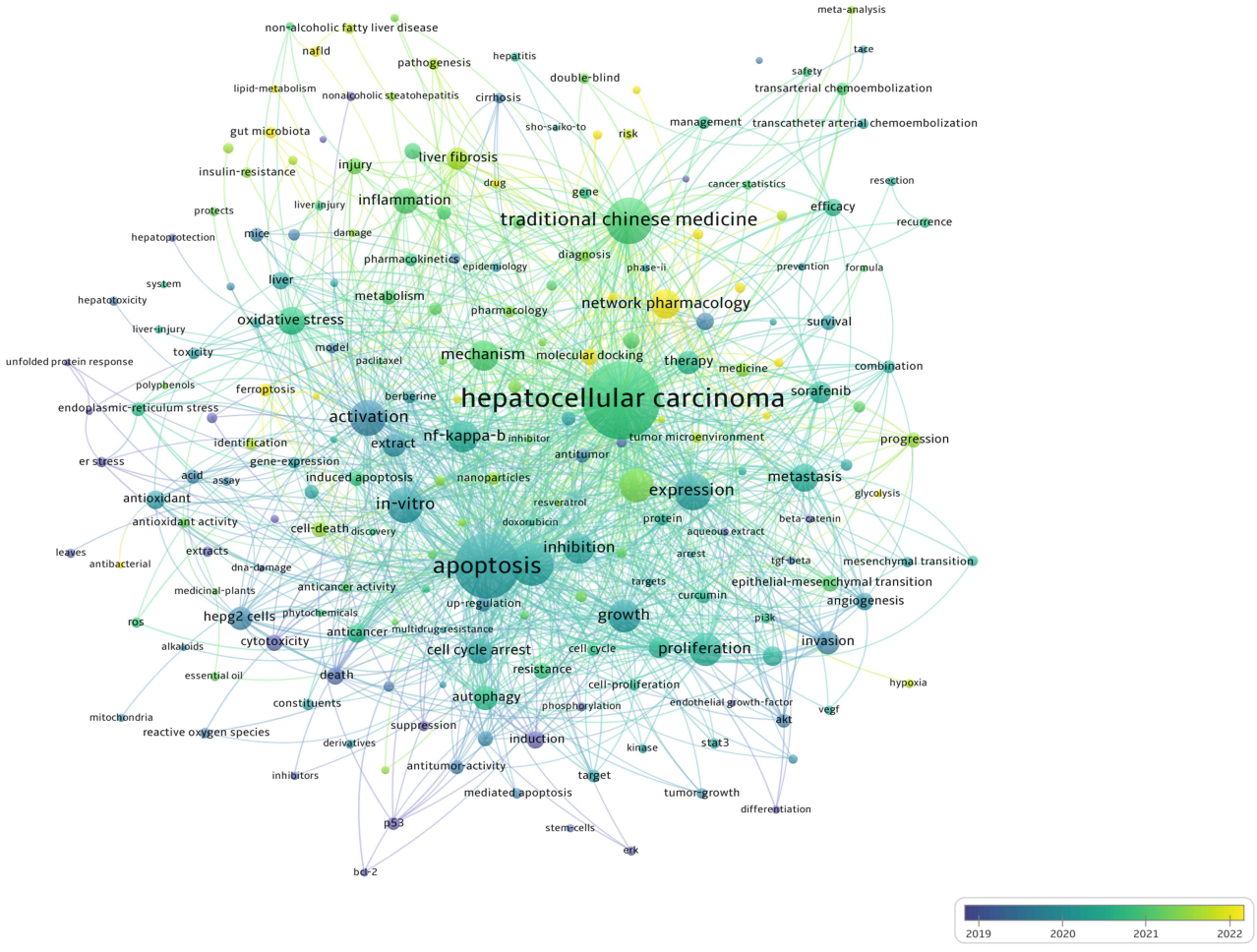

Figure 18 English literature keyword co-occurrence network.

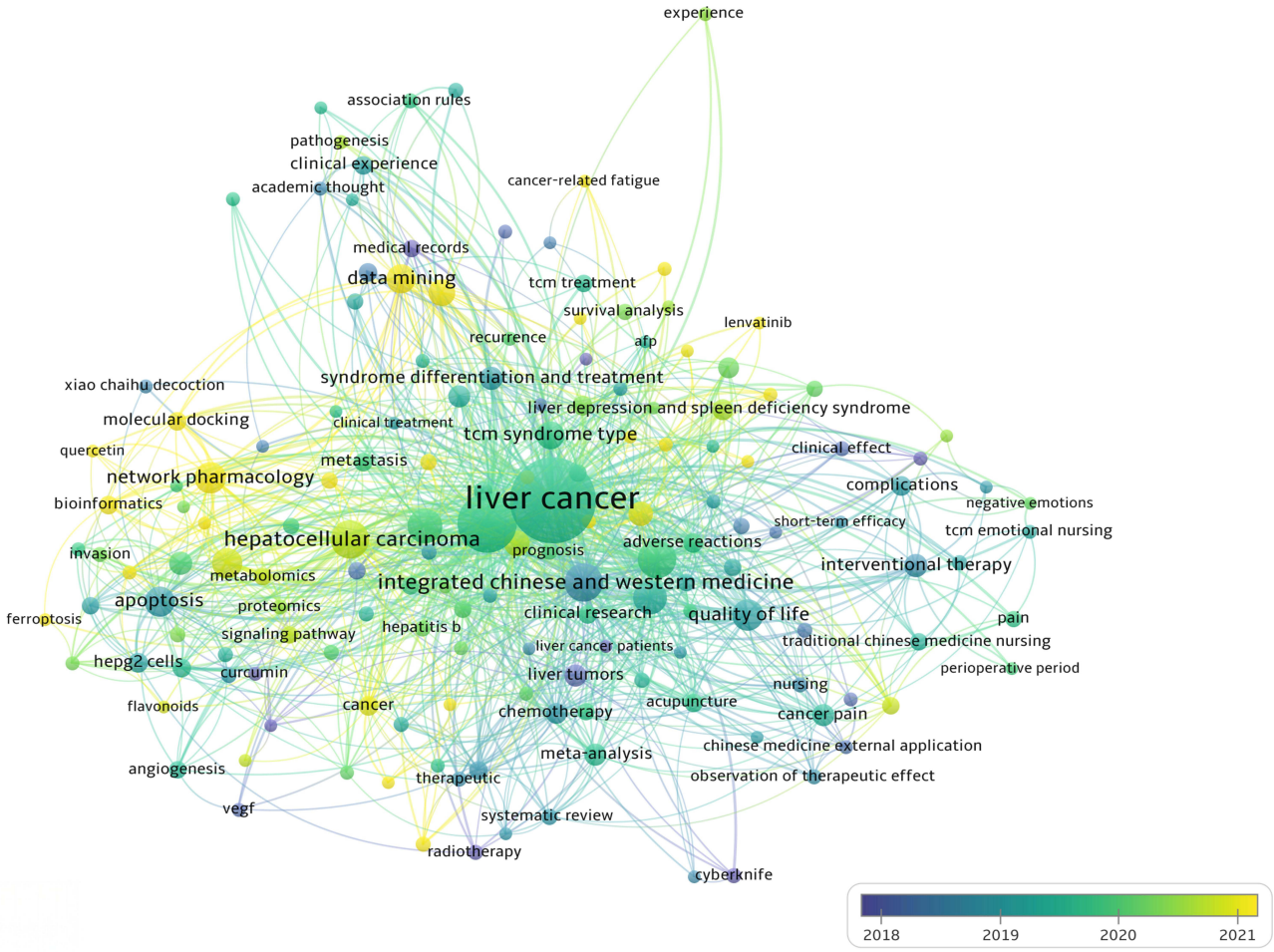

Figure 19 Chinese literature keyword co-occurrence network.

expression (0.11), endothelial growth factor (0.11), hepatitis (0.11), and constituents (0.1), indicating their strong associations and foundational role in specialized research areas.

As shown in Table 6 and Figures 19, apart from "liver cancer," "traditional Chinese medicine," "integrated Chinese–Western medicine," and "hepatocellular carcinoma," high-frequency Chinese keywords include transarterial

Table 6 Top 30 Most Frequent Keywords

No.	Chinese Literature Keywords	Frequency	No.	English Literature Keywords	Frequency
1	Liver cancer	1988	1	Hepatocellular carcinoma	614
2	Traditional chinese medicine	669	2	Apoptosis	451
3	Integrated traditional chinese and western medicine	232	3	Traditional chinese medicine	239
4	Transarterial chemoembolization	186	4	Pathway	212
5	Hepatocellular carcinoma	151	5	Expression	168
6	Review article	146	6	Activation	154
7	Clinical efficacy	131	7	In-vitro	153
8	Network pharmacology	109	8	Liver cancer	133
9	Apoptosis	104	9	Growth	130
10	Mechanism of action	97	10	Proliferation	130
11	Data mining	92	11	NF-κB	120

(*Continued*)

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Table 6 (Continued).

No.	Chinese Literature Keywords	Frequency	No.	English Literature Keywords	Frequency
12	TCM syndrome type	91	12	Inhibition	113
13	Medication rules	73	13	Mechanism	111
14	Living conditions	68	14	Network pharmacology	103
15	Immune function	66	15	Metastasis	98
16	Liver function	57	16	Oxidative stress	96
17	Interventional therapy	47	17	Inflammation	85
18	Proliferation	46	18	Cell cycle arrest	83
19	Famous doctors'experience	43	19	Autophagy	74
20	Meta-analysis	42	20	HepG2 cells	73
21	Quality of life	40	21	Invasion	70
22	Syndrome differentiation and treatment	40	22	Extract	69
23	TCM syndrome	38	23	Therapy	69
24	Clinical observation	38	24	Liver fibrosis	64
25	Liver depression and spleen deficiency syndrome	38	25	Sorafenib	64
26	Liver cirrhosis	35	26	Down-regulation	57
27	Chemotherapy	34	27	Migration	54
28	Chinese medicine compound	33	28	Antioxidant	48
29	Adverse reactions	33	29	Anticancer	47
30	Clinical research	31	30	Angiogenesis	45

chemoembolization, review article, clinical efficacy, network pharmacology, apoptosis, mechanism, data mining, TCM syndromes, medication rules, quality of life, immune function, liver function, interventional therapy, and proliferation. Analysis reveals some overlap with English literature, such as studies on TCM's mechanisms against liver cancer, exploring its regulation of immunity, apoptosis, autophagy, and proliferation. However, Chinese literature emphasizes clinical research, medication rules, data mining, TCM syndromes, clinical efficacy, clinical observation, quality of life, and adverse effects, focusing more on clinical applications of TCM for liver cancer. Based on keyword linkage counts, apart from "liver cancer," "traditional Chinese medicine," "integrated Chinese–Western medicine," and "hepatocellular carcinoma," transarterial chemoembolization (68 links), clinical efficacy (58), review article (57), apoptosis (49), network pharmacology (48), quality of life (45), immune function (43), data mining (43), mechanism (42), TCM syndromes (41), adverse effects (36), proliferation (36), meta-analysis (34), liver function (34), clinical research (31), alpha-fetoprotein (31), interventional therapy (30), autophagy (30), chemotherapy (29), and syndrome differentiation (29) have broad connections and strong influence. CiteSpace statistics show centrality >0.15 for keywords like embolism syndrome (0.36), alpha-fetoprotein (0.36), liver function (0.33), acupuncture (0.28), gut microbiota (0.26), liver cancer (0.23), vascular endothelial growth factor (VEGF) (0.21), invasion (0.19), liver cancer cells (0.19), TCM pharmacology (0.19), complications (0.19), TCM syndrome scores (0.18), cell cycle (0.17), advanced stage (0.17), TCM active components (0.15), and liver fibrosis (0.15), indicating their strong associations and foundational role in specialized research areas.

Analysis of high-frequency keywords combined with Figures 18 and 19 reveals that the most-studied symptoms of liver cancer in this field are cancer-related fatigue and cancer pain. The main adverse reactions studied in liver cancer patients after transarterial chemoembolization (TACE) are post-embolization syndrome and nausea/vomiting. The primary risk factors for liver cancer under investigation include cirrhosis, viral hepatitis, non-alcoholic fatty liver disease, liver fibrosis, and metabolic syndrome. The predominant accompanying negative emotions are anxiety and depression. The main studied TCM syndromes are spleen deficiency syndrome (as a distinct pattern), liver depression and spleen deficiency syndrome, dampness-heat syndrome, qi stagnation and blood stasis syndrome, liver-kidney yin deficiency syndrome, liver qi stagnation syndrome, and phlegm-blood stasis syndrome, with liver depression and spleen deficiency syndrome being the most prominent. Common TCM treatment methods include fortifying the spleen and soothing the

liver, supporting healthy qi and consolidating the root, regulating qi and resolving phlegm to dispel stasis, detoxifying and combating cancer, clearing heat and detoxifying, and replenishing qi and nourishing yin. The primary herbs studied are *Oldenlandia diffusa (Willd). Roxb, Scutellaria barbata D.Don, Curcuma aeruginosa Roxb, Akebiae Fructus, Astragalus membranaceus (Fisch). Bunge*, Panax *quinquefolius L, Ganoderma lucidum (Curtis) P. Karst, Scutellaria baicalensis Georgi, Angelica sinensis (Oliv). Diels, Panax ginseng C.A.Mey, Coptis chinensis Franch*, and *Actinidia chinensis Planch*. Frequently studied formulas include Fuhe Beihua Formula, Xiaochaihu Decoction, Biejia Jian Pill, Ganji Formula, Yipi Yanggan Formula, Dahuang Zhechong Pill, Shuyu Pill, Xiao'ai Jiedu Formula, Jianpi Huayu Formula, Fuzheng Xiaozheng Formula, Yinchenhao Decoction (YCHD), Ganfu Formula, Yiguan Jian, Sijunzi Decoction. Common Chinese patent medicines include Huaier Granule, Cinobufagin (CB), Aidi Injection, Compound Mylabris Capsule, Xihuang Pill, Compound Kushen Injection (CKI), Cidan Capsule, Kangai Injection, Pien Tze Huang. The main studied active compounds are curcumin, quercetin, luteolin, glycyrrhetinic acid, astragaloside IV, berberine (BB), β-sitosterol, emodin, gallic acid, resveratrol (Res), matrine, silymarin, ginsenoside Rg3, and celastrol (CeT). Commonly used TCM external therapies include acupuncture, acupoint application, acupoint injection, and auricular plaster therapy.

Analysis of high-frequency keywords combined with Figures 18 and 19 reveals that research themes on TCM for liver cancer treatment can be broadly categorized into the following 8 groups: 1. TCM treatment methods and theories. This includes studies on TCM diagnostic systems for liver cancer, such as Syndrome differentiation of six meridians, TCM constitution, TCM syndrome distribution in liver cancer, and "treating different diseases with the same method." Research on characteristic TCM therapies includes acupuncture, moxibustion, acupoint application, external herbal compresses, herbal enemas, emotional nursing, auricular plaster therapy, and bloodletting therapy. Studies on TCM treatment principles focus on reinforcing healthy qi and consolidating the root, promoting blood circulation and resolving stasis, clearing heat and detoxifying, soothing the liver and strengthening the spleen, and replenishing qi and nourishing yin. Research on TCM theory and inheritance involves exploring, summarizing, and passing down renowned physicians' experiences, as well as analyzing medical records. These efforts have contributed to discussions on the etiology and pathogenesis of liver cancer and the formation of diagnostic systems. 2. Research on TCM formulas and drugs. This includes classical formulas like Xiaochaihu Decoction, YCHD, Sijunzi Decoction, Biejiajian pills, Shuyu pill, and Xuefu Zhuyu Decoction. Modern compound formulas and single herbs include CKI, cinobufotalin, Huaier Granules, Cidan Capsules, *Astragalus membranaceus (Fisch). Bunge, Oldenlandia diffusa (Willd). Roxb, Scutellaria barbata D.Don*. Active components of Chinese herbs such as ginsenosides, matrine, emodin, BB, and luteolin. Innovations in TCM formulations include nanotechnology applications and targeted delivery systems (eg, liposome co-delivery systems). 3. Combination therapies. Examples include integrating TCM with interventional therapies, surgery, or radiotherapy (eg, transarterial chemoembolization (TACE), radiofrequency ablation, microwave ablation, CyberKnife). TCM combined with targeted therapy, chemotherapy, or immunotherapy (eg, sorafenib, lenvatinib, oxaliplatin, camrelizumab, cisplatin). 4. Clinical research and evaluation metrics for TCM in liver cancer treatment. Efficacy evaluations include survival rate, quality of life, overall survival, and recurrence/metastasis. Safety evaluations cover adverse reactions and toxic side effects. Study designs include meta-analyses, retrospective studies, real-world research, and cohort studies. 5. Application of research methods and tools. Examples are data mining, bibliometrics, network pharmacology, deep learning, molecular docking, bioinformatics, transcriptomics, proteomics, metabolomics, and high-throughput sequencing. 6. Research on TCM's impact on liver cancer symptoms and risk factors. Symptoms include cancer pain, ascites, fever, jaundice, and nausea/vomiting. Risk factors include cirrhosis, liver fibrosis, and viral hepatitis. 7. Biological mechanisms and signaling pathways of TCM in liver cancer treatment. Experimental models often use H22 tumor-bearing mice or HepG2 cells. Key pathways involve PI3K/AKT, MAPK, Wnt/β-catenin, NF-κB, HIF-1α, VEGF, JNK, Nrf2, and STAT3. Tumor biological processes include apoptosis, autophagy, EMT, angiogenesis, immune microenvironment, gut microbiota, endoplasmic reticulum stress, and glycolysis. Molecular mechanisms involve gene expression, lncRNA, microRNA, ferroptosis, metabolomics, proteomics, and transcriptomics. 8. TCM's influence on liver cancer diagnosis and detection markers. Biomarkers include alpha-fetoprotein (AFP), VEGF, and tumor markers. Imaging and functional assessments include magnetic resonance imaging (MRI), liver function, and immune function.

Using CiteSpace software's LLR algorithm to cluster keywords in Chinese and English literature, the clustering visualization results are shown in Figures 20 and 21. Tables 7 and 8 list information such as the size, silhouette value, year, and representative keywords for each cluster.

The Q value for Chinese literature is 0.8864 (>0.3), confirming that the community structure division of this map is significant. The S value is 0.9583 (>0.7), indicating that the clustering is not only efficient but also highly convincing,[22] resulting in a total of 19 clusters. Among them, Cluster #0 is the largest, indicating the highest level of interest. Clusters #6 primarily focus on famous medical case studies or summarizing the experiences of renowned physicians through data mining to analyze medication rules, thereby exploring the traditional Chinese medicine etiology and pathogenesis of liver cancer. Clusters #2, #7, #8, #10, #11, #14, #15, #16, and #18 concentrate on clinical research of traditional Chinese medicine (TCM) in treating liver cancer, including TCM's effects on adverse reactions caused by chemotherapy, targeted therapy, radiofrequency ablation, etc., TCM's impact on the quality of life and survival of liver cancer patients, clinical studies on the efficacy of TCM combined with targeted therapy, chemotherapy, interventional therapy, etc., clinical applications of classical TCM prescriptions like Xihuang Pill and Xiaochaihu Decoction, the application of TCM nursing concepts during the perioperative period of liver cancer, and observations on the clinical efficacy of TCM prescriptions such as Modified Chai Shao Liu Junzi Decoction, Buyi Xiaozheng Decoction, and Jiedu Shugan Decoction on post-interventional complications and liver cancer complications. Other areas include clinical efficacy analysis of TCM in treating mid-to-late-stage liver cancer, safety studies of Chinese herbal medicine and compound prescriptions against

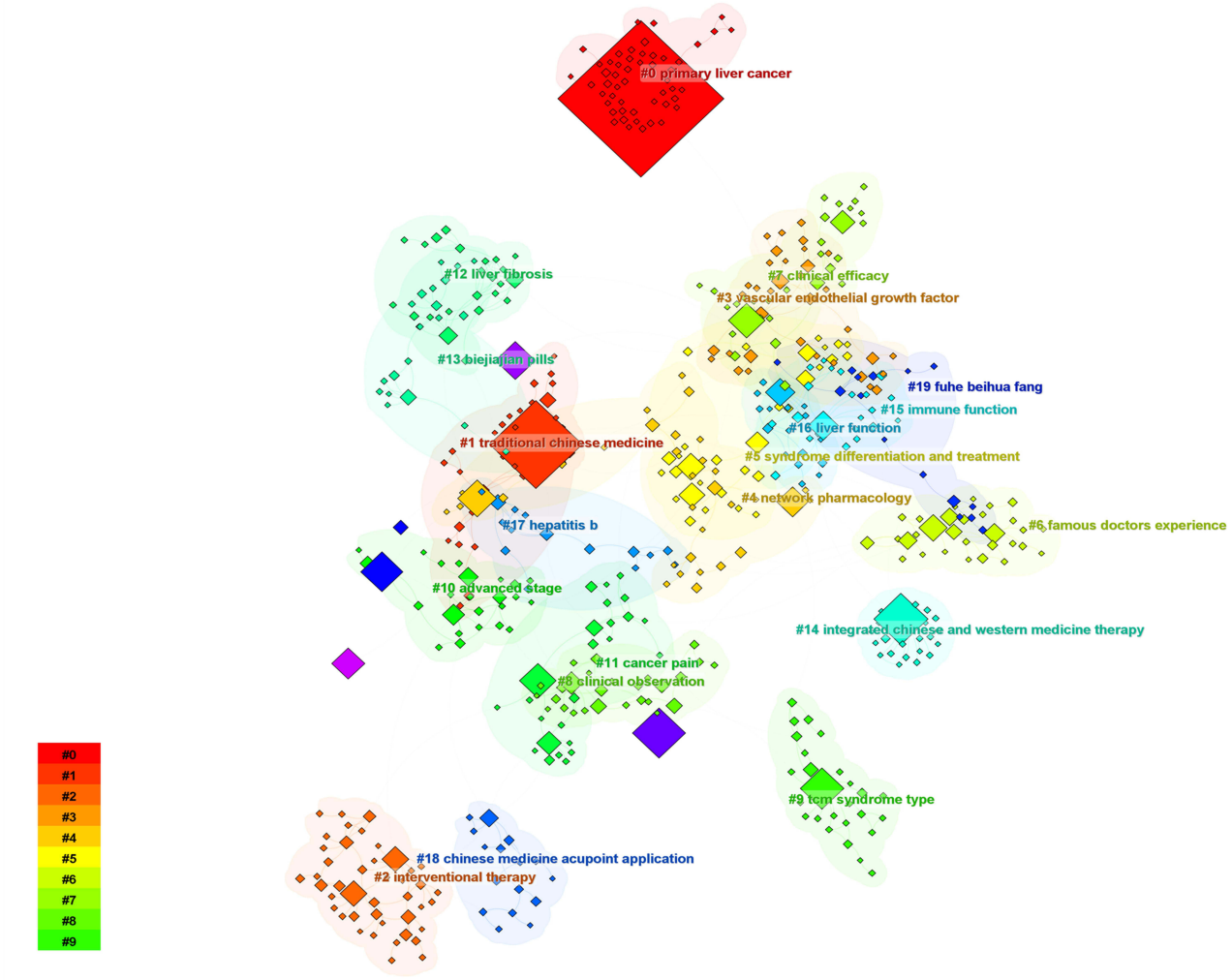

Figure 20 Keyword clustering map of Chinese literature.

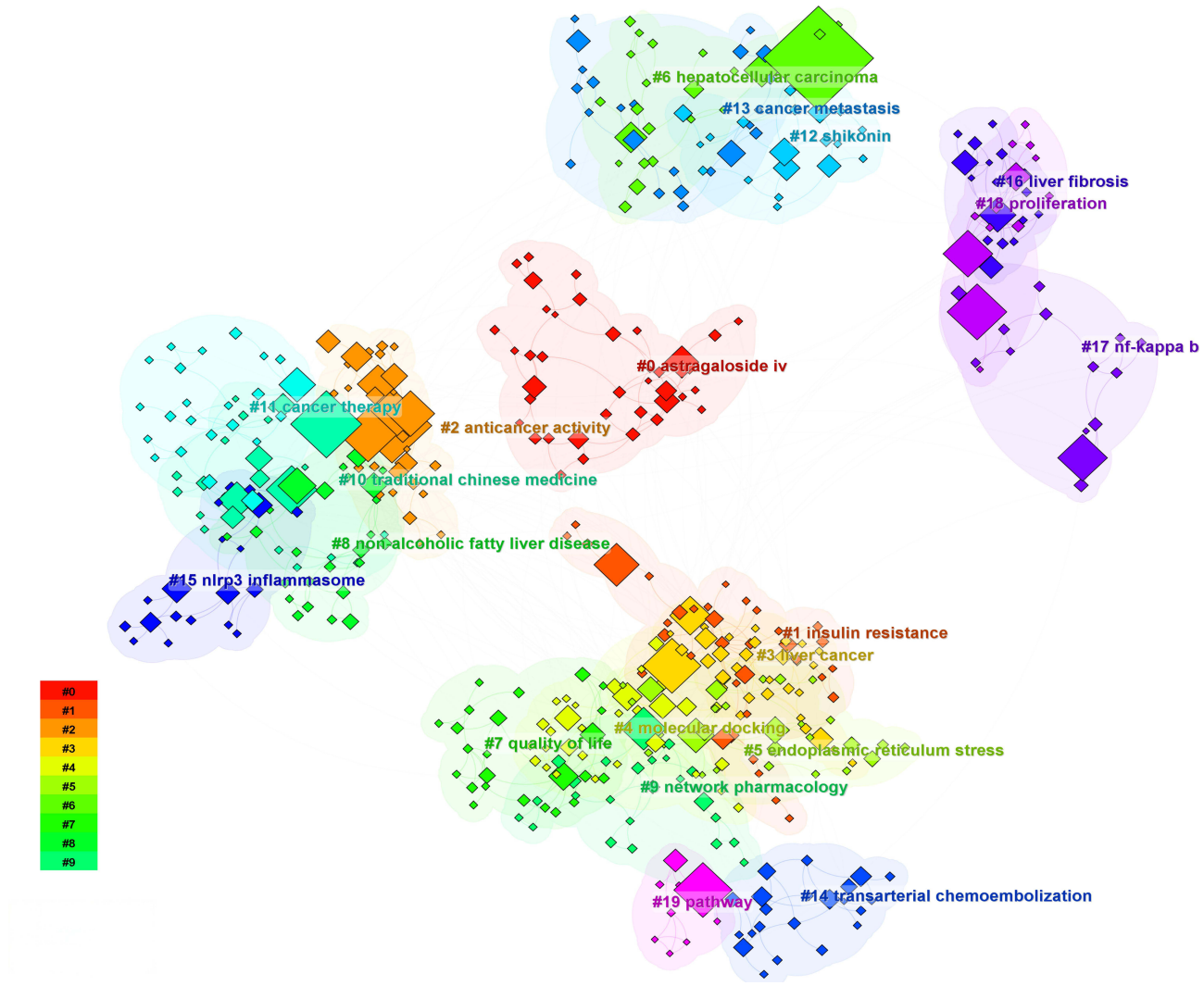

Figure 21 Keyword clustering map of English literature.

liver cancer, consensus on integrated Chinese and Western medicine diagnosis and treatment of liver cancer. Clusters #0, #1, #3, and #4 primarily focus on mechanistic research of TCM in treating liver cancer, including its effects on migration, intestinal flora, VEGF etc., and using network pharmacology to study the anti-liver cancer mechanism of traditional

Table 7 Chinese Literature Keyword Cluster Analysis

ClusterID	Size	Silhouette	Mean (Year)	Label (LLR)
0	62	1	2019	Primary liver cancer; liver cancer; hepatocellular carcinoma; metastasis; integration of traditional chinese and western medicine
1	43	0.961	2020	Traditional chinese medicine; chinese medicine; traditional chinese medicine treatment; intestinal flora; chronic liver disease
2	43	0.962	2019	Interventional therapy; perioperative period; traditional chinese medicine nursing; tcm emotional nursing; tcm nursing
3	36	0.937	2018	Vascular endothelial growth factor; hepatocellular carcinoma cells; pharmacology of traditional chinese medicine; short-term efficacy; liver neoplasms

(*Continued*)

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Table 7 (Continued).

ClusterID	Size	Silhouette	Mean (Year)	Label (LLR)
4	34	0.907	2018	Network pharmacology; clinical application; medication rules; xihuang pills; primary liver cancer
5	31	0.98	2017	Syndrome differentiation and treatment; research progress; efficacy evaluation; chinese medicine compound; liver depression and spleen deficiency
6	30	0.943	2017	Famous doctors experience; medical records; chinese medicine treatment; cidan capsule; clinical experience
7	30	0.934	2020	Clinical efficacy; cell apoptosis; toxicity and side effects; survival rate; chinese medicine prescription
8	27	0.986	2017	Clinical observation; hepatic arterial chemoembolization; chinese medicine external application; combination of traditional chinese and western medicine; cohort study
9	26	0.948	2018	Tcm syndrome type; tcm syndrome; objective index; clinical characteristics; systematic review
10	25	0.945	2019	Advanced stage; adverse reactions; combined therapy; targeted therapy; huachansu injection
11	25	0.887	2018	Cancer pain; data mining; chronic hepatitis b; external application of traditional chinese medicine; hepatitis b-related liver cancer
12	24	0.988	2016	Liver fibrosis; liver cirrhosis; literature research; liver failure; hepatic stellate cells
13	24	0.991	2020	biejiajian pills; cell proliferation; high-throughput sequencing; cell cycle; immune cells
14	23	1	2018	Integrated chinese and western medicine therapy; treatment with integrated traditional chinese and western medicine; integration of traditional chinese and western medicine; liver tumor/integrated chinese and western medicine therapy; consensus
15	22	0.96	2017	Immune function; huangqi sijunzi decoction; huaier granules; jianpi liqi yiliu fang; advanced hepatocellular carcinoma
16	17	0.883	2020	Liver function; inflammatory factors; arterial embolization; yipi yanggan recipe; soothing the stomach and promoting bile secretion
17	17	0.947	2017	Hepatitis b; malignant tumors; hepatitis b virus; bielongruangan decoction; neutrophil/lymphocyte ratio
18	16	0.993	2020	Chinese medicine acupoint application; hepatic artery infusion chemotherapy; laparoscopic liver resection; application effect; gastrointestinal function recovery
19	15	0.958	2019	Fuhe beihua fang; spleen deficiency; blood stasis; t lymphocyte subsets; chemoembolization

Table 8 English Literature Keyword Cluster Analysis

ClusterID	Size	Silhouette	Mean (Year)	Label (LLR)
0	38	0.783	2018	Astragaloside iv; traditional chinese medicine; pd-l1; microrna; cytotoxic activity
1	35	0.87	2019	Insulin resistance; oxidative stress; hepatocellular carcinoma; nonalcoholic fatty liver; high fat diet
2	34	0.833	2019	Anticancer activity; cell cycle arrest; cell death; autophagy; activation
3	32	0.866	2018	Liver cancer; cell growth; randomized controlled trial; primary liver cancer; polysaccharides
4	31	0.808	2020	Molecular docking; apoptosis; traditional chinese medicine; beta-sitosterol; lactobionic acid
5	30	0.907	2017	Endoplasmic reticulum stress; er stress; fatty liver disease; liver cancer; network pharmacology
6	26	0.859	2018	Hepatocellular carcinoma; tumor microenvironment; huaier; doxorubicin; pi3k/akt signaling pathway
7	25	0.864	2018	Quality of life; immune function; systematic review; epithelial-mesenchymal transition; element
8	25	0.88	2020	NON-alcoholic fatty liver disease; fibrosis; nafld; hepatocellular carcinoma; NASH

(*Continued*)

Table 8 (Continued).

ClusterID	Size	Silhouette	Mean (Year)	Label (LLR)
9	24	0.966	2022	Network pharmacology; experimental verification; apoptosis; deep learning; drug discovery
10	24	0.912	2017	Traditional chinese medicine; survival; resection; chinese herbal medicine; therapy
11	23	0.925	2020	Cancer therapy; gastrointestinal cancer; complementary alternative medicine; huaier granule; migration
12	23	0.716	2017	Shikonin; epithelial-mesenchymal transition (emt); chinese herb; caspases
13	23	0.921	2019	Cancer metastasis; cell migration; tcm prescription; igfbp1; mulberry leaf extract
14	22	0.925	2018	Transarterial chemoembolization; combination therapy; unresectable hepatocellular carcinoma; biliary cancer; glucose metabolism
15	20	0.912	2018	Nlrp3 inflammasome; antibacterial activity; caspase-3; constituents; hepg2 cells
16	17	0.951	2018	Liver fibrosis; hepatic stellate cells; hepatic stellate cell; diwu yanggan; hepatic fibrosis
17	16	0.923	2017	Nf-kappa b; traditional chinese medicine; reactive oxygen species; network pharmacology; nuclear factor-kappa b
18	14	0.957	2016	Proliferation; cellular stiffness; expression; akt; chloroquine
19	9	1	2022	Pathway; hepatocellular; anti-angiogenic; suppression; cell cycle phases

Chinese medicine. Clusters #5 and #9 mainly study TCM syndrome type in liver cancer, such as clinical objective indicators of TCM syndromes. Clusters #12 and #17 explores TCM's impact on risk factors for liver cancer occurrence, such as liver fibrosis, hepatitis b virus. Clusters # 13 and # 19 mainly focus on the research of traditional Chinese medicine formulas for anti-liver cancer, such as Biejia Jian Pills and Fuhe Beihua Fang.

For English literature, the Q-value is 0.7351 (>0.3), confirming the significant community structure division of the map. The S-value is 0.875 (>0.7), indicating that the clustering is not only efficient but also highly convincing. A total of 20 clusters were obtained. Clusters #2, #3, #4, #5, #6, #9, #13, #15, #17, #18, and #19 involve studies on the mechanisms and molecular targets of TCM in treating liver cancer using network pharmacology, molecular docking, deep learning, and experimental validation. Clusters #0 and #12 focus on research of anti-liver cancer Chinese herbs and monomeric compounds. Clusters #7, #10, #11, and #14 evaluate the clinical efficacy of TCM in treating liver cancer and multi-disciplinary integrated therapy. Clusters #1, #8, and #16 study TCM's impact on risk factors for liver cancer occurrence, such as non-alcoholic fatty liver disease, liver fibrosis, and insulin resistance.

In an effort to delve into the historical development and transformation of the research area concerning TCM in the prevention and treatment of liver cancer, we used CiteSpace software to map the keyword co-occurrence network in the form of a timeline graph (Figures 22 and 23). This illustration presents the evolutionary shifts in the focal areas of research within this particular domain over the past few years.

Findings reveal that the English-language literature can be categorized into 20 major clusters. Each of these clusters aligns with the research hotspots that emerged during a particular timeframe on the chronological timeline. The data reveals that clusters #2 anticancer activity, #3 liver cancer, #4 molecular docking, #5 endoplasmic reticulum stress, #9 network pharmacology, #16 liver fibrosis, #18 proliferation, and #19 pathway are the core themes of this field, spanning the entire research period. The use of molecular docking and network pharmacology to explore the mechanisms of TCM in treating liver cancer—such as inhibiting cell proliferation, improving liver fibrosis, regulating signaling pathways, and inducing endoplasmic reticulum stress—has been a long-standing international research hotspot. In recent years, representative keywords include cancer pain treatment, cancer-associated fibroblasts, ginsenoside Rg3, post-liver cancer surgery, anti-inflammatory agents, antioxidants, deep learning, bioactive phytochemicals, and *Scutellaria baicalensis Georgi*. The timeline of English literature can be divided into two periods: From 2015 to 2018, emerging research relied on cell experiments and animal models for foundational exploration of TCM in liver cancer treatment, including mechanisms such as apoptosis, antioxidation, anti-inflammation, endoplasmic reticulum stress, NF-κB pathway, and cell cycle arrest, primarily validating the anticancer activity, such as inducing apoptosis and inhibiting proliferation, and

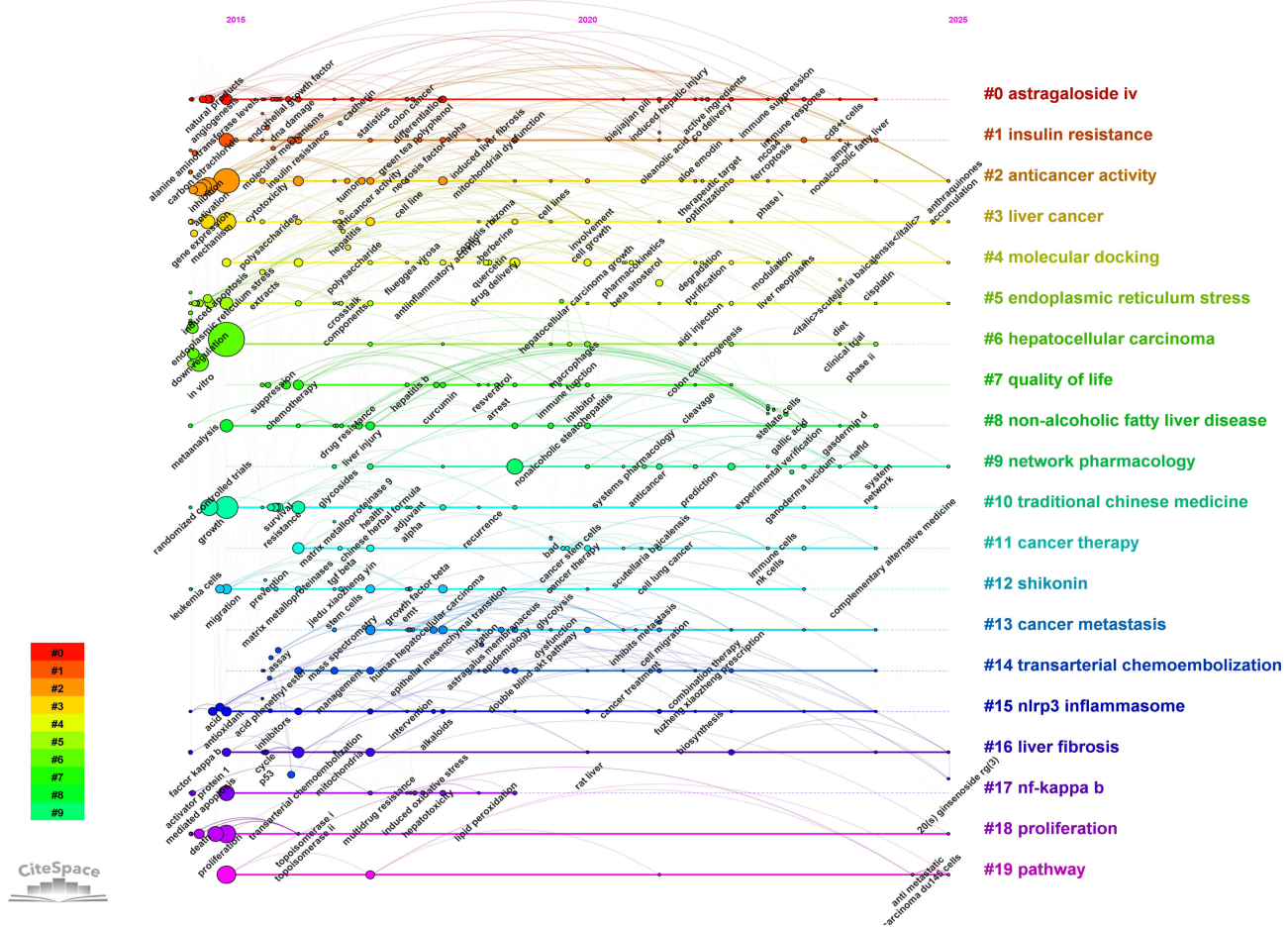

Figure 22 Timeline map of English literature.

mechanisms, like regulating Bcl-2/Bax and reactive oxygen species (ROS) levels, of single TCM components. From 2019 to 2025, research became more in-depth and diversified, not only focusing on clinical validation of TCM formulations (eg, Aidi injection) but also leveraging modern technologies like network pharmacology, molecular docking, bioinformatics, and deep learning to delve into the mechanisms of TCM in treating liver cancer. There were also more attempts in drug innovation, nanotechnology applications, multi-target research, targeted delivery technologies (eg, liposomes, co-delivery systems), and immune microenvironment regulation (eg, macrophage polarization, CD8+ T cell activation). Additionally, research explored the association between metabolic abnormalities (eg, glycolysis dysregulation, lipid metabolism dysregulation, AMPK abnormal activation) and liver cancer, as well as the intervention effects of TCM (eg *Ganoderma lucidum (Curtis) P. Karst*, *Coptis chinensis Franch*). Emerging TCM components and formulations were also studied in depth.

The outcomes indicate that the corpus of Chinese literature can be segmented into 20 principal clusters. Every single one of these clusters corresponds to the research focal points that were prevalent during a distinct phase along the chronological axis. Data shows that #0 primary liver cancer, #1 traditional Chinese medicine, #7 clinical efficacy, #14 integrated Chinese and western medicine therapy, and #16 liver function are core themes in this field, consistently appearing throughout the research period. The clinical efficacy of TCM in treating liver cancer, especially advanced-stage liver cancer, its impact on liver function and immune function in liver cancer patients, studies on the TCM syndromes of liver cancer, the mechanisms of action of TCM in treating liver cancer, the combination of TCM research with network pharmacology, combined TCM and interventional therapy for liver cancer, the experience of renowned doctors in treating liver cancer with TCM, and the Chinese medicine acupoint application as a domestic research hotspot in China have

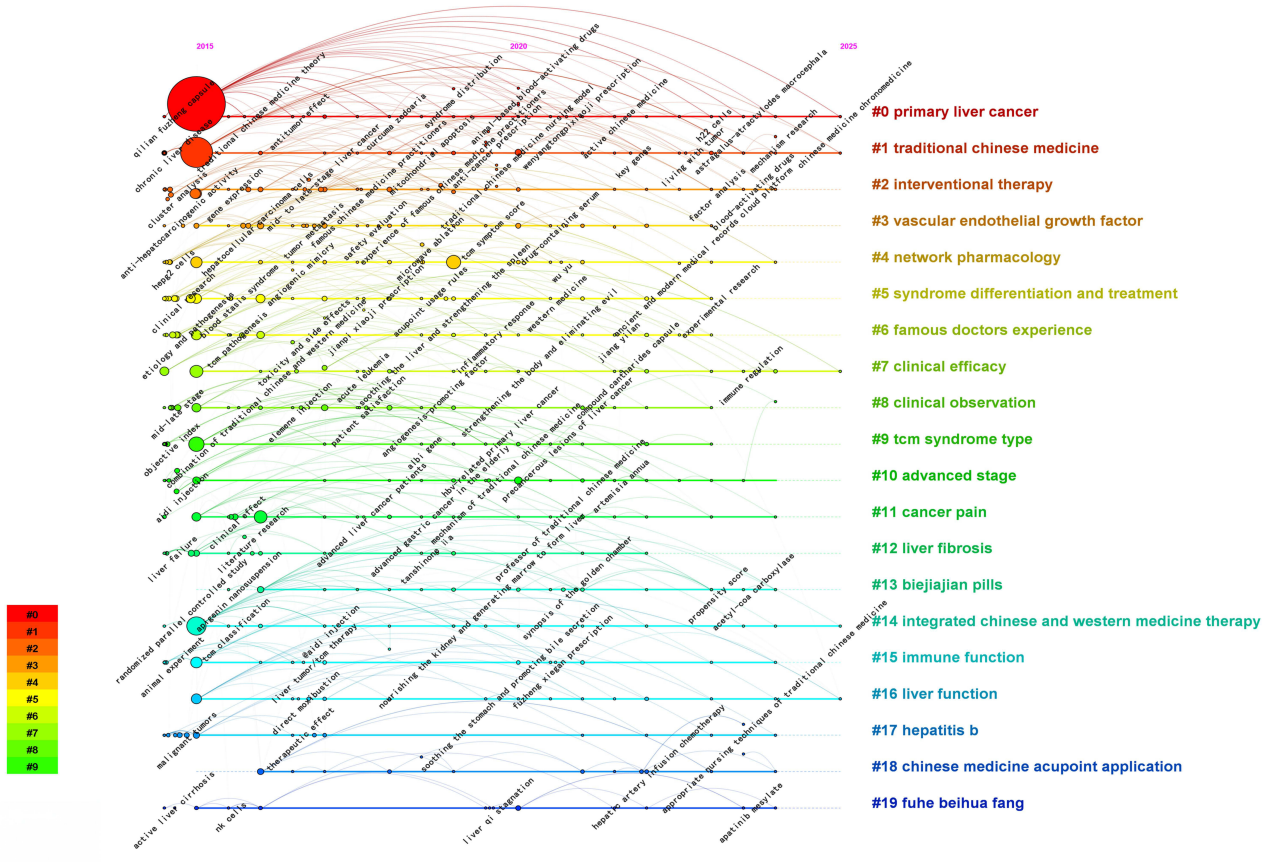

Figure 23 Timeline map of Chinese literature.

persisted for an extended period. In recent years, representative keywords include Modified Yiguan Jian, Peiyuan Guben Formula, TCM chronomedicine, post-intervention therapy, "huchang" theory, gut–liver axis, *Panax ginseng C. A. Mey-Schisandra chinensis (Turcz). Baill* herb pair, immunity, radiomics, and emotional nursing. The timeline of Chinese literature can be divided into two periods: From 2015 to 2018, emerging research focused on clinical studies of TCM in treating liver cancer, such as clinical efficacy, safety, adverse reactions, medication rules, syndrome pattern research, acupuncture treatment, and renowned physicians' experiences. These themes were consistently studied throughout the timeline. From 2019 to 2025, emerging research included novel nano-delivery systems for anti-liver cancer TCM (eg, liposomes for delivering active TCM components), multi-omics technology integration (eg, single-cell sequencing, radiomics, metabolomics), real-world studies (RWS) and network Meta-analyses to validate TCM efficacy, combined therapies of TCM with immunotherapy and targeted therapy, and innovation and exploration of TCM theories (eg, "cancer evil" theory, "zhongzhou" theory, "wood qi sinking," "circular flow of qi," "three stages and six differentiations," "huchang" theory, "triple energizer qi transformation," TCM emotional nursing, TCM chronotherapy for liver cancer, and the five movements and six qi). Research on the mechanisms of TCM in treating liver cancer and studies on anti-liver cancer TCM and its active components spanned the entire period. Mechanistic research evolved from apoptosis, liver fibrosis, epithelial–mesenchymal transition, proliferation, signaling pathways, TCM pharmacology, autophagy, exosomes, and angiogenesis (2015–2018) to ferroptosis, pyroptosis, proteomics, transcriptomics, mitochondria, cell migration, immune regulation, gut microbiota, gut–liver axis, DNA methylation, non-coding RNA, liver regeneration microenvironment, immune microenvironment, and cancer stem cells (2019–2025). Studies on anti-liver cancer TCM and its active components expanded from cinobufotalin, Xihuang Pill, Biejiajian Pill, Fuhe Beihua Formula, Jiedu Granule, *Scutellaria barbata D.Don*, *Astragalus membranaceus (Fisch)*. Bunge, Sijunzi Decoction, Jianpi Fuzheng Decoction, Bielong Ruangan Decoction, Babao Dan Capsule, matrine, Modified Chai Shao Liujunzi Decoction, Jianpi

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Huayu Formula, Jianpi Xiaoji Formula, Curcuma phaeocaulis Valeton, Chaihu Shugan Powder, and *Oldenlandia diffusa (Willd). Roxb* (2015–2018) to Chai Shao Liujunzi Decoction, Dahuang Zhechong Pill, Pien Tze Huang, Sini Powder, CKI, Ganji Formula, Huaier Granule, Compound Banmao Capsule, Panax ginseng C. A. Mey, Sophora flavescens Aiton, Modified Yiguan Jian, Peiyuan Guben Formula, and Banxia Xiexin Decoction (2019–2025).

With the aim of achieving a more distinct discernment of the burgeoning research focal areas within the realm of TCM for the treatment of liver cancer, this study utilized CiteSpace's Bursts analysis function to examine burst keywords (as shown in Figures 24 and 25). The red segments represent the start and end times of the burst keywords.

In English literature, "network pharmacology" had the highest burst strength (11.05), indicating that network pharmacology has garnered significant attention in TCM research for liver cancer treatment, becoming a recent research hotspot. This may be because network pharmacology can systematically analyze the multi-target and multi-pathway mechanisms of TCM, providing new methods and perspectives for modern TCM research. The high burst strength of

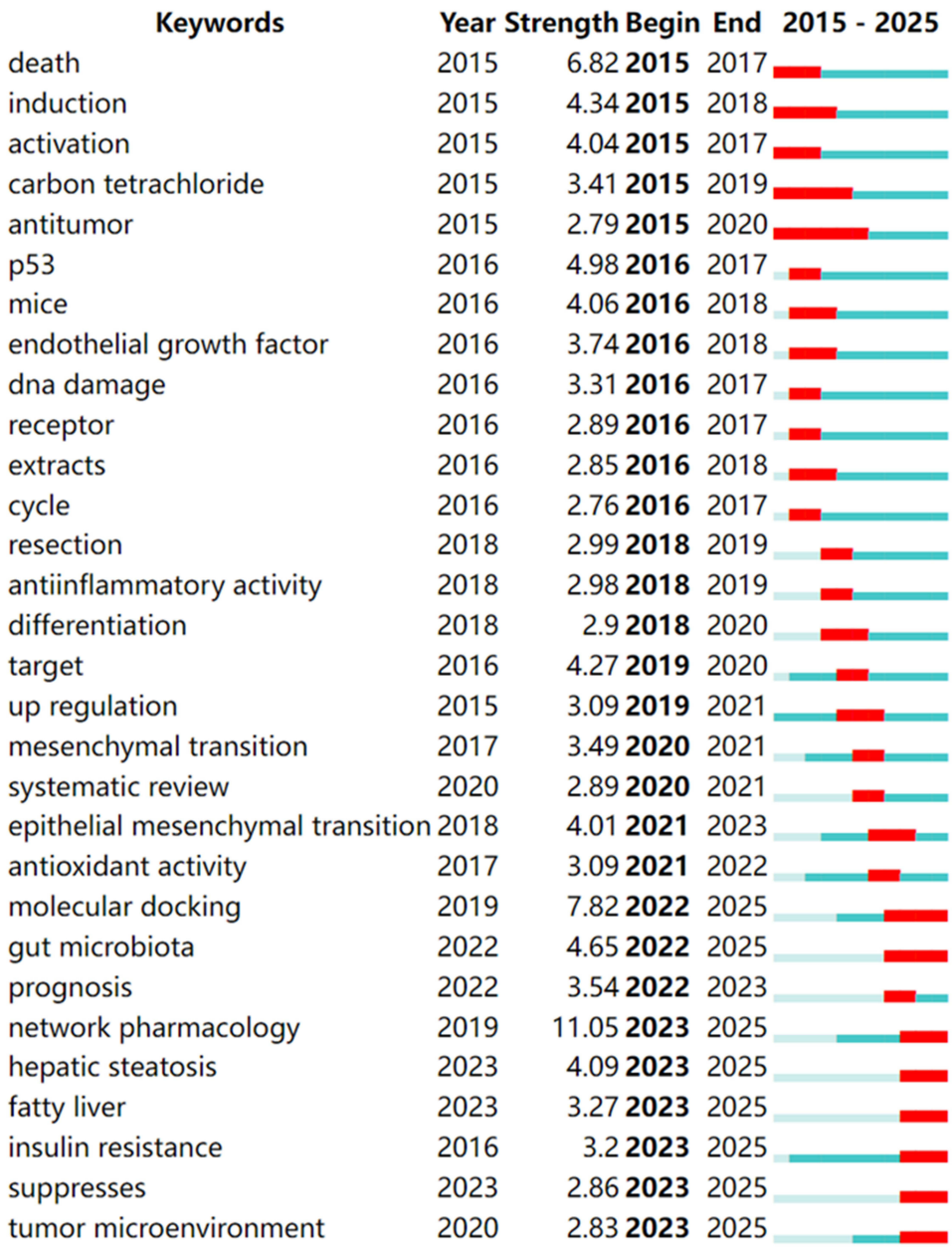

Figure 24 Keyword burst of English literature.

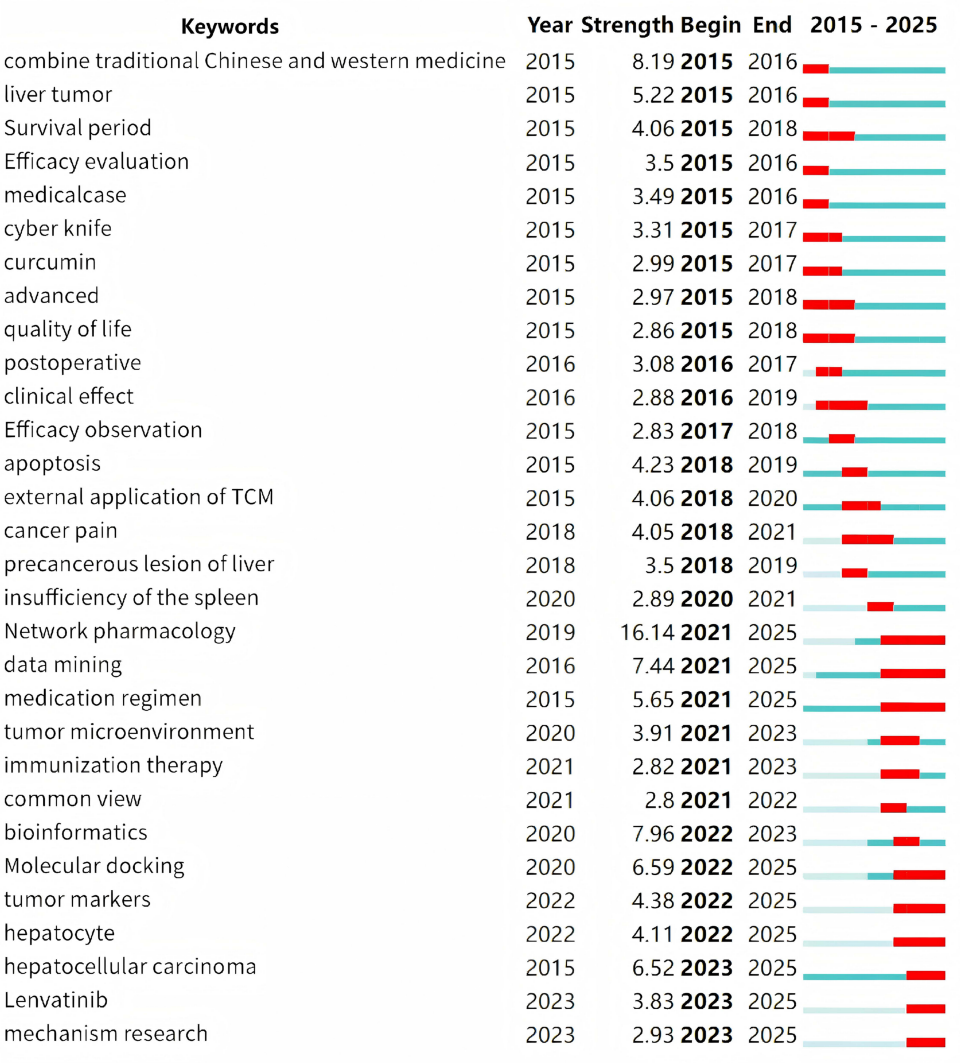

Figure 25 Keyword burst of Chinese literature.

"molecular docking" (burst strength 7.82) highlights the importance of molecular docking technology in studying TCM mechanisms, as it simulates interactions between drug molecules and targets, helping to reveal the molecular basis of TCM. The keyword with the longest burst duration was "antitumor," which persisted from 2015 to 2020, reflecting researchers' sustained focus and in-depth exploration of TCM's role in inhibiting tumor growth and metastasis.

First period (2015–2020): The focus during this period was on basic research and mechanistic exploration of TCM for liver cancer treatment. Hot topics included TCM's antitumor effects (eg, "antitumor"), animal experiments and modeling (eg, "mice," "carbon tetrachloride"), and investigations into TCM's mechanisms against liver cancer (eg, "DNA damage," "receptor," "death," "activation," "P53," "cycle," "antiinflammatory activity," "differentiation"). Second period (2021–2025): Research shifted toward integrating TCM with modern technologies and exploring the liver cancer microenvironment and metabolic abnormalities. Hot keywords such as "network pharmacology," "gut microbiota," and "insulin resistance" reflected the adoption of advanced techniques (eg, network pharmacology, molecular docking) to study TCM's mechanisms (eg, "antioxidant activity") and increased attention to the TME, epithelial–mesenchymal transition, gut microbiota, and metabolic factors (eg, "hepatic steatosis," "fatty liver," "insulin resistance," NASH) in disease progression, as well as TCM's impact on these factors. Key indicators like "prognosis" were also explored. The trend during this period was the modernization and systematization of TCM research, emphasizing interdisciplinary and comprehensive approaches. As of February 2025, "network pharmacology," "hepatic steatosis," "fatty liver," "insulin

resistance," "suppresses," "TME," "molecular docking," and "gut microbiota" remained in burst status, suggesting they may continue to be research hotspots.

In Chinese literature, "network pharmacology" (burst strength: 16.14) also had the highest burst strength and longest duration, indicating the increasing integration of modern scientific technologies, particularly network pharmacology, into TCM research to study multi-target and multi-pathway mechanisms. "Data mining" and "medication rules" also had the longest burst durations, reflecting the growing use of modern techniques like data mining to analyze TCM prescriptions and compatibility rules, summarize academic experiences in liver cancer treatment, and provide theoretical foundations for clinical practice.

First period (2015–2020): Hot keywords included "clinical efficacy," "efficacy evaluation," "CyberKnife," "survival period," "apoptosis," "efficacy observation," "short-term efficacy," and "quality of life," mainly reflecting evaluations of TCM's efficacy in liver cancer treatment and its integration with conventional therapies (eg, CyberKnife). Attention also turned to TCM's effects on cancer-related pain. The primary research component during this stage was curcumin, and TCM-specific aspects like external application of Chinese medicine and case studies became focal points. Research primarily validated TCM's clinical efficacy (eg, improving patient quality of life, treatment outcomes, and survival). Second period (2021–2025): Hot keywords included "data mining," "immunotherapy," "network pharmacology," and "molecular docking," reflecting the adoption of advanced techniques (eg, data mining, network pharmacology, molecular docking, bioinformatics, deep learning) to study TCM's mechanisms and medication rules. Researchers also began focusing on the TME, combining TCM with immunotherapy, studying relationships between TCM syndromes and serum tumor markers, TCM's impact on tumor markers, and the efficacy of TCM combined with targeted drugs (eg, lenvatinib) for liver cancer. In TCM-specific aspects, "spleen deficiency" became a key syndrome element. As of February 2025, "network pharmacology," "data mining," "molecular docking," "medication rules," "tumor markers," "mechanism research," "lenvatinib," "hepatocytes," and "hepatocellular carcinoma" remained in burst status, suggesting they may continue to be research hotspots.

To explore the hot trends in the field of traditional Chinese medicine (TCM) for the treatment of liver cancer, a heatmap was generated for some high-frequency keywords using Origin 2024. As demonstrated in the visualization of Figure 26,

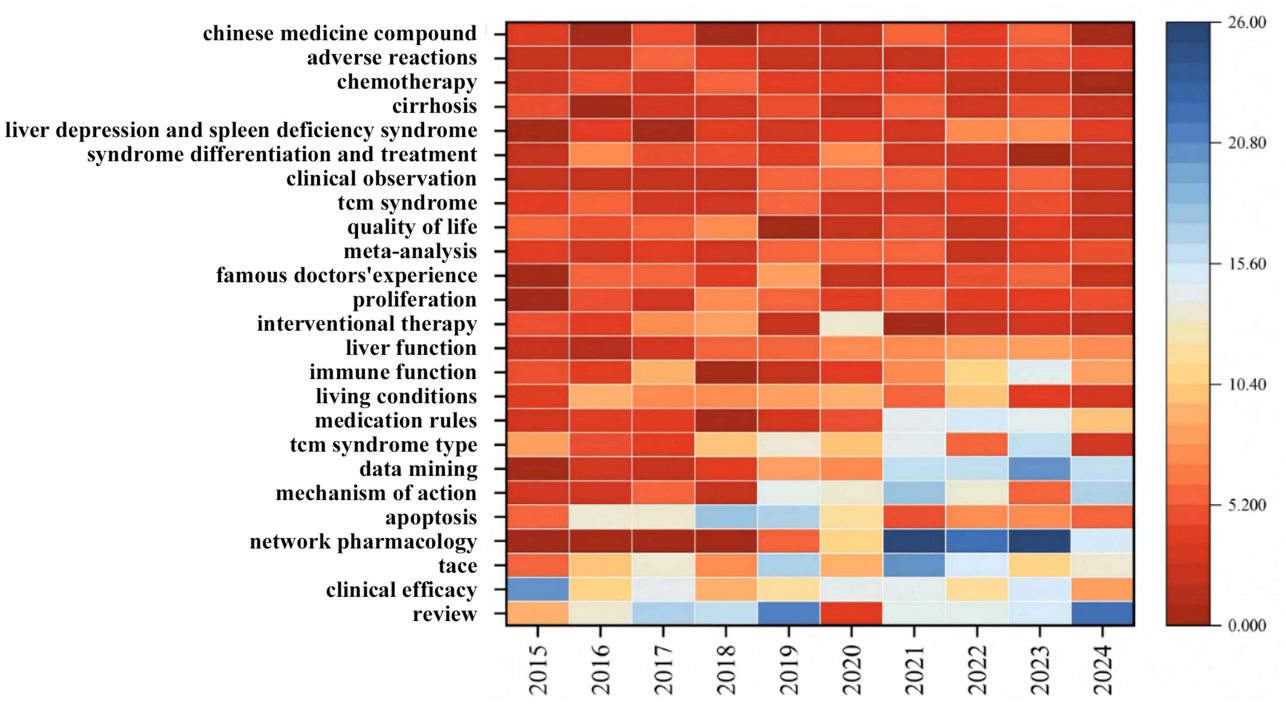

Figure 26 Keyword heatmap of Chinese literature.

Chinese literature can be categorized into the following aspects: (1) Basic research and molecular mechanisms of TCM in treating liver cancer. Among these, the mechanism of apoptosis has garnered significant attention, especially between 2016 and 2020, with its popularity declining after 2020 but remaining at a relatively high level. Proliferation was a focus from 2018 to 2021, after which its popularity declined, while network pharmacology has been a research hotspot in the past five years. With advancements in technical methods, research on the mechanisms of TCM in treating liver cancer has deepened. (2) Clinical research on TCM for liver cancer. Clinical efficacy has been a consistent focus from 2015 to 2024, quality of life gained attention from 2016 to 2022, liver function became notable after 2018, immune function emerged as a hotspot after 2021, cirrhosis drew attention after 2019, and adverse reactions have been a concern since 2017. TCM provides macro and comprehensive functional regulation, the treatment approach beneficial for improving the immune function of liver cancer patients,[23] cirrhosis,[24] liver cancer complications,[25] liver function, post-interventional complications, quality of life, and adverse reactions.[26] Chemotherapy and interventional therapy were prominent from 2017 to 2020, with interventional therapy experiencing explosive growth in popularity in 2020. TACE has been favored from 2015 to 2024. This integrated approach of TCM and Western medicine complements their strengths, significantly enhancing clinical efficacy.[26] (3) TCM characteristics. TCM syndrome and syndrome differentiation and treatment gained attention after 2016, liver depression and spleen deficiency syndrome became notable after 2018, while TCM syndrome types have maintained high popularity since 2015, especially with explosive growth from 2018 to 2023. Syndrome differentiation and treatment is the core of TCM and a vital approach to treating liver cancer, effectively reducing adverse reactions from radiotherapy and chemotherapy, stabilizing conditions, and improving quality of life.[27] Scholars have delved into the biological basis of TCM syndromes through studies linking them with modern medical indicators (eg, tumor markers),[28,29] providing a foundation for personalized TCM treatment. TCM compound prescriptions have gained attention since 2017. With their multi-target and multi-mechanism properties, TCM compound prescriptions offer unique advantages in treating liver cancer, given its complex pathogenesis,[30] the popularity of data mining and medication rules has remained at a high level since 2019 and 2020, respectively, while the interest in famous doctors' experience has shown fluctuating growth since 2016. In recent years, data mining technology has been widely applied in studying renowned physicians' experience and medication rules. (4) In terms of research types, reviews have maintained high popularity since 2015, and meta-analyses have remained at a relatively high level from 2019 to 2021, indicating the promotion of evidence-based medicine and the demand for evidence integration in the field of TCM for liver cancer treatment. In summary, the regulation of immune function in liver cancer patients by TCM, the mechanisms of TCM in treating liver cancer, data mining of medication rules, research on TCM syndromes, and the clinical efficacy of TCM in treating liver cancer represent potential research hotspots and frontier trends.

As shown in Figure 27, English literature can be divided into the following aspects: (1) In basic mechanism research, apoptosis, pathway, expression, activation, growth, and in vitro have been the most popular topics, maintaining high interest from 2015 to 2024, indicating these directions remain core research areas. Cell cycle arrest, proliferation, and NF-κB gained popularity after 2016, while inflammation and oxidative stress have attracted attention since 2019. Metastasis has been a focus since 2017, and invasion has gained favor since 2018. Liver fibrosis has seen increased interest after 2020, and network pharmacology has become a research hotspot in recent years. TCM can regulate and activate the expression of genes, proteins, signaling pathways, miRNAs, etc., to inhibit liver cancer growth and prevent its occurrence. The mechanisms include, but are not limited to, blocking the cell cycle, inhibiting proliferation, inducing apoptosis, reducing invasive ability, immune regulation, inducing pyroptosis, ferroptosis, and autophagy, regulating oxidative stress,[10] exerting anti-inflammatory effects,[31] mediating epigenetic regulation, improving liver fibrosis,[32] activating endoplasmic reticulum stress,[33] and regulating liver cancer cell metabolism and energy.[34] Furthermore, the application of technologies such as network pharmacology has enabled more in-depth research into the mechanisms of TCM in treating liver cancer. (2) In terms of clinical efficacy research on TCM for liver cancer, "efficacy" gained particular attention in 2020, "therapy" has been favored since 2017, and "sorafenib" has been widely discussed since 2020. An increasing number of clinical trials aim to evaluate the therapeutic effects of TCM on liver cancer through double-blind, controlled, and randomized methods. Some TCM products have demonstrated anti-liver cancer effects in clinical trials. In summary, mechanisms such as "cell cycle arrest," "NF-κB," "inflammation," "apoptosis," "pathway," and "network pharmacology" in TCM for liver cancer represent potential research hotspots and trends.

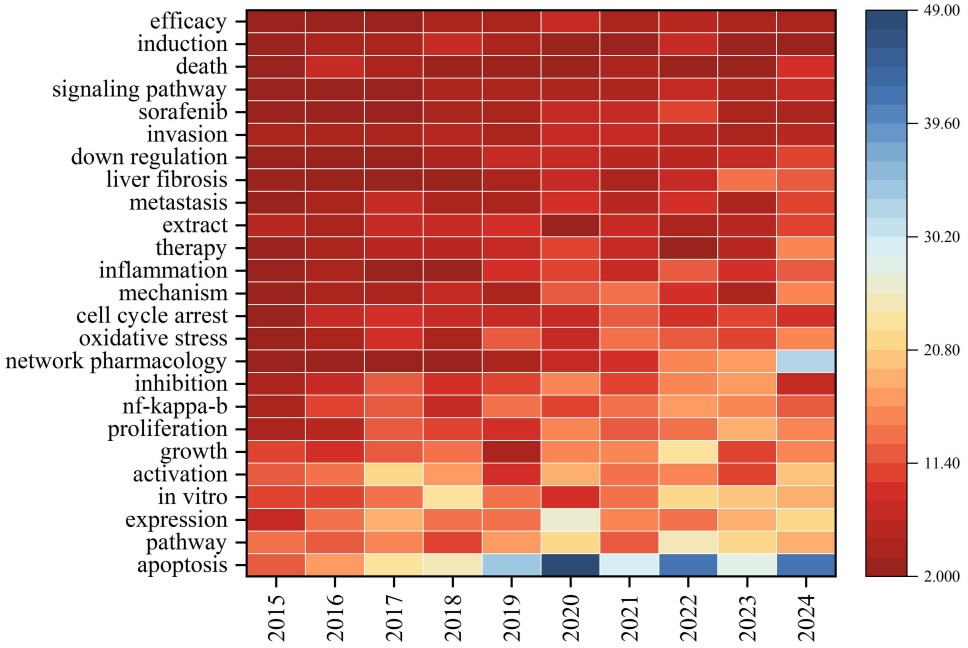

Figure 27 Keyword heatmap of English literature.

Citation and Co-Citation Analysis

The most cited English-language article, "The Pharmacological Activity, Biochemical Properties, and Pharmacokinetics of the Major Natural Polyphenolic Flavonoid: Quercetin," was published in the journal "Foods" with an impact factor of 4.5 and ranked in the JCR Q1 zone, cited 419 times. It discusses how quercetin can inhibit the proliferation of liver cancer through various mechanisms, including cell signaling, binding to cell receptors and proteins, and inhibiting carcinogen-activated enzymes. Quercetin also prevents liver cancer by modulating oxidative stress factors and antioxidant enzymes to hinder its spread, demonstrating hepatoprotective effects.[35] The second most cited article, "Scutellaria baicalensis, the golden herb from the garden of Chinese medicinal plants," was published in the journal "Science Bulletin" with an impact factor of 18.8 and ranked in the JCR Q1 zone, cited 360 times. It focuses on the anticancer potential of *Scutellaria baicalensis Georgi*, where baicalein (BAL) treatment of dividing cells induces DNA damage and leads to cell death. Despite this genotoxic effect, BAL does not induce mutations, a major issue with traditional anticancer drugs, suggesting that BAL and related flavonoids are strong candidates for improved chemotherapy drugs. Additionally, the TCM formula Xiao Chai Hu Decoction, containing *Scutellaria baicalensis Georgi*, can effectively prevent hepatitis C from progressing to liver cancer.[36] The third most cited article, "Milk thistle (*Silybum marianum*): A concise overview on its chemistry, pharmacological, and nutraceutical uses in liver diseases," was published in the journal "Phytotherapy Research" with an impact factor of 6.1 and JCR Q1 ranking, cited 279 times. It primarily discusses how silymarin can inhibit oxidative stress, induce cancer cell apoptosis, block the cell cycle, and regulate mitochondrial pathways, demonstrating inhibitory effects on liver cancer cell growth and synergistic enhancement with chemotherapy drugs (such as sorafenib, doxorubicin, and gefitinib) in in vitro experiments and animal models.[37] The fourth most cited article, "Anticancer activities of TCM and their active components against tumor metastasis," was published in the journal "Biomedicine & Pharmacotherapy" with an impact factor of 6.9 and JCR Q1 ranking, cited 234 times. It highlights the advantages of traditional Chinese medicine in treating liver cancer, such as how Sini San, detoxification formulas, isoorientin, and BB inhibit epithelial–mesenchymal transition (EMT) in liver cancer cells, promote apoptosis, and suppress proliferation, migration, and invasion.[38] The fifth most cited article, "Anticancer Plants: A Review of the Active Phytochemicals, Applications in Animal Models, and Regulatory Aspects," was published in the journal "Biomolecules" with an impact factor of 4.8 and JCR Q1 ranking, cited 213 times. It reviews the anti-liver cancer activity of plants such as *Oldenlandia diffusa (Willd). Roxb, Rabdosia rubescens (Hemsl). H.Hara, Paeonia lactiflora*

Pall, Astragalus membranaceus (Fisch). Bunge, Perilla frutescens (L). Britton, *Coptis chinensis Franch*, and *Morus alba L* leaves.[39]

Among Chinese literature, the most cited article, "Research advances in traditional Chinese medicine treatment for primary liver cancer," cited 102 times. It discusses the TCM etiology, TCM pathogenesis, syndrome differentiation, and the integration of traditional Chinese medicine with modern treatments.[40] The second most cited article, "The Concept of Non-Alcoholic Fatty Liver Disease Attributing to Fatty Liver," was published in "Henan Traditional Chinese Medicine," cited 99 times. It elaborates on the scope of Gan Pi, which applies not only to early-stage fatty liver but also to its severe progression, such as liver cancer, as well as historical perspectives on non-alcoholic fatty liver disease.[41] The third most cited article, "Progress in research on pharmacological effects and application of Chinese medicine Sophora flavescens," was published in "Shandong Chemical Industry," cited 92 times. It describes how *Sophora flavescens* can block the liver cancer cell cycle, inhibit proliferation, suppress telomerase activity, and induce apoptosis.[42] The fourth most cited article, "Summary of TCM syndrome research on primary liver cancer," was published in the "Journal of Traditional Chinese Medicine", with a citation count of 88. It primarily discusses the standardization of liver cancer TCM syndrome, their distribution characteristics, and their relationship with objective indicators.[43] The fifth most cited article, "Study on the medication rule of famous traditional Chinese physicians in the treatment of primary liver cancer based on data mining," was published in the "China Journal of Traditional Chinese Medicine and Pharmacy, with a citation count of 83. It mainly analyzes prescription patterns based on the medical records of renowned TCM experts using statistical methods.[44]

Ultimately, a visual depiction of co-citation patterns within the cited references was created through the utilization of the VOSviewer software. To ensure the analysis focused on significantly cited works, a citation threshold of no less than 25 was established. Following the outlined methodology, a curated set of 32 scholarly articles was pinpointed for a comprehensive co-citation examination. The co-citation interconnections that emerged from this analysis are graphically depicted in Figure 28. Upon scrutiny of the results, it becomes evident that the co-citation framework of the highly referenced literature can be systematically organized into four discernible clusters. These clusters are visually

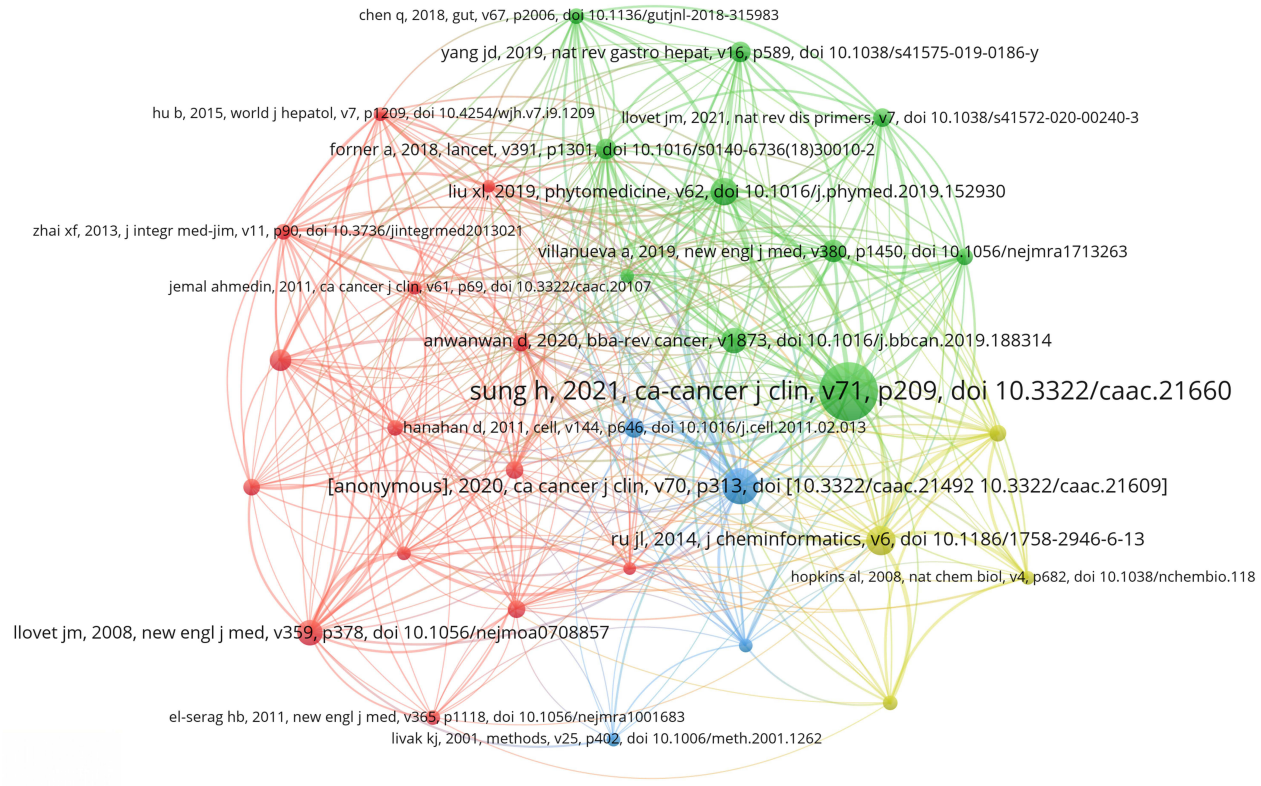

Figure 28 Co-cited reference visualization map.

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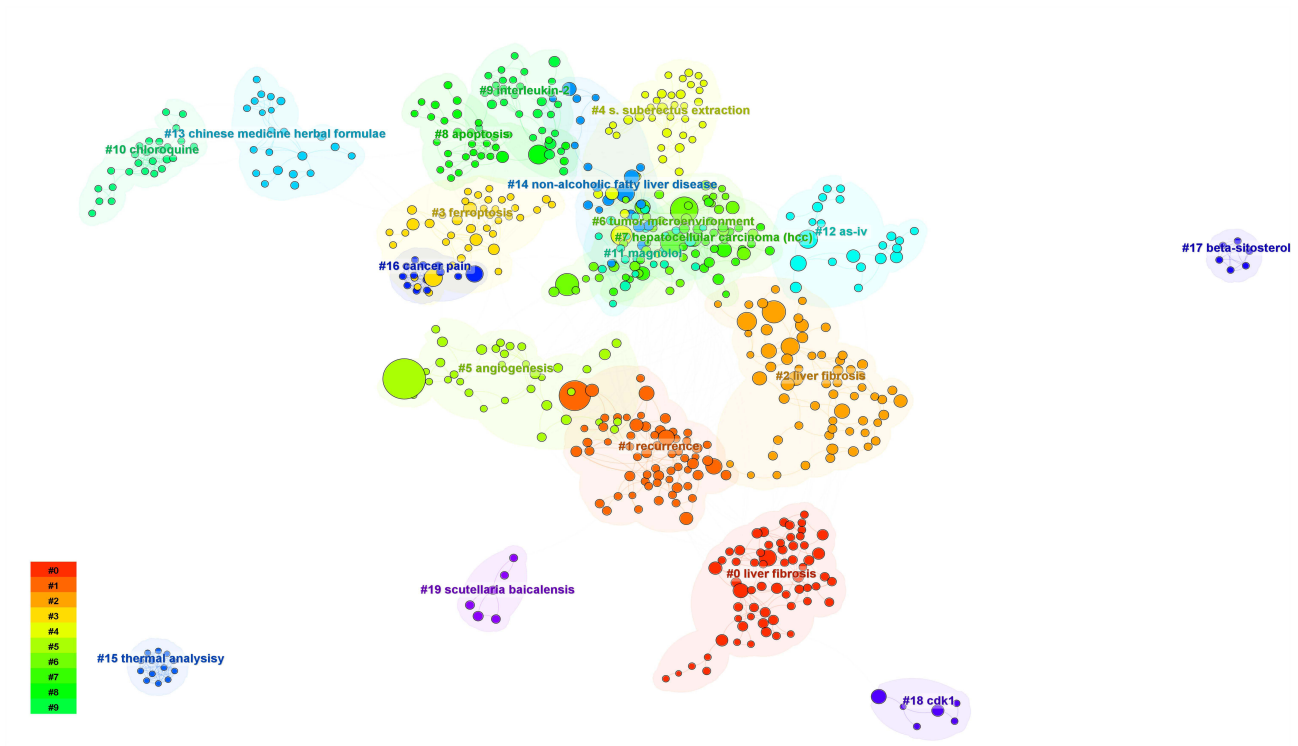

Figure 29 Co-cited reference clustering network map.

distinguished in the figure (Figure 28) by four distinct color codes, facilitating a clearer understanding of the underlying citation dynamics. The red cluster primarily focuses on the epidemiology and global disease burden of liver cancer, clinical treatment advances, and reviews of the efficacy of combining TCM with modern methods in treating liver cancer, as well as the mechanisms of TCM in liver cancer treatment. The green cluster mainly addresses the risk factors, prevention, diagnosis, and treatment of liver cancer, as well as the current status and trends of TCM as an adjuvant therapy in liver cancer treatment, including multicenter RCTs of TCM (eg, Huaier granules) for liver cancer. The blue cluster primarily explores the core characteristics of cancer and their molecular mechanisms, such as using real-time quantitative PCR technology and the $2^{-\Delta\Delta CT}$ method to analyze relative changes in gene expression, as well as how TCM prevents and treats liver cancer by influencing oncogenes, tumor suppressor genes, and epigenetic regulation. The yellow cluster mainly focuses on the application of network pharmacology in the field of TCM.

As shown in Figure 29, through the co-citation reference clustering network view generated by CiteSpace, topics such as liver fibrosis, ferroptosis, TME, angiogenesis, apoptosis, fatty liver, magnolol, astragaloside IV, TCM compound prescriptions, *Scutellaria baicalensis Georgi*, Cdk1 protein, and cancer pain have significantly attracted researchers' attention.

Discussion

The publication trend indicates that in recent years the number of publications in this field in China has stabilized, while international attention has been growing, demonstrating increasing recognition of TCM in treating liver cancer worldwide. Global research communities are actively delineating TCM's mechanisms for liver cancer prevention and management, with China maintaining scholarly dominance while Italy, Singapore, and the United States emerge as pivotal hubs for transnational collaboration. In terms of research institution distribution, Chinese domestic institutions remain the main force, forming large-scale research clusters. Notably, current research collaborations are mostly concentrated within the same institution or region, and cross-regional collaborative studies still need strengthening. Analysis of prolific authors shows that in Chinese literature, teams led by Wang Xianbo, Lv Jianlin, and Zeng Puhua have the highest

publication output. Wang Xianbo's team focuses on standardizing TCM diagnosis and treatment for liver cancer, clinical efficacy validation of TCM for liver cancer, and TCM's regulation of the liver cancer immune microenvironment.[45–47] Lv Jianlin's team emphasizes lncRNA and TCM's anti-liver cancer mechanisms, as well as TCM's targeted intervention in signaling pathways for liver cancer prevention and treatment.[48–50] Zeng Puhua's team focuses on the analysis of medication patterns in traditional Chinese medicine for treating liver cancer, as well as on evidence-based medicine and Meta-analysis.[51–53] Zhai Xiaofeng is the most prolific author, with research primarily focused on standardization and quantification of TCM syndromes.[54–58] In English literature, teams led by Ling Changquan, Wang Wei, and Feng Yibin have the highest publication output. Ling Changquan's team emphasizes the molecular mechanisms of TCM compounds/monomers against liver cancer, such as Jiedu Granules inhibiting angiogenesis, EMT, and pre-metastatic microenvironment formation by regulating signaling pathways (eg, MKK6/p38, MAPK/PI3K-Akt, Smad2/3). Natural components (eg, emodin, oleanolic acid) induce liver cancer cell apoptosis via mitochondrial pathways or specific signaling pathways, along with clinical efficacy validation of TCM for liver cancer prevention and treatment, including real-world studies and randomized controlled trials evaluating TCM's impact on patient survival and gut microbiota.[59–63] Feng Yibin's team focuses on using network pharmacology and multi-omics technology to study the anti-hepatocellular carcinoma effects of TCM compounds and monomers. Their work has shown that examples such as Xianglian Pill, Siwu Decoction, Huanglian Jiedu Decoction, Zuojin Pill, and Huachansu Capsule inhibit liver cancer by inducing tumor cell apoptosis, necroptosis, etc. Monomer components like emodin and betulinic acid suppress HCC progression by regulating the SREBP1 signaling pathway or inhibiting lncRNA *MALAT*1.[64–72] The team led by Wang, Wei focuses on the mechanisms of TCM-induced liver cancer cell death, such as ginsenoside derivatives, tanshinone IIA, and *Scutellaria barbata D.Don* inducing apoptosis or ferroptosis in HCC cells, as well as network pharmacology and multi-target mechanisms, such as the network pharmacology research and experimental validation of dihydromyricetin and active components of *Prunella vulgaris L* against liver cancer.[73–77] One of the major obstacles to the modernization of traditional Chinese medicine (TCM) is the failure to identify the pharmacological effects of active ingredients in herbal formulas, and few prescriptions have undergone scientifically rigorous clinical evaluation to verify their efficacy. However, this situation has been gradually improving in recent years, with an increasing number of clinical trials adopting double-blind, controlled, and randomized methods to assess the therapeutic effects of various TCM treatments. Several traditional formulations and TCM products have been investigated in clinical trials for their anti-HCC effects. Keyword analysis reveals that "clinical efficacy" serves as a high-frequency term and a representative vocabulary in cluster analysis. In timeline analysis, "clinical efficacy" persists throughout the entire research period, with "efficacy evaluation" and "efficacy observation" emerging as burst terms. This underscores that clinical efficacy is the core theme in this field. A literature analysis revealed that CKI,[78] Fuzheng Jiedu Xiaoji Decoction,[79] Huaier Granules,[80] ginsenosides,[81] Banxia Xiexin Decoction,[82] Cinobufacini,[83] Jianpi Liqi Decoction,[84] icaritin (ICT),[85] Jiedu Granules,[86] Kangai Injection,[87] Jinlong Capsule,[88] Kanglaite Injection,[89] and PHY906[90] are among the hot topics in clinical efficacy research. These agents, when used alone or in combination with modern therapies, have been reported in studies to show potential benefits in improving outcomes such as recurrence-free survival (RFS), overall survival rate (OSR), overall survival, progression-free survival (PFS), objective response rate, disease control rate, and extrahepatic recurrence rate (ERR) in HCC patients, while also alleviating adverse reactions associated with therapies such as TACE.

Keyword analysis reveals differences between Chinese and English literature: Chinese studies emphasize clinical efficacy evaluation (accounting for 46.7% of high-frequency keywords) and the inheritance of renowned physicians' experience, forming a syndrome differentiation system centered on liver depression and spleen deficiency. In contrast, English literature focuses on molecular mechanisms (45.6% of keywords frequency). Chinese scholarship focuses on evidence-based clinical studies with human cohorts, whereas international academia prioritizes mechanistic exploration through controlled laboratory experimentation. Chinese and English literature exhibit distinct yet complementary research paradigms. Chinese research is deeply rooted in rich clinical practice, striving to address practical clinical issues while continuously leveraging modern data technologies (such as data mining) to inherit and optimize traditional wisdom. In contrast, international research (primarily published in English) places greater emphasis on utilizing cutting-edge biotechnologies to unveil the microscopic mechanisms underlying the actions of traditional Chinese medicine (TCM). Its extensive international collaboration network provides a strong impetus for innovative research. However,

this scenario also highlights a core gap in current global cooperation. Despite China's absolute dominance in paper output in this field, our analysis reveals that its international collaboration rate (MCP Ratio = 0.074) is significantly lower than that of countries such as Egypt (0.609). This implies that a substantial portion of Chinese research achievements are still being accomplished within a relatively closed domestic system, with their international influence and collaborative potential not being fully unleashed. Current collaborations are mostly limited to data contributions or the application of a single technology, lacking in-depth integration and synergistic innovation that spans from posing clinical questions, theoretical innovation, to technological validation. For instance, combining China's abundant clinical experiences and prescription resources with internationally advanced modeling platforms and mechanistic research capabilities to jointly develop novel TCM-based anticancer drugs or therapies should be a key focus for future collaboration.

Integrated analyses including keyword co-occurrence network analysis, keyword burst analysis, heatmap analysis, citation and co-citation analysis, and keyword timeline visualization analysis indicate that research hotspots are likely to emerge in areas such as mechanisms of action, omics technologies, bioinformatics technology, network pharmacology and molecular docking, TCM syndrome research, TCM theory innovation and exploration, TCM nanodelivery, data mining, and deep learning. Collectively, the subsequent eight segments delineate pivotal emergent trajectories in TCM-based liver cancer interventions, spanning from mechanistic decoding to clinical translation.

Research on TCM Syndrome Types

Syndrome differentiation and treatment represent the cornerstone of TCM theory and practice, providing a critical framework for personalized medicine in HCC management. Although interest in TCM syndrome pattern research declined slightly in 2024, It has stayed at a quite high level over the past few years. Among these patterns, liver depression and spleen deficiency syndrome has garnered particular attention, as it is frequently involved in the efficacy of TCM treatments (eg, Fuhe Beihua Formula, Chai Shao Decoction, Shugan Tiaopi Huayu Decoction, Ganfu Formula, Shenqi Xiaoji Formula, etc.) for HCC.[52,91–96] Among these, omics technologies and tumor markers have emerged as hot keywords in recent years. Deep learning serves as a representative keyword in cluster analysis, while tumor markers have been identified as burst terms, drawing significant attention. Modern technologies such as tumor markers, deep learning, and omics technologies are increasingly being applied to and deepening in the study of traditional Chinese medicine (TCM) syndromes. In addition, TCM syndrome patterns have predictive value for disease outcomes. For instance, one study used TCM syndrome patterns to predict the efficacy of Cinobufacini combined with targeted therapy for HCC and found that patients with excess syndrome showed more significant clinical improvement.[97] Research on the auxiliary role of modern technology in TCM syndrome differentiation is increasing. For example, one study incorporated radiomics into the TCM syndrome classification of primary liver carcinoma, demonstrating the effectiveness of a super-resolution reconstructed radiomics model in differentiating various TCM syndromes of primary liver carcinoma (such as liver depression and spleen deficiency syndrome, qi stagnation and blood stasis syndrome, and liver-kidney yin deficiency syndrome), particularly by boosting the model's predictive power through enhanced image resolution.[98] Another study utilized deep neural networks to explore the nonlinear relationships between unstructured data such as TCM symptoms, signs, tongue manifestations, and pulse conditions and TCM syndrome types of liver cancer, establishing an objective and quantitative syndrome classification model to improve the accuracy and scientificity of TCM syndrome differentiation.[99] Objective research on TCM syndrome types has also been a hotspot in recent years. One study found that Golgi protein 73 is most highly expressed in liver-kidney yin deficiency syndrome (common in advanced stages), indicating that it might function as a delicate marker for TCM syndrome differentiation in advanced liver cancer.[100] Research investigating the correlation between TCM syndrome classifications of primary liver cancer and serum tumor markers revealed that the syndrome characterized by liver depression and spleen deficiency is predominantly associated with elevated levels of carcinoembryonic antigen (CEA), liver-gallbladder dampness-heat syndrome by high expression of CEA and AFP, liver-heat blood stasis syndrome by high expression of γ-glutamyl transpeptidase (γ-GT2), carbohydrate antigen 19–9 (CA19-9), and AFP, spleen deficiency dampness encumbrance syndrome by high expression of γ-GT2 and CA19-9, and liver-kidney yin deficiency syndrome by high expression of AFP.[101] In conclusion, the bibliometric hotspots in TCM syndrome research chart a course for its future: the creation of a validated, quantifiable framework that

can seamlessly interface with conventional medical decision-making, ultimately enhancing the precision and efficacy of integrated liver cancer care.

Mechanisms of Action

The term "mechanism" serves as a high-frequency term in both Chinese and English literature, running through the entire research period in timeline analysis. As a representative term in cluster analysis, it stands as a core theme in this field. This indicates that the pharmacological mechanisms of TCM in treating liver cancer have received sustained attention and are being continuously explored in depth through extensive research. However, the exact mechanisms of action remain incompletely understood. This article will elaborate on the current hotspot mechanisms in the following sections (Figure 30).

Cell Death

The centrality of "cell death" reaches as high as 0.15, and it serves as a representative term in cluster analysis. This highlights its significant status in the research field. This demonstrates that inducing and regulating cell death represents the core mechanism by which TCM inhibits the proliferation of liver cancer, forming the cornerstone of research in this field. A more in-depth timeline analysis reveals a dynamic evolutionary landscape: although apoptosis, as a classic pathway, continues to command high attention, underscoring its fundamental status, the emergence of ferroptosis, autophagy, and pyroptosis as explosive hotspots marks a shift in the research focus of this field from a single apoptotic pathway to a broader cell death network encompassing emerging modes of cell death. This evolution reflects the

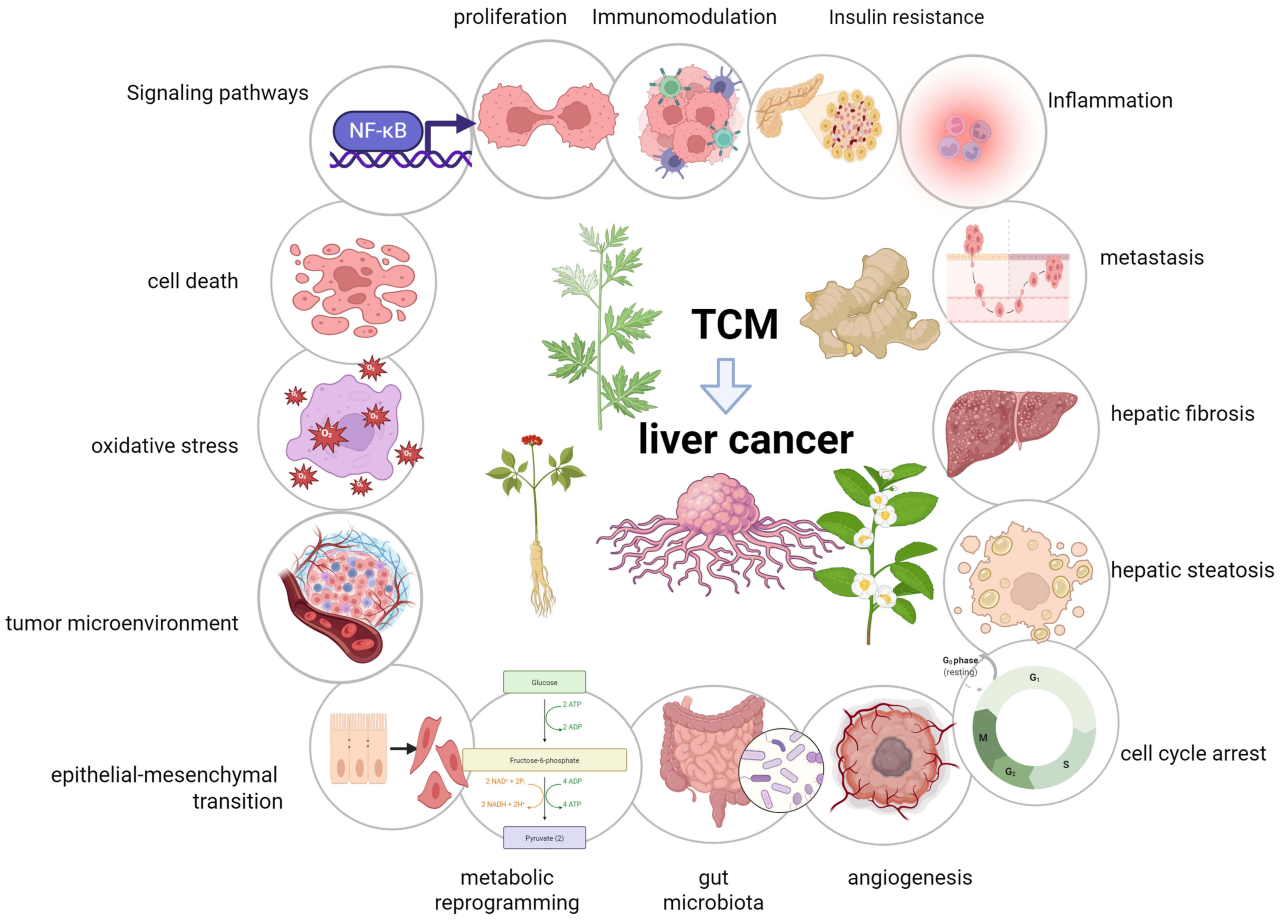

Figure 30 Hotspot mechanisms of traditional Chinese medicine in liver cancer prevention and treatment.

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academic community's ongoing exploration of new strategies to leverage different death mechanisms to overcome drug resistance and activate anti-tumor immunity.

Apoptosis serves as a high-frequency term in both Chinese and English literature, and is a burst term and a representative term in cluster analysis. Although the popularity of apoptosis has declined in recent years, it remains at a relatively high level. The sustained high frequency of "apoptosis" represents the foundational pillar of this research. Analysis of the incorporated literature reveals that key apoptosis-related targets and pathways, such as Bax, Bcl-2, cleaved caspase-3, PI3K/Akt/Stat3, P53/cytochrome C/poly (ADP-ribose) polymerase (PARP), Hsp90β, cyclin-dependent kinases (CDKs), and NF-κB. Furthermore, several TCM compounds and active ingredients, including *Sorbaria sorbifolia (L). A.Braun* flavonoid derivatives,[102] Da Chaihu Decoction,[103] *Scutellaria baicalensis Georgi* extract,[104] and Fuzheng Huajie Decoction,[105] have been demonstrated to induce apoptosis in HCC cells by modulating these specific pathways and targets.

Ferroptosis has garnered significant attention, emerging as a hot topic in recent English literature. It also stands out as a representative thematic term in co-citation literature cluster analysis. Analysis of the incorporated literature reveals that pivotal regulators, such as the SIRT1/YY1/GPX4 signaling axis and *ATF3*, represent the core research focus in ferroptosis. TCM active ingredients, including oxymatrine[106] and sophoridine derivatives,[107] have been demonstrated to induce ferroptosis in HCC cells by targeting these specific signaling pathways and related ferroptosis-associated targets.

Timeline analysis indicates that pyroptosis has become a research hotspot in recent years. Further literature review reveals that molecules such as Caspase-3/GSDME and *ATF4* are hotspot molecule and pathway regulating pyroptosis in recent years. Moreover, certain traditional Chinese medicines or their active ingredients, including germacrone (GM),[108] Cannabidiol (CBD),[10] and *Curcuma aeruginosa Roxb*, can induce pyroptosis in liver cancer cells by targeting these molecules, thereby inhibiting tumor progression.

Autophagy, as a high-frequency keyword and representative term in cluster analysis, exhibits an extensive network of connections with other terms in keyword co-occurrence analyses of both Chinese and English literature, underscoring its broad influence and drawing significant scholarly attention. The role of autophagy in HCC is context-dependent, functioning as either a tumor-suppressor or a pro-survival mechanism. Intriguingly, several TCM derived compounds appear to exploit the tumor-suppressive aspect of autophagy to inhibit HCC progression. PI3K/Akt/mTOR, LC3, p62, among others, are popular targets and pathways associated with autophagy. TCM or their active ingredients, such as digoxigenin[109] and arsenic trioxide (ATO),[110] can induce autophagy in liver cancer cells by regulating these pathways or targets.

Proliferation and Cell Cycle Arrest

Proliferation, as a high-frequency keyword and representative term in cluster analysis, demonstrates extensive connectivity with other terms in keyword co-occurrence analyses of both Chinese and English literature, underscoring its broad influence. Through timeline analysis and keyword heatmap visualization, it is evident that while its prominence has slightly declined post-2021, it remains at a relatively high level. This indicates that directly inhibiting cell proliferation remains a fundamental mechanism for verifying the anti-liver cancer efficacy of TCM. Cell cycle arrest, another high-frequency keyword with substantial connectivity in English literature keyword analyses (centrality = 0.19) and serving as a representative cluster term, highlights its significant influence and pivotal role in TCM-based HCC research. Timeline and heatmap analyses reveal a steady increase in its prominence since 2016. This dynamic change reveals an important shift in the study of TCM's anti-hepatocarcinoma mechanisms: shifting from generally confirming the effect of "inhibiting proliferation" to precisely analyzing the underlying mechanism of 'how proliferation inhibition is achieved by intervening in cell cycle checkpoints. Analysis of the incorporated literature reveals that key targets and pathways for cell cycle arrest and proliferation include Cdc25C, JNK, PINK1-PRKN, the ATM/CHEK2/KNL1 axis, the ATM-dependent p53-p21-CDK1 pathway, the CHK1-CDC25C cascade, and AKT/mTOR. Furthermore, several TCM and TCM active ingredients, such as β,β-Dimethylacrylalkannin,[111] Kaempferol,[112] Cucurbitacin B,[113] Ailanthone,[114] and *Oldenlandia diffusa (Willd).Roxb*.,[115] have been shown to suppress HCC progression by modulating these specific mechanisms.

Tumor Microenvironment

Keyword analysis reveals that the TME has emerged as a hot topic in recent years. Burst detection analysis indicates that TME remains a burst term through 2025, while also serving as a representative thematic term in co-citation reference cluster analysis. These findings underscore its sustained scholarly attention. The shift from a cancer-cell-centric view to targeting the TME represents a shift in cancer therapeutics. The emergence of TME as a burst term reflects the growing recognition within TCM research of the importance of modulating the immunosuppressive and pro-tumorigenic niche of HCC, aligning with the holistic and systemic principles of TCM itself. Analysis of the incorporated literature reveals that vascular endothelial growth factor A (VEGFA), hypoxia-inducible factor 1α (HIF-1α), lysyl oxidase-like 2 (LOXL2), *TWIST, CDH1*, indoleamine 2,3-dioxygenase (IDO1), interferon-gamma (IFNγ), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor-α (TNF-α), C–C motif chemokine ligand 2 (CCL-2), WNT1, β-catenin, NF-κB, mitogen-activated protein kinase (MAPK), protein kinase B (AKT), SRC kinase (SRC), adenomatous polyposis coli (APC), cholic acid, taurocholic acid, and deoxycholic acid are popular key targets, signaling pathways, or metabolites associated with the tumor immune microenvironment, inflammatory microenvironment, and hypoxic microenvironment. The most popular studied cellular mechanisms involve the regulation of immune cell populations such as CD8+ T cells, myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and tumor-associated macrophages (TAMs), as well as microvessel density (MVD). Furthermore, traditional Chinese medicines or their active components, such as Huaier,[116] phenylethanol glycosides,[117] YIV-906,[118] Gehua Jiecheng Decoction,[119] and YCHD,[120] can modulate the tumor microenvironment by targeting these key elements.

Oxidative Stress

Oxidative stress has emerged as a high-frequency keyword and representative term in cluster analysis, demonstrating extensive connectivity with other terms in English literature keyword co-occurrence networks. Notably, "antioxidant activity" has been identified as a burst term, while keyword heatmap analysis reveals sustained research intensity since 2019. These findings collectively indicate that oxidative stress and antioxidant mechanisms constitute focal topics in TCM-based HCC therapy. This profoundly reveals a core and increasingly recognized paradigm in the field of TCM research against liver cancer: regarding redox homeostasis as a pivotal and regulable therapeutic target, rather than merely focusing on antioxidation. The sustained research fervor indicates that this domain is evolving from the early, crude notion of "antioxidation" towards a refined strategy of "bidirectional and precise modulation" of oxidative stress. There is a close linkage between oxidative stress and the onset of HCC,[121] and oxidative stress can promote the metastasis of liver cancer.[122] Interestingly, this dual-faced role is highlighted by findings that, conversely, inducing excessive oxidative stress can also directly kill liver cancer cells. This paradox underscores the necessity of a bidirectional and precise modulation strategy, rather than a simplistic antioxidation approach. Literature analysis reveals that the modulation of oxidative stress involves key functional targets, such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), NF-κB, thioredoxin reductase, and antioxidant enzymes like superoxide dismutase and catalase, and is commonly assessed by specific biomarkers of oxidative damage, such as 8-hydroxy-2'-deoxyguanosine (8-OHdG). Several TCM compounds, including mangiferin,[123] gingerol,[124] and deoxyelephantopin,[125] have been shown to inhibit HCC progression by precisely modulating these targets, thereby restoring redox homeostasis.

Epithelial–Mesenchymal Transition

EMT has been identified as one of the burst terms and a representative keyword in cluster analysis, demonstrating sustained research interest in this field. The reason for its long-term attention lies in its role as a key driving force behind liver cancer invasion and metastasis. The emphasis placed on it in TCM research signifies that this field has delved into the mechanistic exploration of combating the aspect of liver cancer—metastasis. The timeline reveals that research in this area started early and has maintained its research enthusiasm, reflecting a consensus in the academic community: inhibiting or reversing EMT is a strategy for blocking liver cancer metastasis, and TCM demonstrates unique advantages in multi-target regulation in this process.[126] Analysis of the included literature reveals that the hotspot targets and signaling pathways related to EMT include NF-κB/NLRP3/β-catenin, *CCL20, CDH1, CDH2, VIM*, ERK1/2, *c-Myc, CD133, CD44*, AKT/GSK3β/β-catenin, TGF-β, *SNAIL*, among others. Various traditional Chinese medicines (TCMs) or

active ingredients derived from TCMs, such as Yangzheng mixture,[127] Schisandra lignan,[128] Huqi Zhengxiao Decoction,[129] matrine,[130] hydroxygenkwanin,[131] among others, can regulate these targets and pathways to inhibit or reverse EMT.

Metabolic Reprogramming

Although metabolic reprogramming does not rank among high-frequency burst terms, timeline analysis and keyword co-occurrence studies reveal that glycolysis and lipid metabolism have emerged as novel research hotspots in recent years. This indicates that metabolic reprogramming recognized as one of the hallmarks of cancer is receiving increasing scholarly attention.[132] It precisely uncovers an emerging and highly promising frontier in TCM research against liver cancer: targeting the abnormal energy metabolism of tumor cells and the metabolic remodeling of the TME. This trend indicates that the field is transcending traditional research on proliferation/death signaling pathways and delving into the "metabolic vulnerabilities" of tumors, aiming to inhibit tumor progression by targeting and disrupting their energy and nutrient supply. TCM demonstrates its unique advantages in multi-component and multi-target regulation in this domain. Literature analysis reveals that the hotspot targets and pathways associated with metabolic reprogramming include lactate dehydrogenase A *(LDHA*), hexokinase 2 (*HK2*), and pyruvate kinase M2 (*PKM2*), as well as the ROS/P38 MAPK/P53 signaling cascade, *GLUT1, ABCG2, MDR1*, the AMPK/SREBP1/FASN axis, and aspartate-alanine-glutamate metabolism. Multiple traditional Chinese medicines (TCMs) or their bioactive components, such as Sini Decoction polysaccharide complex,[133] icariin,[134] saikosaponin D,[135] cinobufacini injectione,[136] and dihydroartemisinin,[137] have been shown to modulate these targets or pathways, thereby regulating glucose, lipid, and amino acid metabolism in hepatocellular carcinoma cells and ultimately inhibiting tumor growth.

Gut Microbiota

Analysis of keyword co-occurrence and timeline diagrams identifies the gut microbiota as a prominent and enduring research focus, which is underscored by its continued status as a burst term into 2025 and a high centrality (0.26). This highlights its pivotal role in Traditional Chinese Medicine (TCM) and liver cancer research, signaling a shift in anti-HCC strategies: from direct tumor cell targeting to indirect inhibition via remodeling the gut–liver axis ecology. A central goal of this field is to unravel how TCM compounds, by modulating the structure and metabolic output of the gut microbiota, remotely regulate hepatic immune and metabolic homeostasis to influence HCC progression. By analyzing the included literature, it can be observed that the hot-topic microbial groups in the research include Firmicutes, Bacteroidetes, Proteobacteria, *Bacteroides, Lactobacillus, Eubacterium, Bacteroides fragilis,* and so on. The popular mechanisms involved encompass enhancing bile salt hydrolase activity, modulating the *Bacteroides fragilis*-glycoursodeoxycholic acid-farnesoid × Receptor/retinoid × receptor α-mTOR axis, and enhancing short-chain fatty acid production, among others. Various traditional Chinese medicines or their active ingredients, such as Xiayuxue Decoction,[138] CeT,[139] Jiawei Xiaoyao San,[140] and *Panax ginseng C. A. Mey*,[141] can regulate the abundance of these microbial groups and thereby inhibit the progression of liver cancer through the aforementioned mechanisms.

Angiogenesis

Angiogenesis is a high-frequency term and a representative thematic word in the clustering of co-cited references, with a centrality of 0.13, indicating that it is a crucial aspect in the research of TCM and liver cancer. From the timeline diagram, it can be observed that research related to angiogenesis in this field commenced relatively early, collectively underscoring its foundational role in TCM research against liver cancer. The TCM provides a rich natural source for developing multi-target anti-angiogenic therapies, with research evolving from merely characterizing inhibitory effects to systematically revealing their multi-level, multi-pathway synergistic mechanisms. Modern studies have demonstrated that traditional Chinese herbs can inhibit tumor angiogenesis through multiple mechanisms, such as suppressing pro-angiogenic factor expression, elevating anti-angiogenic factor levels, suppression of endothelial cell proliferation, attenuation of MVD in HCC tissues, and modulation of associated signaling cascades, thereby inhibiting tumor angiogenesis.[142] By analyzing the included literature, it is found that the hotspot targets and pathways for anti-tumor angiogenesis include basic fibroblast growth factor (bFGF), VEGF/ERK/HIF-1α, MMP2, MMP9, Akt1, IL-6, IL-1β, IL-17, TNF, TIMP1, EMMPRIN, etc. Various traditional Chinese medicines or their active monomers, such as saikosaponin

B2,[143] *Oldenlandia diffusa (Willd). Roxb*.,[144] Jianpi Huayu Decoction,[145] and Ganqingning Formula,[146] can modulate these targets or signaling pathways to exert anti-angiogenic effects.

Hepatic Steatosis and Hepatic Fibrosis

Fatty liver is a representative term in cluster analysis. From the burst word analysis, it can be seen that both fatty liver and hepatic steatosis remain as burst terms in 2025, indicating that they are still hot topics in recent years. Liver fibrosis and liver cirrhosis are high-frequency words and representative terms in cluster analysis, with liver fibrosis having a centrality as high as 0.15. Timeline analysis reveals that liver fibrosis has been a consistent theme throughout the entire research period. Liver fibrosis is a representative thematic word in the co-citation reference clustering analysis, demonstrating that it is a core topic in this field. Liver cirrhosis has also garnered significant attention. Keyword heatmap analysis shows that the popularity of liver cirrhosis and liver fibrosis has increased since 2019 and 2020, respectively, indicating that they are hot topics in recent years in this field. The sustained prominence of these terms reflects their established biological significance: fatty liver, liver fibrosis, and cirrhosis represent crucial stages in the progression from chronic liver disease to cancer. Implementing early liver-protective treatments and promptly controlling the progression of chronic liver diseases are of significance for preventing liver cancer. This reveals an shift in the field of TCM research on combating liver cancer: moving the focus of treatment earlier in the disease process, and committing to intervening in the key pathological processes through which chronic liver diseases progress to liver cancer, so as to prevent the occurrence of liver cancer. This trend highlights the promising application prospects of TCM's concept of "preventive treatment of disease" in the prevention and treatment of liver cancer. Analysis of the included literature reveals that the hotspot targets and pathways for liver fibrosis include Smad7, TGF-βR1, Smad2, Smad3, long-chain acyl-CoA synthetase 4 (*ACSL4*), miR-193a-3p, and *TGF-β2*, among others. Various traditional Chinese medicines and their monomers, such as CKI and Taohong Siwu Decoction, can exert anti-liver fibrosis effects by regulating these targets or signaling pathways. For hepatic steatosis, the hotspot targets and pathways involve mature sterol regulatory element-binding protein 1c (mSREBP1c), carbohydrate-responsive element-binding protein (ChREBP), AMPK/PGC1α, PPARα, carnitine palmitoyltransferase 1α (*CPT1α*), acyl-CoA oxidase 1 (*ACO1*), miR-373, AKT serine/threonine kinase 1 (*AKT1*), and the AKT-mTOR-S6K pathway, among others. Multiple traditional Chinese medicines and their monomers, such as BAL and BB, can exert anti-hepatic steatosis effects by modulating these targets or signaling pathways.

Metastasis

Metastasis, migration, and invasion are all high-frequency terms. Notably, invasion has a centrality as high as 0.19. Furthermore, migration and invasion are representative terms in cluster analysis, indicating that metastasis, migration, and invasion are focal points of research in this field. This aligns with the clinical reality that the invasion and migration of malignant cells are among the leading causes of mortality in HCC patients. Tumor migration and invasion represent a multiple steps and factors process involving the regulation of numerous signaling pathways. Therefore, targeting these signaling molecules to interfere with tumor metastasis is one of the strategies employed in TCM for treating HCC metastasis. Analysis of the included literature indicates that EGFR-TFEB, miR-532-5p/CXCL2, mTOR, and β-catenin are hot molecules and pathways associated with metastasis. TCM formulas or their active monomers, such as Jiedu Recipe,[147] CeT,[148] and BB,[149] can suppress HCC metastasis by modulating these targets and pathways.

Inflammation

Inflammation and anti-inflammatory activity are, respectively, high-frequency terms and burst terms. Moreover, in the analysis of keywords in English literature, inflammation exhibits an extremely high number of connections with other terms, indicating its broad influence and drawing attention from researchers. It reveals an evolution in the field of TCM research against liver cancer: shifting from directly killing tumor cells to targeting "tumor-associated inflammation". Inflammatory responses release various pro-inflammatory cytokines, which may promote the proliferation, invasion, and metastasis of HCC cells.[150] Analysis of the included literature reveals that popular inflammation-related targets and pathways include the PI3K/AKT/NF-κB pathway, as well as key molecules such as IL-6, TNF-α, *STAT3*, IL-2, and IFN-γ. Notably, numerous traditional Chinese medicines or their bioactive monomers, such as Liuweiwuling Tablet,[151] total

saponins extracted from *Astragalus membranaceus (Fisch). Bunge*,[152] and rosmarinic acid,[153] have demonstrated the ability to modulate these targets or pathways, thereby inhibiting inflammation in HCC.

Insulin Resistance

Insulin resistance (IR) is a representative term in cluster analysis and remains a burst term in 2025, suggesting that it is a current research hotspot. The liver is a key regulatory organ for human metabolism, and liver cancer is often associated with metabolic alterations. IR frequently triggers metabolic disorders, including hyperglycemia, hyperinsulinemia, abnormal lipid metabolism, and chronic low-grade inflammation. Lipid metabolism disorders may lead to non-alcoholic fatty liver disease. All these factors are implicated in the development of liver cancer, thereby increasing the risk of its occurrence. IR participates in various metabolic processes and signal transduction pathways in the body, promoting the progression of liver cancer by altering the TME, mediating tumor cell immune evasion, and affecting autophagic activity.[154] Analysis of the included literature reveals that popular insulin resistance-related targets and pathways encompass *G6PC, PEPCK*, Akt, JNK, and miR-125a-5p, among others. Notably, numerous traditional Chinese medicines (TCMs) or their bioactive monomers, such as Ginsenoside Rg1.[155] and Dioscin, have demonstrated the ability to modulate these targets or pathways, thereby regulating insulin resistance in HCC.[156]

Immunomodulation

Immunomodulation has emerged as a hot topic in recent times, while immune function stands out as a high-frequency keyword with an exceptionally large number of connections to other terms in keyword analysis, making it a representative term in cluster analysis. The timeline analysis reveals that immune function has been a central theme throughout the entire research period, underscoring its significance as a core subject in this field. According to the keyword heatmap, immune function has also been a hot topic in recent years. TCM has been demonstrated to possess immunomodulation properties. They can restore immune surveillance and enhance immune responses against HCC by upregulating immunostimulatory factors or downregulating immunosuppressive factors, acting on multiple targets in various ways to exert antitumor effects.[10] Analysis of the included literature reveals that popular tumor immune-related targets and pathways encompass interleukin-12 (IL-12), JAK2/STAT3, glucocorticoid receptor (GR), MHC-I, granzyme B, IFN-γ, TNF-α, and the miR-122-3p/UBE2I/NF-κB/PD-L1 axis, among others. At the cellular level, key mechanisms include promoting the maturation of bone marrow-derived dendritic cells (BMDCs), facilitating the infiltration of CD8+ T cells, mature dendritic cells, and MHC-I-positive cells. Notably, numerous traditional Chinese medicines (TCMs) or their bioactive monomers, such as Yupingfeng Powder,[157] ginsenoside Rh1,[158] luteolin,[159] and Liu Jun Zi Decoction,[160] have demonstrated the ability to modulate these targets or pathways, thereby ameliorating the immunosuppressive microenvironment in HCC.

Signaling Pathways

Pathways are high-frequency keywords, exhibiting an extremely large number of connections with other terms. The timeline analysis reveals that pathways have persisted as a core theme throughout the entire research period, indicating their centrality in this field. This supports a shift in TCM research on combating liver cancer: namely, the research focus is increasingly shifting from the regulation of single targets to the multi-target, systematic regulation of signaling networks. It reflects that the occurrence and progression of liver cancer are driven by multiple signaling pathways, and the multi-component nature of TCM precisely endows it with a unique advantage in intervening in this network. For example, TCM or their active compounds, such as Xihuang Pill, *Curcuma aeruginosa Roxb, Alpinia officinarum Hance*, ginsenosides, and tubuloside B, can exert anti-liver cancer effects by modulating pathways like Gsk-3B/B-Catenin,[161] Pi3K/Akt/Mtor,[162] Mek/Erk,[163] Csf-1/Pi3K/Akt,[164] NF-κB/*ST6GAL*1,[165] *ATM*/*CHEK2*/*KNL*1,[112] p53,[166] Erk1/2,[128] Stat3-Pdl1,[167] Foxo,[168] Hippo-Yap,[169] among others. Among them, the NF-κB signaling pathway, as a high-frequency term and representative vocabulary in cluster analysis, exhibits an exceptionally large number of connections with other terms in keyword analysis, thus garnering particular attention. From the timeline chart, it is evident that research related to NF-κB commenced relatively early. According to literature reports, the activity of the NF-κB signaling pathway in HCC tissues is higher than that in adjacent non-cancerous tissues. Changes in its expression level show a certain correlation with the clinical manifestations of HCC patients and play a regulatory role in processes such as proliferation,

invasion, apoptosis, and immune evasion of HCC.[170] Some traditional Chinese medicines or their monomer components, such as buddleoside,[171] methyl gallate,[172] Catalpol,[173] Moscatilin,[174] Biejiajian Pill,[175] may inhibit HCC by regulating the NF-κB signaling pathway.

Network Pharmacology and Molecular Docking

"Network pharmacology" is a high-frequency term. Both network pharmacology and molecular docking remain in a burst state as of 2025. Molecular docking has a notably high centrality of 0.15. According to the keyword heatmap, network pharmacology has maintained extremely high popularity since 2019. In timeline analysis, network pharmacology spans the entire research period. Network pharmacology has a vast number of connections with other terms. It indicates that network pharmacology and molecular docking are the core themes in this field. The Network pharmacology enables the complex holistic regulatory effects of TCM to be analyzed and predicted using modern scientific language, significantly expediting the modernized elucidation of its mechanisms of action and the discovery of precision drugs. Driven by this research trend, numerous traditional Chinese medicines or their monomeric compounds, such as *Amorpha fruticosa L* essential oils,[176] herb pair *Adenophora stricta Miq–Ophiopogon japonicus (Thunb). Ker Gaw*l,[177] *Oldenlandia diffusa (Willd). Rox*b,[178] and Peanut skin,[179] have been investigated as representative examples of the application of network pharmacology and molecular docking methods. The hot targets and signaling pathways identified through network pharmacology and molecular docking include Notch, *IL6, TNF*, AGE-RAGE, phosphorylated AKT, *AKT1, MYC, CASP3, ESR1, EGFR*, and *JUN*, among others. Experimental verification has shown that the aforementioned traditional Chinese medicines or their active ingredients can inhibit HCC cells via these targets or pathways.

Omics Technologies

From timeline analysis and keyword co-occurrence network analysis, it can be seen that keywords such as transcriptomics and metabolomics have emerged as hot topics of focus in recent years. Omics technologies provide an unprecedented, systematic perspective for dissecting the multi-component, multi-target, and holistic regulatory nature of TCM. By enabling high-throughput, unbiased data acquisition, they facilitate the identification of numerous potential biomarkers and therapeutic targets, thereby laying a solid foundation for elucidating complex mechanisms of action, discovering novel active ingredients, and advancing precision medicine. Precisely under this research trend, numerous traditional Chinese medicines or their monomeric compounds, such as xanthomicrol,[180] Di Wu Yang Gan Capsule,[181] Huachansu tablets,[182] CB[183] have become representative cases for the application of omics technologies. The hot targets and signaling pathways for liver cancer identified through omics technologies in the aforementioned Chinese herbal medicines include PI3K/Akt/MMP9, *RAP1*, arachidonic acid, ATM/CHK2/p53, CDK1, among others. It provides molecular-level validation for their multi-targeted and synergistic mechanisms of action.

Bioinformatics

From timeline analysis and keyword co-occurrence network analysis, it is evident that bioinformatics has emerged as a hot topic in recent years and stands out as a burst term with relatively high burst intensity, indicating its status as a focal point in the field. The application of bioinformatics technology in TCM research provides technical support for the analysis of massive biological data. It accelerated the integration of TCM with systems biology and significantly propelling mechanistic elucidation and modernization. Due to this, a series of studies have employed this technology to conduct in-depth explorations into the mechanisms by which TCM herbs, such as She Lian Capsule,[184] quercetin, CeT, BB, cantharidin,[185] Aitongxiao prescription,[186] *Scutellaria barbata D. Don*,[187] treat HCC. The hot targets and signaling pathways for HCC identified through bioinformatics in the aforementioned Chinese herbal medicines include PI3K-Akt, TNF, IL-17, *TOP2A, CYP1A2, CYP2B6, IGFBP3, AURKA, BIRC5, CCNB1, CDKN3, TYMS, MAP3K4*, miR-199a-3p, *CDK1, CDK4, SRC*, and *E2F1*, among others. These applications underscore the indispensable role of bioinformatics in modernizing TCM research and elucidating its complex mechanisms of action.

Nano-Delivery of Traditional Chinese Medicine

From the keyword timeline analysis, it can be seen that TCM nano-delivery has garnered attention as a research hotspot in recent years. Chinese herbal medicine monomers exhibit immense potential in the treatment of liver cancer. Nevertheless, certain monomers application is limited by low solubility, poor bioavailability, inadequate tumor accumulation,[188,189] a narrow therapeutic window, high toxicity, and non-targeted accumulation outside solid tumors.[190] To overcome these challenges, nanocarriers provide substantial benefits, such as enhanced bioavailability, remarkable passive or active targeting capabilities, and stimuli-responsive drug release. An analysis of the included literature indicates that popular nanocarriers encompass poly(2-(N-oxide-N,N-diethylamino) ethyl methacrylate)-b-poly (ε-caprolactone) copolymer (OPDEA-PCL), galactose-modified fifth-generation (G5) polyamidoamine dendrimers (G5-Gal), dual-modified liposomes combining hyaluronic acid and Hep1-6 liver cancer cell membranes (HMCLPs), and glycyrrhetinic acid-conjugated nanocarriers, among others. The incorporation of anti-tumor active ingredients from TCM, such as ICT,[188] Res,[189] CeT,[190] and BB,[191] into nanocarriers has demonstrated immense potential in advancing the treatment of HCC.

Data Mining and Deep Learning

Data mining is a high-frequency term and the one with the longest duration of burstiness, remaining in a state of burstiness even in 2025. In keyword analysis, it has an extremely large number of connections with other terms and stands as a representative term in cluster analysis, drawing significant attention. Moreover, the keyword heatmap reveals that data mining has maintained extremely high popularity since 2019. Deep learning, as a representative keyword in the past two years, has also garnered considerable attention. Together, they signal an ongoing shift in TCM anti-HCC research: the exploration of traditional empirical knowledge with data-driven discovery based on massive datasets and intelligent algorithms. The essence of this transformation lies in converting TCM clinical practices and herbal formula knowledge into computable, minable, and optimizable data objects, thereby systematically unlocking the scientific laws and clinical value they embody. Commonly used methods in data mining and deep learning include complex co-occurrence networks, association rule analysis, latent structures, cluster analysis, Bayesian network analysis, multi-scale convolutional neural networks, and genetic algorithms. Research based on these methods has identified multiple core herbal formula combinations, such as *Atractylodes macrocephala Koidz* and *Codonopsis pilosula (Franch). Nann*f,[192] *Astragalus membranaceus (Fisch). Bunge* and *Scutellaria barbata D.Don*,[193] Huqi Powder,[194] and combinations of *Strychnos nux-vomica L, Gleditsia sinensis Lam*, and *Psoralea corylifolia* L.[195] Additionally, core therapeutic approaches identified include replenishing qi and strengthening the spleen, clearing heat and detoxifying, and promoting blood circulation to remove stasis.[196]

Innovation and Exploration in TCM Theory

From the keyword timeline analysis, it is evident that the innovation and exploration of TCM theories have emerged as research hotspots in recent years, with the latest theories including the Zhongzhou (Middle Jiao) theory, the "circular flow of qi" theory, the Triple Burner Qi Transformation theory, and the Protective Field theory, among others. By returning to and deepening the inherent theoretical framework of TCM, guided by its holistic perspective, dynamic outlook, and the principle of treatment based on syndrome differentiation, we aim to establish unique and more fundamental concepts and strategies for the prevention and treatment of liver cancer. This transformation seeks to address numerous bottlenecks encountered by modern medicine in liver cancer prevention and treatment. It highlights the distinctive wisdom and contemporary value of TCM theories in managing complex diseases. For example, the Zhongzhou (Middle Jiao) theory advocated by TCM liver disease expert Guan Youbo proposed the principle of "regulating the liver, spleen, and kidneys, with Zhongzhou as the priority" for treating liver diseases. Professor Guan believed that the spleen is the primary organ affected in liver diseases, and stomach qi is the "critical juncture of life and death." He emphasized that in treating liver cancer should prioritize Zhongzhou.[197] Huang Yuanyu, a Qing Dynasty physician, pioneered the "circular flow of qi"

theory. Research indicates that according to this theory, its core pathogenesis being the "sinking of Wood Qi," where liver stagnation leads to cancer. The treatment of liver cancer should involve comprehensive regulation of the five internal organs

(heart, liver, spleen, lungs, and kidneys).[198] Another study introduced the Protective Field theory into liver cancer treatment and proposed corresponding treatment principles, such as balancing Yin and Yang, dynamically attacking and tonifying, regulating pectoral qi to promote the formation of a holistic protective field, securing unaffected areas first, protecting the lung's intrinsic protective field, soothing the liver and promoting bile flow to facilitate urination and defecation, and providing pathogens with an exit route.[199] A study guided by the Triple Burner Qi Transformation theory proposed dynamic syndrome differentiation and treatment for liver cancer patients. It pointed out that during the Qi stagnation-pathogenic excess stage, detoxification and triple burner differentiation are key; during the pathogenic excess-cancer toxin dominance stage, the focus should be on the Middle Burner while considering the Upper and Lower Burners; and during the cancer toxin dominance-Yin-Yang separation stage, the emphasis should shift to the Lower Burner while balancing Yin and Yang.[200] Research has indicated that the liver exhibits significant rhythmicity in its TCM functions of dispersion and blood storage. The development of liver cancer are closely associated with disruptions in biological rhythms. Modern studies have confirmed that staying up late, shift work, and irregular eating habits can disrupt the expression of the liver's circadian clock genes, affecting metabolism, immunity, and DNA repair, thereby accelerating the deterioration of liver cancer. Time-based medical treatment strategies of TCM for liver cancer have been proposed, such as restoring biological rhythms through measures like adjusting sleep, eating on time, and maintaining regular routines to improve liver function and quality of life.[201] In addition, some medical practitioners have also applied theories such as "Five Movements and Six Qi,[202] Three Stages and Six Discriminations" academic theory,[203] Emotion-focused nursing based on TCM theory[204] to the treatment of liver cancer as well as to the elucidation of its etiology and pathogenesis. More and more traditional Chinese medicine theories about liver cancer are being explored, innovated, inherited, and applied to clinical practice of TCM.

Strengths and Limitations of the Study

This study possesses several strengths. First, this study is the first comprehensive bibliometric analysis specifically focused on the application of TCM in liver cancer research over the past decade (2015–2025). Second, the analysis encompassed 11,230 publications from four major databases (CNKI, Wanfang, VIP, and WOS), including both Chinese and English literature. This dual-language approach provides a more holistic and less biased view of the global research landscape. Third, we employed a range of bibliometric and visualization tools (CiteSpace, VOSviewer, R, COOC, etc.) to conduct multi-dimensional analyses, including publication trends, collaboration networks, keyword co-occurrence, cluster analysis, and burst detection. This multi-faceted methodology offers robust insights into the evolution, current hotspots, and intellectual structure of the field. This study has several limitations. First, while we utilized major databases, some relevant publications from other regional or specialized databases might have been missed. Second, our search strategy, although comprehensive, may not have captured all relevant articles due to the variability in keyword usage and indexing across different databases. Third, bibliometric analysis primarily reflects quantitative trends and patterns in the literature; it does not directly assess the detailed scientific findings of the individual studies included. Finally, the field is evolving, and new trends may emerge after our data collection cut-off date (February 2025).

Future Research Directions

First, Chinese herbal medicines represent a valuable resource of natural drugs in China. However, the direct targets or pathways of many anti-tumor Chinese medicine active ingredients remain unclear. By drawing on current research approaches used in Western medicine to investigate drug functional targets and pathways, traditional Chinese medicine could achieve widespread application in the treatment of liver cancer and even other diseases. Second, more long-term, high-quality RCTs and real-world studies are warranted to conclusively demonstrate the efficacy of TCM therapies in improving survival, quality of life, and reducing recurrence rates. As TCM interventions become more widely accepted, it is crucial to conduct systematic and rigorous assessments of their safety profiles. Future clinical trials and post-marketing surveillance should prioritize the documentation of adverse reactions, interactions between TCM and other drugs, as well as quality control of TCM products. Third, the potential of TCM as an adjuvant therapy to enhance the efficacy and reduce the side effects of conventional treatments, such as TACE, targeted therapy, and immunotherapy, should become a key research focus. Relevant studies should explore the mechanisms by which TCM sensitizes tumors to these therapies, for example, by modulating the immune microenvironment or reversing drug resistance. Finally,

developing standardized, evidence-based treatment protocols for the integration of TCM and Western medicine represents a crucial step forward. Mechanistic research on TCM for the treatment of HCC should delve deeper into current research hotspots, such as the regulation of the TME, ferroptosis, pyroptosis, metabolic reprogramming, and the gut–liver axis, utilizing in vivo models and multi-omics technologies for in-depth investigation.

Conclusion

TCM research on liver cancer treatment is in a phase of continuous development internationally, while in China it is maturing, yet overall, it demonstrates a positive growth trend and vast potential. Clinical efficacy, mechanisms of action, omics technologies, bioinformatics technology, network pharmacology and molecular docking, TCM syndrome research, TCM theory innovation and exploration, TCM nanodelivery, data mining, and deep learning are likely to remain hotspots in TCM research for liver cancer treatment. Research on TCM for liver cancer treatment should further enhance interdisciplinary and cross-regional collaboration, continue leveraging advanced technologies, and deepen the communication and integration between TCM and modern medicine, so as to more comprehensively and systematically explore the potential of TCM in the treatment of liver cancer.

Abbreviations

Recs, records; HCC, hepatocellular carcinoma; TCM, traditional Chinese medicine; WOSCC, Web of Science Core Collection; TACE, transarterial chemoembolization; EMT, epithelial–mesenchymal transition; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; OSR, overall survival rate; ERR, extrahepatic recurrence rate; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; γ-GT2, γ-glutamyl transpeptidase; CA19-9, carbohydrate antigen 19-9; PARP, poly (ADP-ribose) polymerase; CDKs, cyclin-dependent kinases; ROS, reactive oxygen species; GM, Germacrone; CBD, Cannabidiol; ATO, arsenic trioxide; ATM, ataxia telangiectasia-mutated; CHK1, checkpoint kinase 1; TME, tumor microenvironment; MVD, microvessel density; VEGFA, vascular endothelial growth factor A; HIF-1α, hypoxia-inducible factor 1α; LOXL2, lysyl oxidase-like 2; IDO, indoleamine 2,3-dioxygenase; MDSCs, myeloid-derived suppressor cells; IFNγ, interferon-gamma; IL-6, interleukin-6; IL – 10, interleukin-10; TNF-α, tumor necrosis factor-α; CCL-2, C–C motif chemokine ligand 2; VEGF, vascular endothelial growth factor; MAPK, mitogen-activated protein kinase; AKT, protein kinase B; SRC, SRC kinase; APC, adenomatous polyposis coli; YCHD, Yinchenhao Decoction; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; DEN, Diethylnitrosamine; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; LDHA, lactate dehydrogenase A; HK2, hexokinase 2; PKM2, pyruvate kinase M2; LDH, lactate dehydrogenase; bFGF, basic fibroblast growth factor; CKI, Compound Kushen Injection; BAL, Baicalein; mSREBP1c, mature sterol regulatory element-binding protein 1c; ChREBP, carbohydrate-responsive element-binding protein; CPT1α, carnitine palmitoyltransferase 1α; ACO1, acyl-CoA oxidase 1; AKT1, AKT serine/threonine kinase 1; IL-12, interleukin-12; BMDCs, bone marrow-derived dendritic cells; GR, glucocorticoid receptor; CB, Cinobufagin; ATXP, Aitongxiao prescription; ICT, Icaritin; OPDEA-PCL, poly(2-(N-oxide-N,N-diethylamino)ethyl methacrylate)-b-poly(ε-caprolactone); NPs, nanoparticles; Res, Resveratrol; G5, fifth-generation polyamidoamine; Gal, galactose; CeT, Celastrol; HMCLPs, Dual-modified liposomes combining hyaluronic acid and Hep1-6 liver cancer cell membrane; BB, Berberine; BB-GA NDs, combining berberine with glycyrrhizic acid to form a nano-drug; MRI, magnetic resonance imaging; RCTs, randomized controlled trials.

Data Sharing Statement

The original data of the study are detailed in this article. The datasets generated and analyzed during the current study are available from the corresponding author, Bao-chen Zhu.

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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 there are no competing financial interests or personal affiliations that might influence the research presented in this publication.

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