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Research Trends on Nanomaterials and Hepatocellular Carcinoma From 1999 to 2024: A Bibliometric Analysis

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Objective: Extensive exploratory studies have been conducted and promising progress has been made in the use of nanomaterials for the diagnosis and treatment of hepatocellular carcinoma (HCC). Here, we aimed to reveal the evolution and trends in this field through bibliometric analysis.

Methods: English-language publications (1999–2024) in the field of nanomaterials and HCC were retrieved from the Web of Science database, and eligible articles were selected for bibliometric analysis (data extraction, statistical analysis, and visualization) using VOSviewer and Citespace software.

Results: A total of 1617 eligible publications were analyzed. The number of publications increased rapidly from 2012 and peaked in 2020. China contributed the most publications, and the United States had the most citations. The Chinese Academy of Sciences was the most influential institution. The "International Journal of Nanomedicine (DOVE Medical)" published the most articles, while "Biomaterials (Elsevier)" was the most influential journal. Jie Tian had the highest number of publications, and Dan Shao had the highest average citation per article. Keyword analysis revealed that nanoparticles for targeted drug delivery, therapy and imaging of HCC were research hotspots. Keywords with citation bursts in the last three years included photodynamic therapy, sorafenib, and tumor microenvironment. Nano-vaccines, nano-antibodies, and synergistic therapies were emerging therapeutic strategies. A total of seven clinical trials were published, but to date there have been no major breakthroughs in HCC therapy using nanomaterials.

Conclusion: Research on nanomaterials and HCC has shown an overall upward trend, with research hotspots and frontiers focusing on nanoparticle-targeted chemotherapies, photodynamic therapy, and related tumor microenvironment research.

Keywords: hepatocellular carcinoma, nanomaterials, bibliometric analysis, research trends, research hotspots

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and the third leading cause of cancer-related deaths.[1] Furthermore, due to its high incidence and mortality associated with chronic liver disease, HCC poses a significant global health burden.[2,3] The primary challenges in diagnosing HCC are the difficulty in early detection, especially in small lesions, and the lack of effective serum biomarkers. Additionally, current imaging techniques and biopsy have certain limitations in the diagnosis of HCC.[4,5] The diversity of treatment options for HCC, including surgery, liver transplantation, and local and systemic therapies, each with their own indications and limitations, complicates the therapeutic landscape. Factors such as poor drug targeting, low response, drug resistance, tumor multiplicity, and high recurrence further increase the complexity of treatment.[4,6–8] Consequently, there is an urgent need for new technologies and methods in the diagnosis and treatment of HCC.

Nanomaterials, defined as materials within the nanometer range (1–100 nm), possess unique physical, chemical, optical, magnetic, mechanical, and biological properties. In recent years, there have seen promising advancements in the

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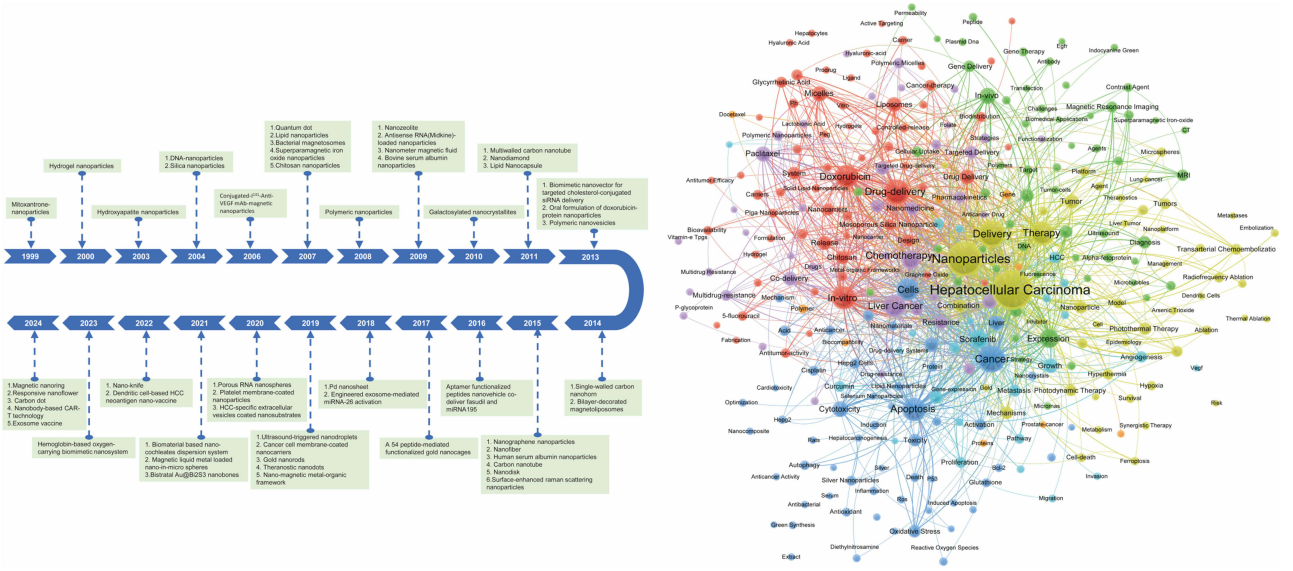
Graphical Abstract



application of nanomaterials for early diagnosis and precise targeted therapy in oncology.[9] In the realm of tumor diagnosis, nanomaterials enhance early detection and diagnostic accuracy through highly sensitive probes and functionalized particles.[10,11] As high-resolution imaging contrast agents, nanomaterials have improved the precision of imaging technologies. Additionally, nanotechnology supports non-invasive methods such as liquid biopsy, reducing the invasiveness of traditional tissue biopsies.[12,13] These advancements provide powerful tools for early tumor detection, accurate diagnosis, and non-invasive testing, significantly addressing the limitations of traditional diagnostic methods. In tumor treatment, traditional chemotherapy, biotherapy and immunotherapy face challenges such as low drug delivery efficiency, uncontrolled toxic effects, complex tumor microenvironment, insufficient immune response, drug resistance, and/or poor targeting specificity. Nanomaterials, with their high surface area and penetration capabilities, enhance drug delivery efficiency and possibly improve therapeutics.[14] They can modulate the tumor microenvironment and improve the efficacy of immunotherapy.[15] Nanomaterials facilitate combination therapies to overcome drug resistance and enhance targeting through multifunctional modifications.[16] Specific nanomaterials such as gold nanoparticles,[17] graphene oxide,[18] carbon nanotubes,[19] and polymer nanoparticles[20] have demonstrated significant advantages in tumor treatment.

Nanomaterials possess multiple unique properties. Certain nanomaterials, including gold nanoparticles, CeO2 and ferromagnetic nanoparticles, exhibit enzyme-like catalytic activities. These nanozymes can have active catalytic surfaces similar to protein enzymes such as oxidase (OXD), peroxidase (POD), catalase (CAT), and superoxide dismutase (SOD).[21–23] Other nanomaterials (eg, mesoporous silica, carbon-based, manganese-based) inherently possess immunogenicity, serving as immune adjuvants to enhance the immunogenicity of weak antigens, thereby inducing stronger immune responses.[24–26] Some nanomaterials interact with cancer cells or biological proteins through bioactive components, triggering immunogenic cell death (ICD) via mechanisms such as ferroptosis,[27,28] autophagy,[29] and necroptosis,[30] independently regulating cell fate. Certain nanomaterials (eg, monosulfide nanoparticles, engineering exosome disguised nanoplatform, gold based, carbon based) possess excellent photothermal conversion efficiency, optical properties, and near-infrared photosensitization efficiency.[31–35] Because of the properties of nanomaterials, researchers have developed various nanomaterial-based local therapeutic strategies, including photothermal, photodynamic, near-infrared, and sonodynamic therapies, as well as combination strategies.[31,36–38]

Bibliometrics analysis, a discipline that applies mathematical and statistical methods to quantitatively analyze the literature, provides critical insights into the distribution, quantitative relationships, and trends of scientific research in

a given field. It supports academic research, discipline development, technology evaluation, and information services. VOSviewer[39] and CiteSpace[40] are highly recognized and frequently used software in bibliometrics analysis. Some bibliometric analysis focus on HCC, while most are related to the progression, mechanisms, and therapy of HCC.[41–44] Furthermore, there are only a few bibliometric studies on nanomaterials in oncology, particularly in HCC. Wang et al explored current trends and emerging patterns in the use of nanomaterials for ovarian cancer, focusing on ICD and metal-organic frameworks.[45] Liu's team and Ling et al identified hot topics in gastric cancer and nanomaterials research, such as silver nanoparticles, anticancer mechanisms, and green synthesis.[46,47] Darroudi et al reviewed the progress and future trends in the application of magnetic nanoparticles for colorectal cancer treatment.[48] Currently, the application of nanomaterials in the field of HCC has garnered significant attention from researchers. However, there is a lack of bibliometric analysis in this area. This study aimed to fill this gap by utilizing bibliometric techniques to extract, analyze, and visualize data on research involving nanomaterials and HCC in order to showcase the research progress, reveal the current hotspots, and predict future trends in this field.

Methods

Search Strategy

Web of Science core collection (WOSCC) database, as one of the widely utilized databases by researchers, encompasses over 20,000 authoritative and high-impact international academic journals from around the world. It includes comprehensive citation records of numerous high-quality scientific papers. Due to its extensive temporal coverage, citation linking, data quality, analytical tools, international recognition, and regular updates, WOSCC has become the primary source for identifying all relevant publications and conducting general statistical analyses in bibliometric research. In this study, we performed a literature search in the WOSCC database on July 10, 2024. The search strategy was set as follows: (TS = (hepatocellular carcinoma) OR (liver cancer) OR (liver tumor) OR (primary hepatic carcinoma) OR (primary liver cancer)) AND TS = (Nano*), with the time span set from January 1, 1999, to June 30, 2024. The document type was limited to articles, excluding other types such as reviews, book chapters, meeting abstracts, and retracted publications. The language of the articles was restricted to English. The literature meeting these criteria will proceed to the subsequent evaluation and screening stage.

Screening Criterion

After the initial selection of article type and language, our team members Mao-Sheng Liu and Si-Si Zhong carefully reviewed and evaluated the title and abstract of all the literature. Only studies relevant to the main focus of our research were included, while articles on intrahepatic cholangiocarcinoma or secondary liver tumors were excluded. Any controversial literature was referred to Kun-He Zhang for a final decision. All publications related to HCC and nanomaterials were analyzed, including in vitro cell models, in vivo animal models, preclinical research, and clinical studies (such as clinical trials), covering various aspects such as diagnosis (molecular markers and imaging) and treatment (drugs, surgery, locoregional therapy, etc.)

Data Extraction, Analysis and Visualization

The selected literature was exported in plain text format for subsequent bibliometric analysis and visualization. The software used for bibliometric analysis and visualization included VOSviewer (Version 1.6.19), Citespace (Version 6.3. R1), and Microsoft Office Excel and PowerPoint (Version 2019). VOSviewer employed its built-in algorithms for multiple analyses and visualizations: (1) Constructing collaboration networks among countries, institutions, and authors. (2) Extracting and clustering keywords, and constructing network visualizations of keyword co-occurrence and overlap visualizations over time. (3) Calculating citation counts for the included literature and identifying the top ten most-cited articles. Citespace was mainly used to create keyword timelines and conduct burst analysis of keyword citations. Using Microsoft Office Excel, a trend chart was created to illustrate the publication and citation volumes. Microsoft Office PowerPoint was used to draw timeline diagrams of different nanomaterials and technologies in the field of HCC, timeline nodes of new strategies involving nanomaterials in HCC treatment, and schematic diagrams of imaging techniques involving nanomaterials in HCC.

Results

Analysis of Annual Publications

A total of 11,704 articles on nanomaterials and HCC were retrieved in the WOSCC database, and 1617 eligible articles were included in the present study (Figure 1).

We analyzed the annual publication and citation counts of the 1617 included articles and found an overall increase in publication volume from 1999 to 2020, with a peak in 2020 (n = 188), despite minor fluctuations in 2016 and 2019, and a decline in publication volume from 2021 to 2023 (Figure 2A). However, the cumulative publication volume showed a steady increase. The annual citation volume trend indicated a rapid growth period starting from 2010 (n = 1253), peaking in 2020 (n = 5263), followed by a similar declining trend over the next three years, paralleling the annual publication volume. The total citation volume mirrored the total publication volume, showing a consistent upward trend over the years (Figure 2B).

Analysis of Publication Volume and Collaboration Among Countries and Institutions

A total of 195 countries have published literature in this field, and the top 10 countries with the most publications are shown in Table 1. The country with the highest contribution to publication volume is China (n = 1115), accounting for 69.0% of the total. The United States ranks second (n = 218, 13.5%), followed by India (n = 108, 6.7%) and Egypt (n = 87, 5.4%). The remaining top ten countries each have fewer than 70 publications. Figure 3A presents the co-authorship network among countries, highlighting the collaboration network of the 18 countries with at least nine publications. China demonstrates the strongest inter-country collaboration network, with total strength link (TLS) = 1039, followed by the United States (TLS = 648) and India (TLS = 250). TLS is defined as the cumulative weight of connections between a node and all other nodes in a network, which serves as a metric to measure the intensity of links between nodes.

Over a span of 26 years, a total of 5479 institutions have published literature related to HCC and nanomaterials. Table 2 lists the top ten institutions with the most publications. The institution with the highest contribution is the Chinese Academy of Sciences (CAS) (n = 97), accounting for 6.0% of the total publications, followed by Sun Yat-sen University (n = 75, 4.6%) and Zhejiang University (n = 56, 3.5%), and the other institutions contribute less than 50 publications each. Figure 3B illustrates the co-authorship network among institutions, with the CAS showing the strongest inter-institution collaboration network (TLS = 1039), followed by the University of the Chinese Academy of Sciences (TLS = 648) and Sun Yat-sen University (TLS = 250).

Analysis of Author Publication Volume and Collaboration

Using VOSviewer, we identified 9400 authors who have published articles in the field of HCC and nanomaterials. Table 3 lists the top ten authors by publication volume in this field. The top four authors are Jie Tian (n = 17), Jing Li (n = 16), Robert J. Lee (n = 13), and Yang Liu (n = 13). The publication volume of the top ten authors ranges between 10 and 20 articles, indicating that the publication contributions among authors are relatively balanced, without significant disparities and with a generally dispersed distribution of publication volume. Figure 4A illustrates the network of author collaborations, with Dan Shao having the highest TLS (64), followed by Jing Li (TLS = 53) and Zheng Wang (TLS = 52). In terms of average citations per paper, Dan Shao has the highest average citation count at 62.7, followed by Robert J. Lee and Xiao-Long Liu at 49.1 and 48.7, respectively. Among the top ten authors, two are affiliated with the Chinese Academy of Sciences, two with Jilin University, and two with Central South University.

Analysis of Journal Publication Volume and Co-Cited Networks

There are 405 journals that have published literature in this field. We analyzed the top 12 journals with the highest contribution to the publication volume in this field (Table 4). The journal with the largest number of publications is the "International Journal of Nanomedicine (DOVE Medical)" (n = 94), followed by "Biomaterials (Elsevier)" (n = 48) and "ACS Applied Materials & Interfaces (American Chemical Society)" (n = 39). The journal with the highest total citation count is "Biomaterials (Elsevier)". The journal with the highest IF and average citation per article is also "Biomaterials (Elsevier)" (IF = 12.8, average citation = 79.8). The Impact Factor (IF) of a journal and average number of citations per

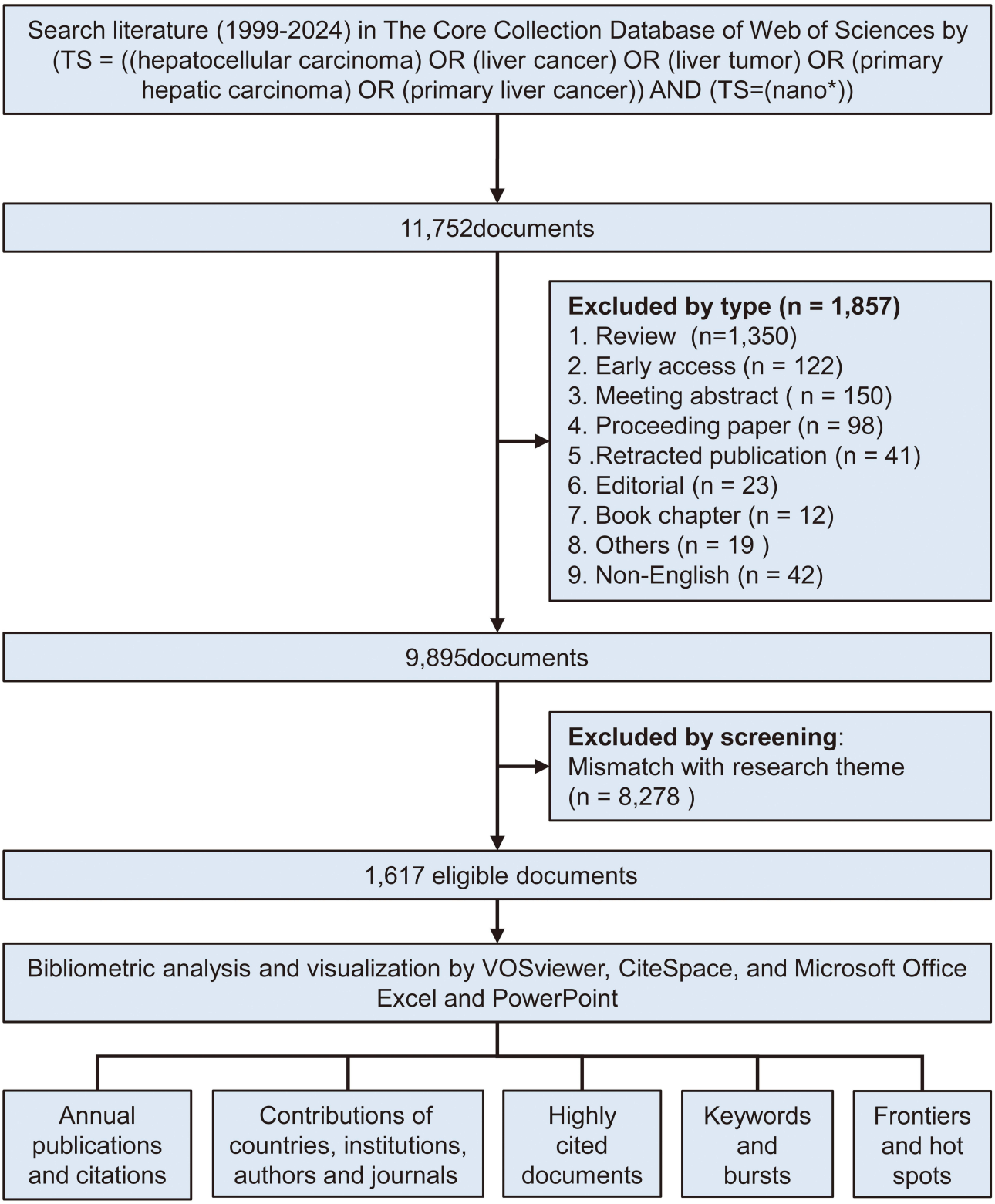


Figure 1 The flowchart of this study. An asterisk (*) at the end of a search term serves as a right truncation wildcard, which expands the term's stem to match all possible suffix variants sharing the same stem, thereby enhancing recall.

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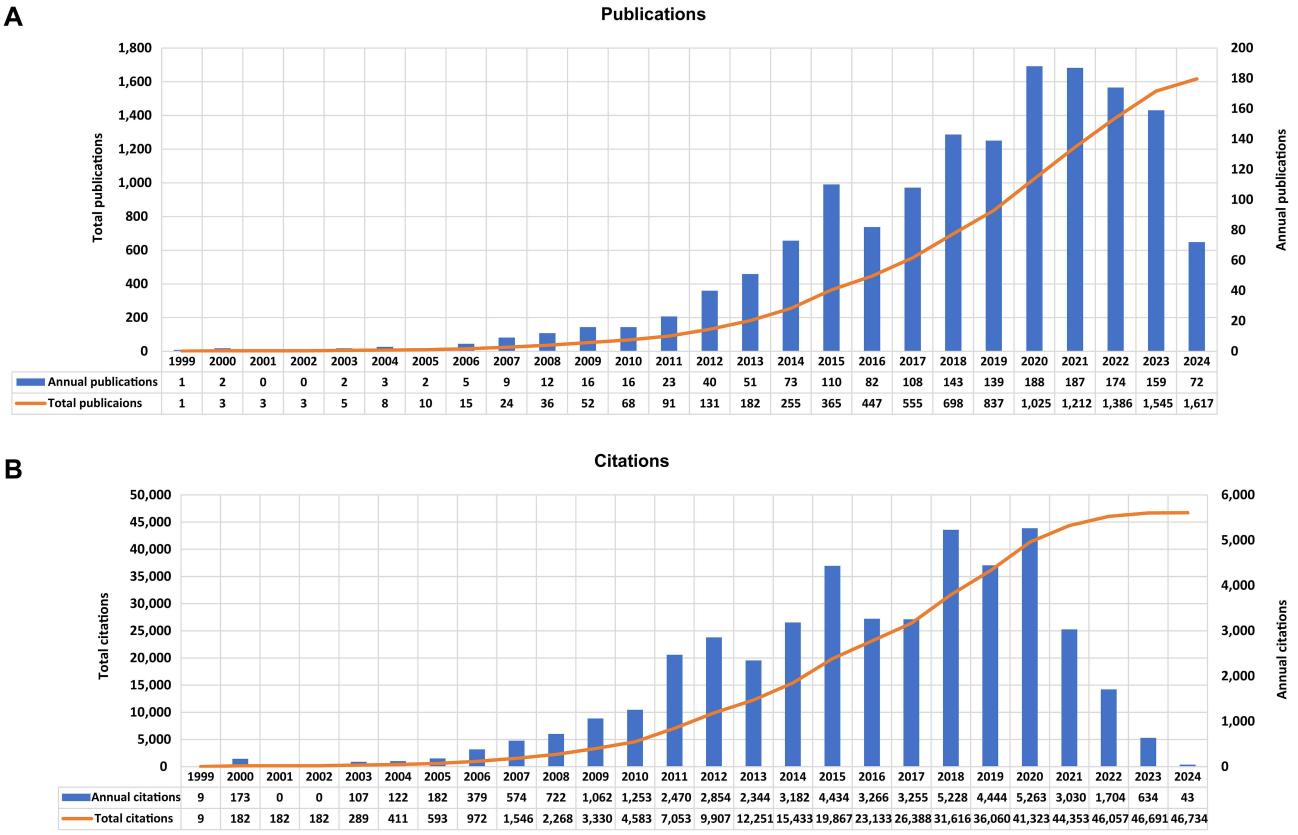

Figure 2 Trend analyses of publication and citation counts. (**A**) Annual and total publications from 1999 to 2024. (**B**) Annual and total citations from 1999 to 2024.

article are important indicators of the quality of publications. Figure 4B illustrates the co-citation network of journals in the field of nanomaterials and HCC, with the top three journals being "Biomaterials (Elsevier)" (n = 2392, TLS = 2204), "Journal of Controlled Release (Elsevier)" (n = 1831, TLS = 1708), and "ACS Nano (American Chemical Society)" (n = 1352, TLS = 1280). Overall, "Biomaterials (Elsevier)" is the most influential journal in this field.

Hotspots and Trends in the Field of Nanomaterials and HCC

Keyword Occurrence and Co-Occurrence Analysis

By analyzing the frequency of keyword occurrences, we can identify the research hotspots in a given field. Using the VOSviewer software, we extracted all keywords, a total of 5721, with 276 keywords appearing more than 10 times. Table 5 lists the top 20 most frequent keywords, of which 14 keywords appeared more than 100 times.

Table 1 Top 10 Countries Contributing to Publications on Nanomaterials and HCC

Rank	Country	Total Publications (%)	Total Citations	Average Citations
1	China	1115 (69.0)	31,135	27.9
2	USA	218 (13.5)	10,540	48.4
3	India	108 (6.7)	3667	34.0
4	Egypt	87 (5.4)	1738	20.0
5	Saudi Arabia	64 (4.0)	1390	21.7
6	South Korea	56 (3.5)	2235	39.9
7	Iran	43 (2.7)	833	19.4
8	Italy	28 (1.7)	924	33.0
9	Japan	27 (1.7)	1245	46.1
10	Germany	20 (1.2)	573	28.7

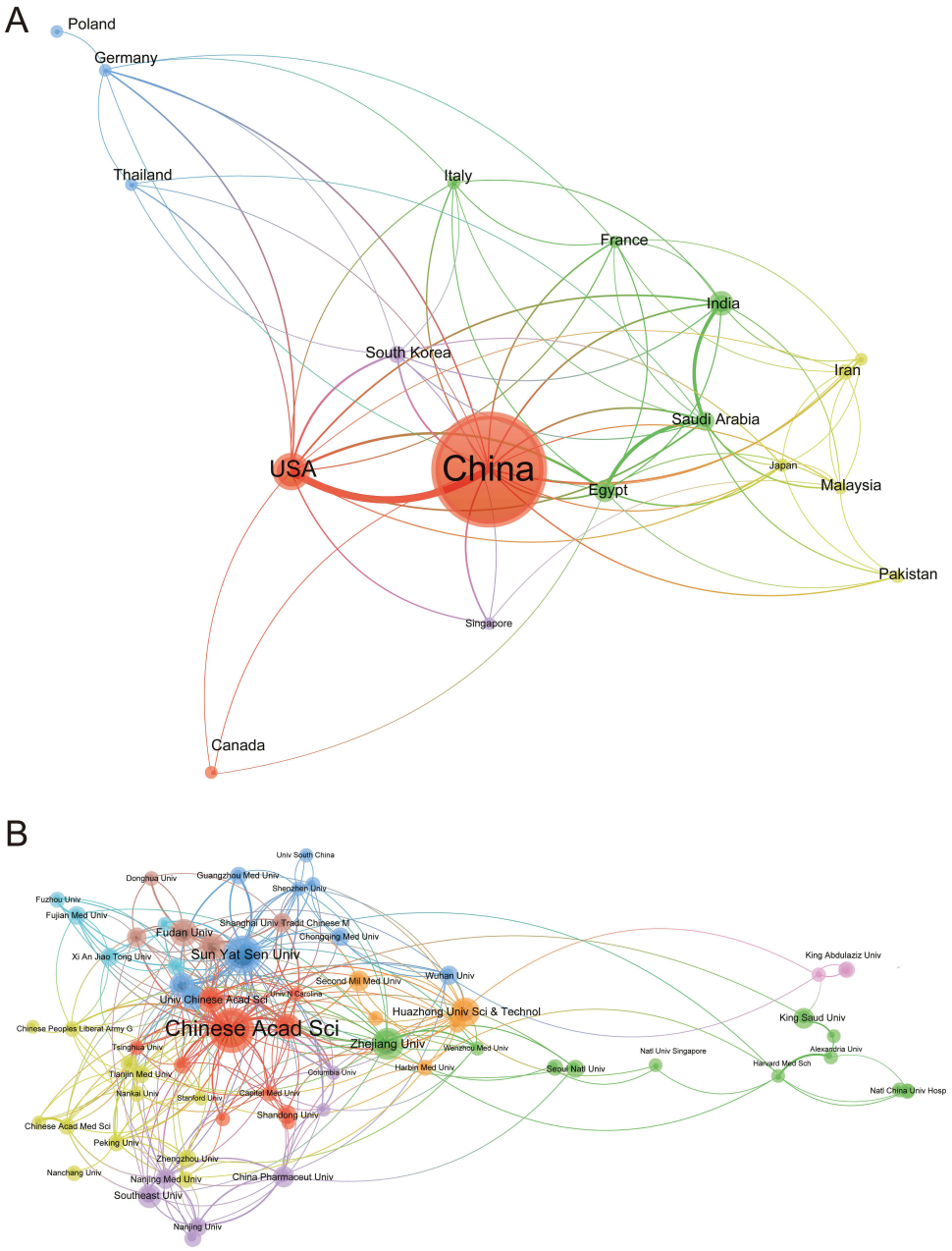

Figure 3 The co-authorship and journal co-citation networks in the field of nanomaterials and HCC. (**A**) Countries; (**B**) Institutions.

Figure 5A illustrates the co-occurrence network of these keywords, where different colors represent different keyword clusters and varying distances indicate their relational proximity. These keywords are grouped into seven clusters. The largest cluster, in red, consists of 68 items, primarily related to drug delivery and nanomaterials, including keywords such as "drug delivery", "doxorubicin", "in vitro", "drug", "targeted delivery" and "chitosan". The second largest cluster, in green, comprises 65 items focused on diagnosis and therapy, with keywords like "therapy", "diagnosis", "gene delivery", "in vivo" and "MRI". The third cluster, in cyan, contains 57 items related to the antitumor mechanisms of nanomaterials, including "apoptosis", "gold nanoparticles", "cytotoxicity", "oxidative stress", "autophagy", "anticancer" and "genotoxicity". The fourth cluster, in yellow, includes 44 items related to HCC treatment methods, such as "transarterial chemoembolization", "dendritic cells", "microwave ablation", "immunotherapy", "photodynamic therapy", "photothermal therapy", "radiofrequency ablation" and "tumor microenvironment". The fifth cluster, in purple, consists of 29 items mainly involving HCC progression and sorafenib-related keywords like "hepatocellular carcinoma", "HCC",

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Table 2 Top 10 Influential Institutions in the Field of Nanomaterials and HCC

Rank	Institution	Total Publications (%)	Total Citations	Average Citations	Country
1	Chinese Academy of Sciences	97 (6.0)	4793	49.4	China
2	Sun Yat-sen University	75 (4.6)	2348	31.3	China
3	Zhejiang University	56 (3.5)	1558	27.8	China
4	Huazhong University of Science and Technology	48 (3.0)	1710	35.6	China
5	Fudan University	43 (2.7)	1302	30.3	China
6	Shanghai Jiao Tong University	39 (2.4)	1148	29.4	China
7	University of Chinese Academy of Sciences	39 (2.4)	1381	35.4	China
8	Jilin University	38 (2.4)	1615	42.5	China
9	Southern Medical University	37 (2.3)	805	21.8	China
10	Jinan University	33 (2.0)	1204	36.5	China

Table 3 Top10 Active Authors of Publications in Nanomaterials and HCC

Rank	Author	Publications	Total Citations	Average Citations	Institution and Country
1	Tian, Jie	17	461	27.1	Chinese Academy of Sciences, China
2	Li, Jing	16	476	29.8	Jilin University, China
3	Lee, Robert J	13	638	49.1	Jilin University, China
4	Liu, Yang	13	268	20.6	Chinese Academy of Sciences, China
5	Shao, Dan	13	816	62.8	South China University of Technology, China
6	Wang, Wei	13	605	46.5	Central South University, China
7	Chen, Yan	12	434	36.2	Qiqihar Medical College, China
8	Liu, Xiaolong	12	578	48.2	Fujian Medical University, China
9	Liu, Ying	12	384	32.0	Jinzhou Med University, China
10	Fang, Chihua	11	355	32.3	Central South University, China

"angiogenesis", "invasion", "metastasis", "migration", "proliferation", "pathways" and "sorafenib". The sixth cluster, in turquoise, comprises 21 items related to drug release from nanomaterials, including "drugs", "drug release", "encapsulation", "nanoparticles" and "nanomedicine". The seventh cluster, in yellow-orange, contains 19 items focused on chemotherapy resistance in HCC, with keywords such as "accumulation", "biocompatibility", "cancer stem cells", "multidrug-resistance", "p-glycoprotein" and "chemotherapy".

Figure 5B presents an overlay visualization of the average activity of co-occurring keywords over different years. It shows that keywords appearing between 2016 and 2018 are colored from purple to cyan, while those appearing after 2018 until 2020 or later are colored from cyan to yellow. For example, keywords such as "gene delivery", "PLGA nanoparticles", "contrast agents" and "superparamagnetic iron-oxide" appeared earlier, whereas "photodynamic therapy", "photothermal therapy", "immunotherapy" and "green synthesis" emerged in more recent research.

Temporal Evolution and Emerging Trends in Research

Timeline visualization provides a clear view of the evolution of different keywords over time, allowing researchers to identify trends and patterns within a research field, which helps pinpoint popular topics or keywords during a particular time period and highlights the focus of academic attention. To further explore and reveal research hotspots and future trends, we utilized CiteSpace software to visualize keyword timelines and conduct citation burst analysis. Figure 6 shows annual time slices, with the top 10% of keywords within each slice, filtered by g-index (K = 25). Based on this criterion and internal software calculations, the visualization includes 590 nodes across 11 cluster timelines. Before 2015, the focus was primarily on those related to "targeted drug delivery", "magnetic resonance imaging" and "in vitro experiments". After 2015, there is a noticeable

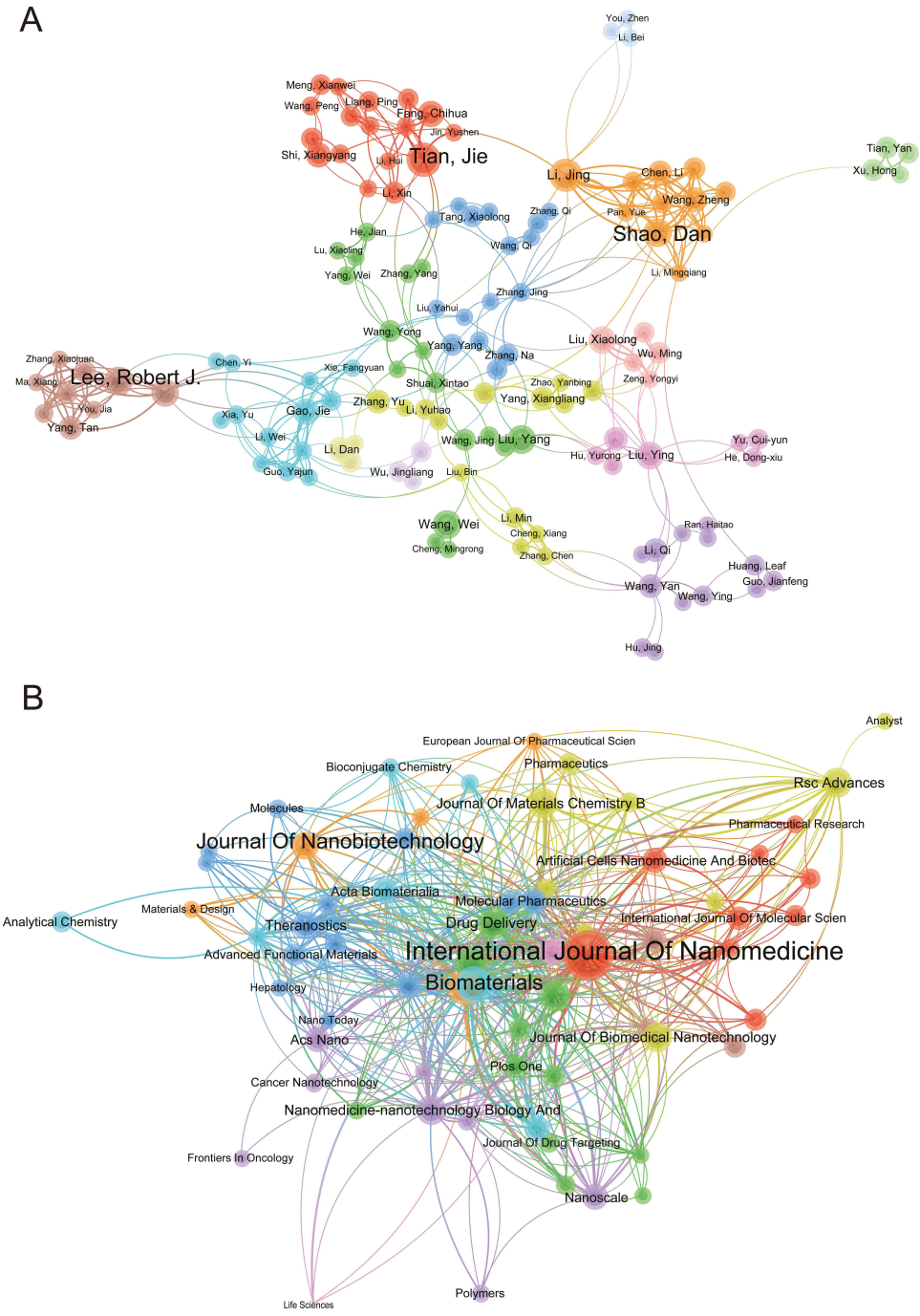

Figure 4 The co-authorship and journal co-citation networks in the field of nanomaterials and HCC. (**A**) Authors; (**B**) The co-citation of cited journals.

shift toward keywords such as "apoptosis", "transarterial chemoembolization" and "photodynamic therapy" as well as emerging therapeutic concepts such as "tumor microenvironment", "immunotherapy" and "dendritic cells".

Figure 7 displays the top 35 keywords with the strongest citation burst. The earliest burst keyword is "Adriamycin" starting in 2007 and lasting eight years with a burst strength of 3.78. The keywords with the longest burst durations are "iron oxide nanoparticles" (2009–2017) and "in vivo" (2010–2018). The shortest burst duration is two years, including keywords such as "identification", "nanoplatform", "nanomedicine", "targeted therapy" and "glycyrrhetinic acid". The keyword with the strongest burst strength is "gene delivery" (burst strength = 9.08, 2013–2016), followed by "in vivo" (burst strength = 7.66, 2010–2018) and "photodynamic therapy" (burst strength = 5.72, 2019–2024). In the past three

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Table 4 Top 12 Influential Journals Ranked by Publications on Nanomaterials and HCC

Rank	Journal	Publications	Total Citations	Average Citations	IF and Zone (2023)
1	International Journal of Nanomedicine	94	2964	31.5	6.6, Q1
2	Biomaterials	48	3832	79.8	12.8, Q1
3	ACS Applied Materials & Interfaces	39	1517	38.9	8.3, Q1
4	International Journal of Pharmaceutics	33	1249	37.9	5.3, Q1
5	Colloids AND Surface B-Biointerfaces	32	816	25.5	5.4, Q1
6	Drug Delivery	31	773	24.9	6.5, Q1
7	Journal of Materials Chemistry B	29	1070	36.9	6.1, Q1
8	Journal of Biomedical Nanotechnology	28	471	16.8	NA
9	Nanomedicine-Nanotechnology Biology and Medicine	28	1207	43.1	4.2, Q2
10	RSC Advances	28	430	15.4	3.9, Q2
11	Theranostics	24	1370	57.1	12.4, Q1
12	Journal of Nanobiotechnology	23	378	16.43	11.4, Q1

Table 5 Top 20 Most Frequent Keywords in the Field of Nanomaterials and HCC

Rank	Keywords	Counts
1	Hepatocellular Carcinoma	685
2	Nanoparticles	503
3	Drug Delivery	308
4	Cancer	307
5	Delivery	302
6	Therapy	220
7	Apoptosis	215
8	Doxorubicin	210
9	In-vitro	204
10	Liver Cancer	198
11	Cells	191
12	Sorafenib	134
13	Chemotherapy	134
14	Expression	134
15	In-vivo	92
16	Cytotoxicity	90
17	Paclitaxel	85
18	Micelles	80
19	Growth	74
20	Liver	74

years, keywords with significant citation bursts include “photodynamic therapy”, “sorafenib”, “hepatocellular carcinoma (HCC)”, “tumor microenvironment” and “progression”.

To further understand the timeline of nanomaterials in HCC research, three subtypes of timelines were created (Figure 8). Figure 8A shows the appearance timeline of different types of nanomaterials and nanotechnologies in the HCC research, Figure 8B illustrates the timeline of new HCC treatment strategies involving nanomaterials, and Figure 8C displays the timeline of nanomaterial-based imaging in HCC.

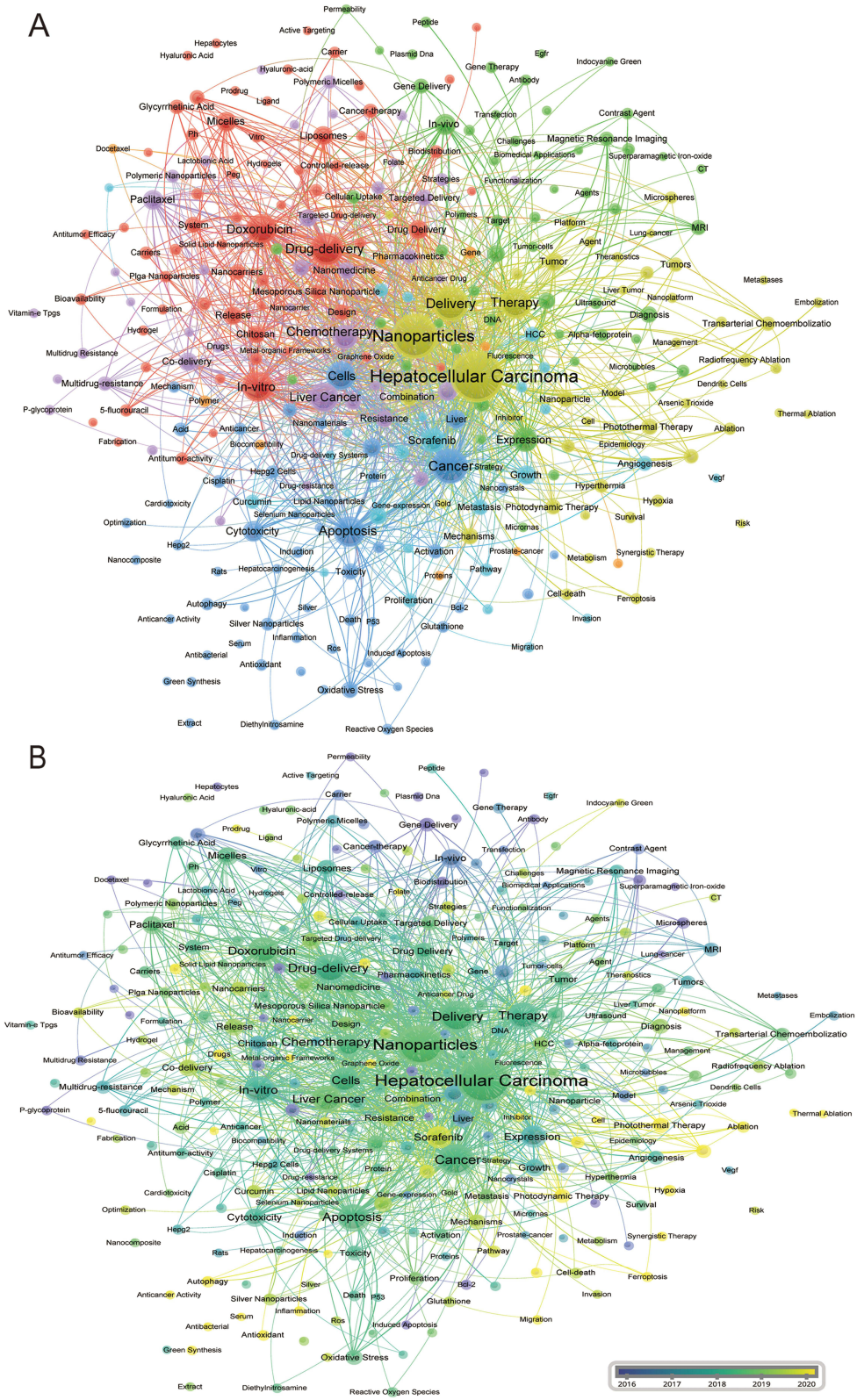

Figure 5 The keywords co-occurrence network visualization (**A**) and overlay visualization (**B**).

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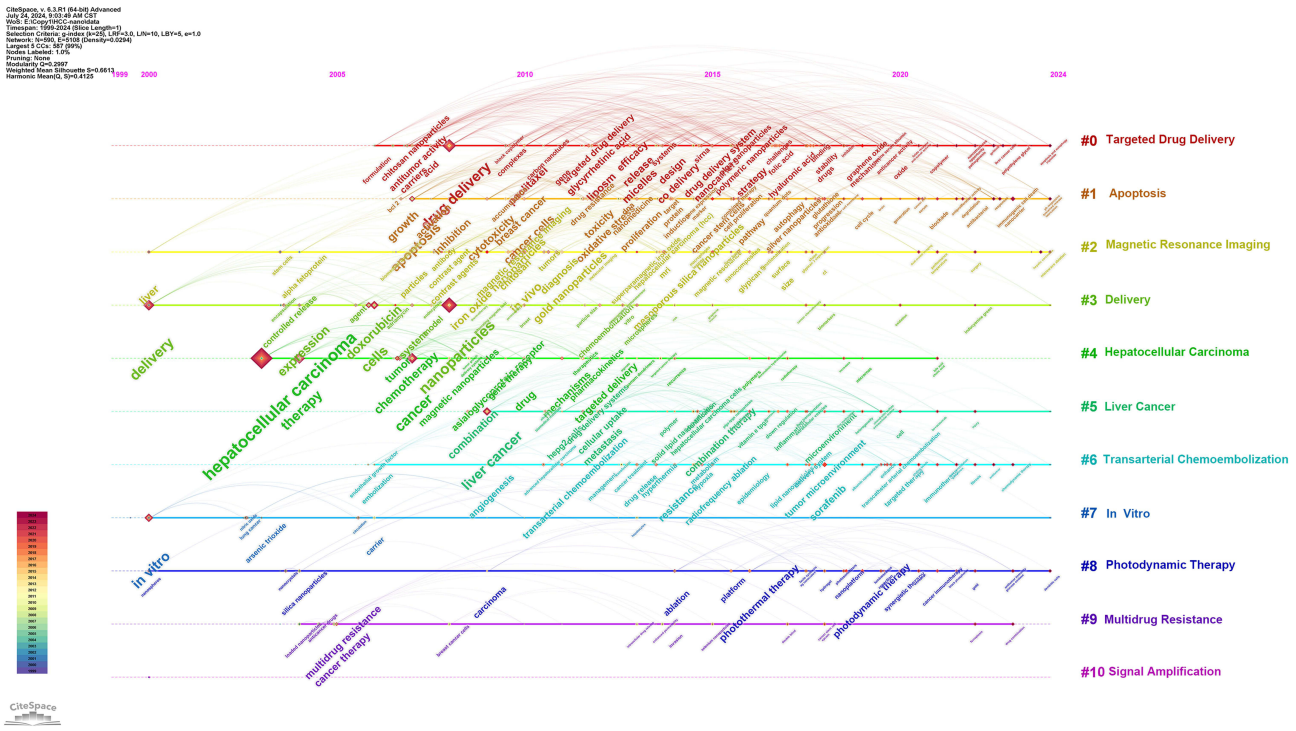

Figure 6 The timeline of keywords in the field of nanomaterials and HCC. The layout arranges keywords according to the chronological order of their first occurrence. Each visual element represents a specific keyword, while the relative size of these elements reflects their frequency.

Analysis of Highly Cited Papers

Highly cited papers typically represent influential research within a given field. Table 6 lists the top ten highly cited papers in the field of nanomaterials and HCC. All the papers were published between 2009 and 2020. The top three most cited papers include two from the United States and one from India. China has the highest number of highly cited papers with five, within two of them coming from the Chinese Academy of Sciences (CAS). Regarding the research directions of these highly cited papers, five are related to drug delivery, two to the mechanisms of nanomaterials, and two to imaging and therapy of HCC.

Analysis of Clinical Trials in the Field of Nanomaterials and HCC

To date, there are seven clinical trial articles in this field (Table 7), with five on treatment and two on MRI imaging. Among the types of clinical trials, five are randomized controlled trials, four are related to HCC treatment, and one is related to MRI. The number of cases ranges from a minimum of 13 to a maximum of 397. The study with the highest number of cases (n = 397) was published in "The Lancet Gastroenterology & Hepatology (Elsevier)" in 2019, titled "Doxorubicin-loaded nanoparticles for patients with advanced hepatocellular carcinoma after sorafenib treatment failure (RELIVE): a Phase 3 randomized controlled trial". The conclusion was that doxorubicin-loaded nanoparticles did not improve overall survival in HCC patients who had failed prior sorafenib treatment.

The most recent clinical trial, published in the "Journal of Magnetic Resonance Imaging (Wiley)" in 2023, is entitled "IOP Injection, A Novel Superparamagnetic Iron Oxide Particle MRI Contrast Agent for the Detection of Hepatocellular Carcinoma: A Phase II Clinical Trial", which included 52 patients and concluded that iron oxide nanoparticle m-PEG-silane (IOP) injection is safe and effective as an MRI contrast agent for the diagnosis of HCC in the limited number of cases.

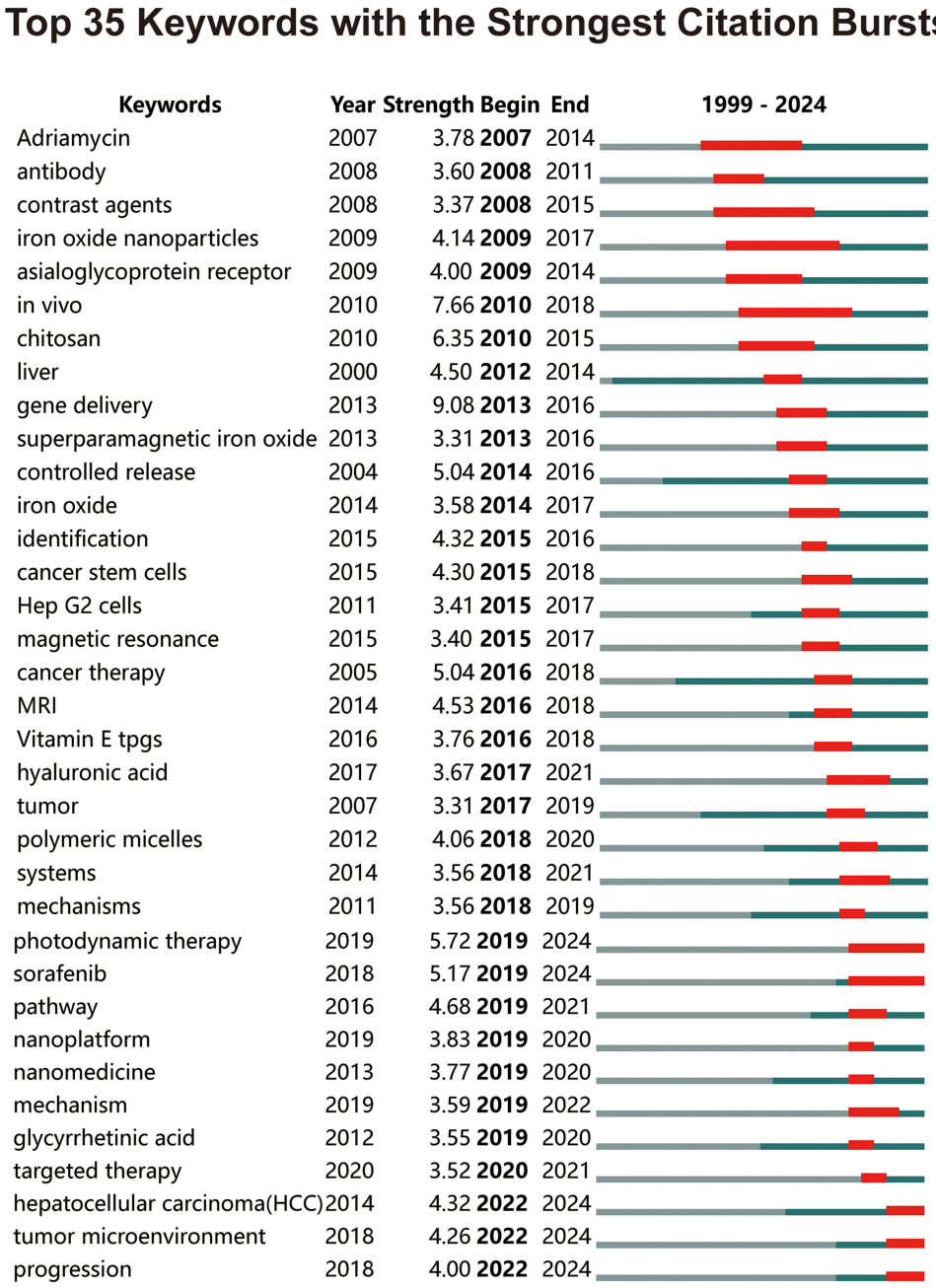

Figure 7 Top 35 keywords with the strongest citation bursts in the field of nanomaterials and HCC. The deep blue color denotes the temporal span of the keyword, while the red color signifies the burst periods characterized by intensive application of the keyword.

Discussion

General Information

In this study, we used bibliometric techniques to analyze the publication and citation trends of publications on the application of nanomaterials in HCC research from 1999 to 2024. The first paper in this field was published in 1999, which reported the antitumor effects of liver-targeted mitoxantrone-nanoparticles and demonstrated higher antitumor efficacy and lower acute toxicity in orthotopic and ectopic tumor models in nude mice with human liver cancer compared to free mitoxantrone (DHAQ) and doxorubicin (ADR).[66]

Publication trends in the field of nanomaterials and HCC can be divided into four distinct periods. The first period, from 1999 to 2011, was characterized by slow growth, with the annual publication count increasing slightly from one to 23 papers.

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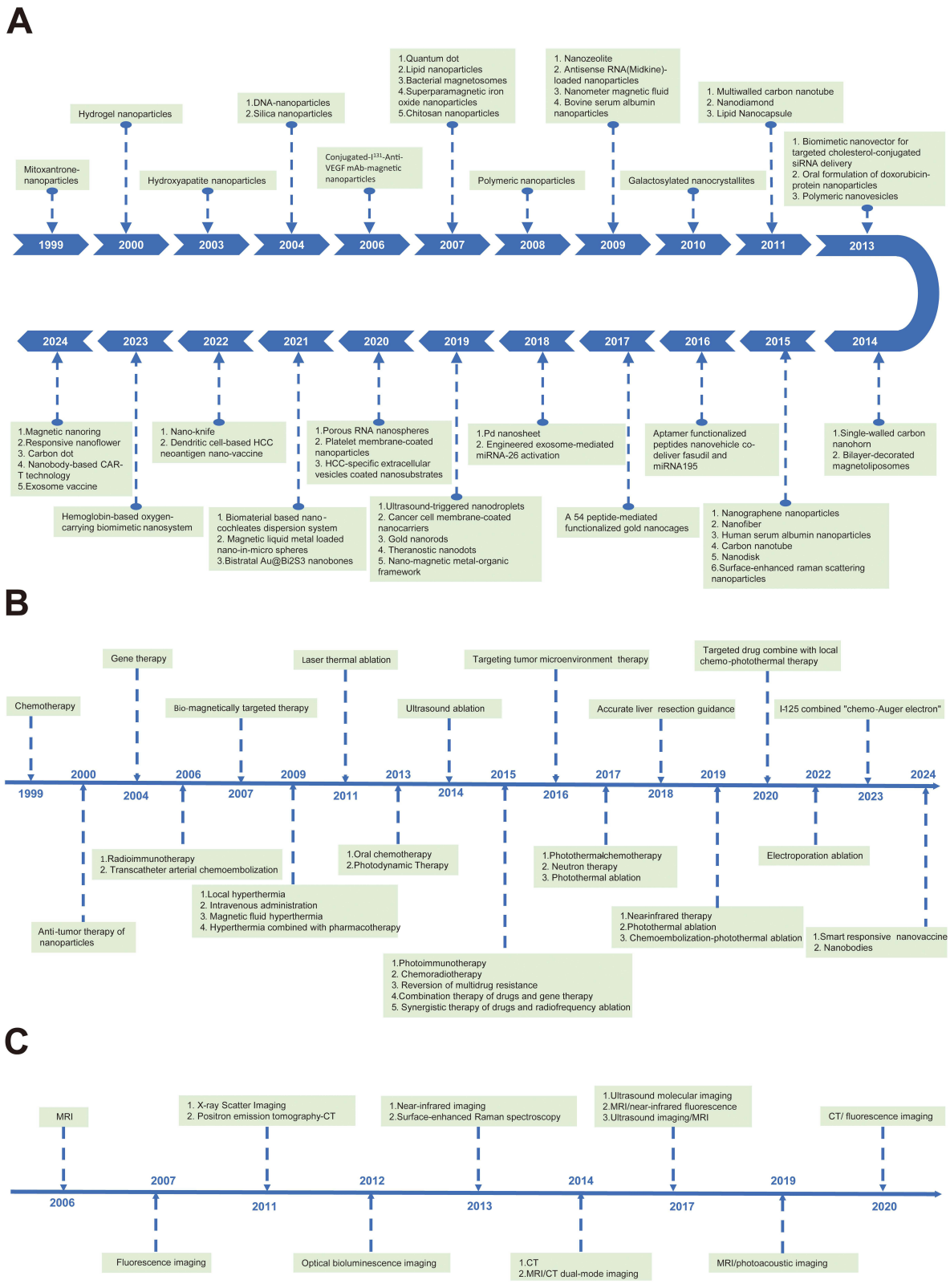

Figure 8 The timeline of nanomaterials and HCC. (**A**) The timeline of nanomaterials and techniques in HCC research. (**B**) Timeline of nanomaterial-based treatment strategies in HCC research. (**C**)Timeline of nanomaterial-based imaging in HCC.
Abbreviations: MRI, Magnetic Resonance Imaging; CT, Computed Tomography Imaging.

Table 6 Top 10 Influential Articles Ranked by Citations in the Field of Nanomaterials and HCC

Rank	Title	Citations	Institution and Country	Journal	Year
1	The targeted delivery of multicomponent cargos to cancer cells by nanoporous particle-supported lipid bilayers[49]	869	University of New Mexico, USA	Nature Materials	2011
2	Zinc oxide nanoparticles induce oxidative DNA damage and ROS-triggered mitochondria mediated apoptosis in human liver cells (HepG2)[50]	594	CSIR-Indian Institute of Toxicology Research, India	Apoptosis	2012
3	Nanodiamond therapeutic delivery agents mediate enhanced chemoresistant tumor treatment[51]	472	University of California, USA	Science Translational Medicine	2011
4	In vivo delivery of silica nanorattle encapsulated docetaxel for liver cancer therapy with low toxicity and high efficacy[52]	292	Chinese Academy of Sciences, China	ACS Nano	2010
5	M6A-mediated upregulation of LINC00958 increases lipogenesis and acts as a nanotherapeutic target in hepatocellular carcinoma[53]	283	Wannan Medical College, China	Journal of Hematology & Oncology	2020
6	Multifunctional doxorubicin loaded superparamagnetic iron oxide nanoparticles for chemotherapy and magnetic resonance imaging in liver cancer[54]	268	Utah-Inha DDS Institute, Korea.	Biomaterials	2010
7	An ultrasound activated vesicle of Janus Au-MnO nanoparticles for promoted tumor penetration and sono-chemodynamic therapy of orthotopic liver cancer[55]	264	Fuzhou University, China	Angewandte Chemie	2020
8	Copper oxide nanoparticles induced mitochondria mediated apoptosis in human hepatocarcinoma cells[56]	264	King Saud University, Saudi Arabia	PLoS One	2013
9	The performance of docetaxel-loaded solid lipid nanoparticles targeted to hepatocellular carcinoma[57]	253	Chinese Academy of Sciences, China	Biomaterials	2009
10	Engineered exosome-mediated delivery of functionally active miR-26a and its enhanced suppression effect in HepG2 cells[58]	248	Henan University of Science and Technology, China	International Journal of Nanomedicine	2018

Table 7 Clinical Trials in the Field of Nanomaterials and HCC

Author and Year	Nanomaterials	Application	Cases	Design	Country
Dudeck et al 2006[59]	Superparamagnetic iron oxide particles	MRI	13	Unknown	Germany
Zhou et al 2009[60]	Mitoxantrone-loaded nanoparticles	Therapy	108	Randomized controlled trial	China
Merle et al 2017[61]	Doxorubicin-loaded nanoparticles	Therapy	49	Randomized controlled trial	France
Merle et al 2019[62]	Doxorubicin-loaded nanoparticles	Therapy	397	Randomized controlled trial	France
Chen et al 2022[63]	Nano-microbubbles	Therapy	36	Unknown	China
Zhang et al 2022[64]	Nano-knife	Therapy	152	Randomized controlled trial	China
Chiang et al 2023[65]	Superparamagnetic iron oxide particle	MRI	52	Randomized controlled trial	China

This may be attributed to the limited treatment options for HCC and the slow development of nanomaterials during this time. The second period, from 2011 to 2019, saw a rapid growth phase. Following a near doubling of publications in 2011, the annual number of papers increased significantly, reflecting a sustained interest in the field. This surge in research activity is largely related to the emergence of novel therapeutic approaches, such as photodynamic therapy (PDT) and photothermal therapy (PHT), new immunotherapies, molecularly targeted drugs, and the rise of personalized precision medicine.[67] The field reached a plateau between 2020 and 2021 (the third period), with the highest annual publication count peaking at 188 papers. This was followed by a slight decline in the number of publications from 2022 to 2023 (the fourth period), suggesting that the initial enthusiasm was tempered by the realization of the various challenges associated with the application of nanomaterials in medical treatments. Further in-depth research is required to address these challenges (biocompatibility, instability of drug release, safety/potential toxicity, metabolism, and clearance et al[68–71]) and may lead to a new growth phase in this field.

Overall, citation trends showed a gradual increase. The relatively low citation count in 2021 can be attributed to the proximity of the study's retrieval date, indicating that a longer period is needed to accurately assess the impact of articles from this period.

The three countries with the highest publication output in this field are China, the United States, and India, collectively accounting for 89.2% of the total publications. China leads in the number of publications and has the most extensive network of international collaborations, while the United States stands out for the impact of its individual publications. This intense research activity in China is likely linked to the epidemiology and current treatment status of HCC in the country. China is globally recognized as having the highest burden of HCC, with Chinese patients comprising half of the world's HCC cases.[1] The prominence of the United States in the impact of individual publications may be linked to its robust research strength and extensive international collaborations. Research conducted in the United States is often highly innovative and influential, garnering widespread attention globally. The early diagnosis and treatment of HCC in China face significant challenges. As China's economic power has grown, the government has increasingly funded cancer research, including HCC, to encourage scientists to delve deeply into the field, develop new therapeutic drugs or methods, and bring new hope to the diagnosis and treatment of HCC, especially in the therapeutic field.

The complexity of treatment and the generally poor prognosis of HCC, as well as China's large population with a high incidence and prevalence of HCC, have driven a national urgency to improve the outcome of the disease. This urgency, combined with increased research funding, has resulted in the top ten institutions and authors in this field predominantly being from China. Among the top ten institutions, those affiliated with the CAS have published 146 papers, with the highest citation counts and average citations per paper. Furthermore, CAS exhibits the strongest intensity of inter-institutional collaboration, making it the most influential, prolific, and active institution in this field. This prominence may be attributed to the academic influence of CAS as the highest academic institution for natural sciences in China, with the strongest comprehensive research capabilities among research institutes and advantages in the application of major national scientific projects. The most prolific author is Jie Tian, also affiliated with CAS. Among the top ten authors, two are from CAS, but when considering average citations per paper, Shao Dan leads. Therefore, the most influential authors in this field are Jie Tian and Shao Dan.

High-Impact Literature

Articles with high citations indicate significant impact in a field. We have presented the top ten most cited papers in the field of nanomaterials and HCC. Although no articles from the past three years are included (likely due to the time gap between publication and our search), these highly cited publications demonstrate the application of nanomaterials in in vitro and in vivo studies of targeted therapy, drug delivery, and diagnostics for HCC.

There are four highly cited articles on in vitro studies. Ashley et al[49] developed a selective, low-toxicity, customizable and high-capacity nanoporous carrier that fused liposomes with a nanoporous silica core to create a "protocell" nanocarrier with multiple targeting peptides, fusogenic peptides, and PEG-modified supported lipid bilayers. This nanocarrier showed 10^4 times higher affinity for target HCC cells than for non-target cells (hepatocytes, immune cells), with potential to transport therapeutic agents (chemotherapeutics and nucleic acids) and diagnostic agents (quantum dots). It also demonstrated enhanced endosomal escape, enabling delivery to specific organelles. Additionally, this nanocarrier effectively killed drug-resistant HCC cell lines, showing a 10^6-fold improvement over comparable liposomes. Sharma et al[50] investigated the hepatotoxicity and potential molecular mechanisms of zinc oxide nanoparticles using human HCC HepG2 cells and found that these nanoparticles reduced cell viability and induced apoptosis through oxidative DNA damage and ROS-triggered, mitochondria-mediated pathways involving JNK and P38. Siddiqui et al[56] found that copper oxide nanoparticles (CuO NPs) induced apoptosis in HCC HepG2 cells via a mitochondria-mediated pathway. Liang et al[58] used engineered exosomes loaded with miR-26a to target HepG2 cells expressing scavenger receptor class B type 1, and the exosomes could reduce tumor cell proliferation and migration, which proposed a new strategy for targeted tumor gene delivery.

Some of highly cited articles are in vivo studies. Chow et al[51] used nanodiamonds as DOX delivery carriers to treat chemoresistant tumors in murine models of liver and breast cancer and exhibited that the nanocarriers had good biocompatibility, could conjugate multiple drugs, overcame intracellular drug efflux, significantly inhibited tumor growth, and promoted apoptosis, with reduced in vivo toxicity and enhanced chemotherapy efficacy compared to free

DOX. Li et al[52] used electrostatic adsorption to load hydrophobic docetaxel into PEGylated silica nanotubes (SN-PEG) and showed that the half-maximal inhibitory concentration (IC50) was significantly reduced to 7% of free docetaxel in cell models, the inhibition rate of ectopic tumors in mice increased by 15%, and toxicity was low, demonstrating an efficient and low-toxicity nanodrug delivery platform. Zuo et al[53] found that LINC00958 was abnormally expressed in HCC tissues and associated with prognosis and progression, so they developed a PLGA-based nanoplatform encapsulating LINC00958 siRNA for HCC treatment, which was release-controlled, targeted, and safe, and showed good antitumor effects. Maeng et al[54] developed polymeric nanoparticles that showed better antitumor effects than free DOX and commercial liposomal DOXIL in animal models and higher imaging sensitivity than conventional contrast agents even at lower iron concentrations, making them promising for HCC treatment and MRI imaging. Xu et al[57] synthesized docetaxel-loaded solid lipid nanoparticles targeting liver cancer and theirs in vivo antitumor effects were superior to non-targeted nanoparticles and Taxotere, with no adverse effects on healthy or fibrotic livers and low systemic toxicity. Lin et al[55] developed Au-MnO nanoparticles coated with PEG and ROS-sensitive polymers to form ultrasound (US) and glutathione (GSH) dual-responsive vesicles; upon US irradiation, the vesicles decomposed to enhance penetration, and further GSH-triggered MnO degradation to allow for infrared imaging and T1-MR dual-modal imaging, as well as synergistic SDT/CDT to inhibit primary liver tumor growth.

Research Topics and Trends

We conducted a multidimensional analysis of keywords and revealed seven major clusters: targeted drug delivery, diagnosis and therapy, molecular mechanisms, therapeutic approaches, sorafenib, drug release, and multidrug resistance. From the frequency analysis of keyword co-occurrence, we found that the most frequently used nanomaterials are zero-dimensional nanomaterials, specifically nanoparticles, which are materials with three dimensions ranging from 1 to 100 nm.[72] Research has predominantly focused on the application of nanomaterials as drug delivery vehicles, with doxorubicin and sorafenib being the most commonly used drugs.

Doxorubicin, introduced in 1976 for its efficacy against advanced HCC, remains a classical chemotherapeutic drug for HCC.[73] It inhibits nucleic acid synthesis by intercalating into DNA, thereby controlling tumor growth. However, systemic administration of doxorubicin lacks targeting specificity and can cause significant damage to patients. To reduce systemic toxicity and increase tumor-selective cytotoxicity, researchers developed transarterial chemoembolization (TACE), which involves the precise selection of tumor-feeding vessels using contrast agents (superselection) and the infusion of chemotherapeutic drugs and embolic agents into these vessels.[74] By the superselective TACE technique, doxorubicin delivered via local arterial infusion can control some tumors, but it faces issues such as tumor capsule, multiple tumors, drug resistance, leakage, and neovascularization, repeated procedure and overall suboptimal outcome.[75,76] Furthermore, the vascular occlusive effect of TACE is transient and may induce the upregulation of angiogenic and growth factors, thereby accelerating tumor progression.[77]

In 2007, the molecularly targeted drug sorafenib was approved for the treatment of unresectable HCC and remains a first-line therapy for HCC.[3,78] Additionally, “in vitro” and “cell” are highly co-occurring keywords, indicating that most studies are conducted using in vitro HCC cell models. The most involved biochemical process in the nanomaterial-based HCC treatment is “apoptosis”, also known as programmed cell death (PCD),[79] indicating that tumor cell apoptosis is the hot topic of nanomaterial-based therapy.

Nanomaterials in HCC Diagnostic and Therapy

Nanomaterials have shown great potential in the diagnosis of HCC. In liquid biopsy, the use of various nanomaterials (such as gold nanoparticles, graphene oxide, TiO2@Ag nanostructures, and quantum dots) for signal amplification can enhance the detection of early HCC serum biomarkers (AFP, AFP-L3), circulating tumor cells, and exosomes with high sensitivity and specificity.[80–83] In the field of imaging, including fluorescence imaging, ultrasound, CT, and MRI, various nanomaterials such as superparamagnetic iron oxide nanoparticles,[65] gold nanoparticles,[84] quantum dots,[85] Prussian blue nanoparticles,[86] and human serum albumin nanoparticles[87] have been studied as imaging agents, demonstrating that these nanomaterials have good biocompatibility and can serve as fluorescent probes or contrast agents for targeted tumor imaging, with promising potential for early diagnosis of HCC.

Nanomaterial-based therapies can be categorized into three main types: drug-based therapy, localized therapy, and combination therapy (either drug-drug, localized-localized, or drug-localized combinations). Nanomaterial-based drug therapies have several advantages, including improved targeting (through functionalization,[88] enhanced responsiveness,[89] intelligent release control[89]), the enhanced permeability and retention (EPR) effect available, reduced toxicity, and improved biocompatibility. In nanomaterial-based drug therapies, targeting can be active or passive, based on the targeting mechanism, and focused on either tumor cells or the tumor microenvironment, depending on the target.

Nanomaterial-based localized therapies, such as photodynamic therapy,[90] photothermal therapy,[91] and sonodynamic therapy,[92] leverage the unique properties of nanomaterials, including physical, chemical, and biological properties. For example, hollow gold nanoparticles with photothermal conversion properties have been utilized to load doxorubicin, achieving a combination of TACE with photothermal ablation therapy in animal models.[91]

We also mapped the timeline of new strategies involving nanomaterials in HCC treatment. The timeline indicates that early applications of nanomaterials were primarily involved single-mode therapies. Since 2015, there has been an increase in combination therapies, reflecting a trend toward more diverse and synergistic treatment approaches. In the past two years, new therapeutic concepts such as nanobodies[93] and nanovaccines[94] have also emerged. Nanobodies are single-domain antibodies (sdAbs), also known as VHH antibodies or camelid antibodies, a type of heavy-chain antibodies (HCAbs) found in the camelid, Chondrichthyes, which are naturally deficient in light chains. Nanobodies, which are only 10% the molecular weight of conventional antibodies, retain the full antigen-binding capacity of HCAbs. They exhibit high specificity, strong affinity, enhanced stability, and low immunogenicity, making them easily amenable to humanization. These features have led to their widespread use in biochemical mechanism research, structural biology, and the diagnosis and treatment of diseases such as cancer.[95] Nanovaccines are an emerging vaccine technology that leverages nanomaterials as carriers to enhance vaccine immunogenicity and efficacy. The concept of nanovaccines involves the use of various nanocarriers to control the release of antigens and adjuvants, thereby eliciting a more robust immune response. Nanovaccines exhibit unique advantages in several areas, including immune response, antigen presentation efficiency, multivalent vaccine development, stability, reduced toxicity, and personalized design. They show great promise for application in the field of cancer therapy.[96]

Theranostics, a concept that combines diagnosis and therapy, is also interpreted by nanomaterials with both therapeutic and diagnostic functions. Some nanomaterials in this field combine imaging capability with localized treatment. For example, mesoporous composite nanoparticles have been developed for dual-modal imaging (ultrasound/MRI) and synergistic chemo-/thermo-therapy.[97] In another study, a micellar nanomedicine loaded with sorafenib and superparamagnetic iron oxide nanoparticles (SPIONs) with dual reduction and pH responsiveness was designed to provide MRI imaging and molecular targeting capability.[98]

Although there are a few clinical trials investigating the application of nanomaterials in HCC, most results have been unsatisfactory, except for some promising small-scale MRI studies. The clinical application of nanomaterials faces numerous challenges, including quality control in nanomaterial preparation, ensuring drug delivery efficiency, biocompatibility, toxicity to major organs, and unclear molecular mechanisms, indicating that there is still a long way to go.

Limitations

This bibliometric study has several limitations: First, the search was conducted within a single database, WOSCC, without including other databases or academic search engines, and the language of the articles was limited to English, which may miss some relevant articles. However, the WOSCC database covers the majority of relevant articles in a given field, and researchers tend to publish their high-quality work in English in international journals for wider dissemination, so our inclusion criteria are unlikely to affect the results and conclusions of the present study. Second, the extraction, analysis, and processing of keywords and data relied on software, which does not provide a fully systematic review of the field, but it does provide a general overview of research hotspots and trends. Third, due to the date of the search, the analysis of citation counts and keywords may be affected by the limited timeframe, and some high-impact papers may not have been thoroughly captured, requiring further updates and refinements.

Conclusion

The field of nanomaterials and HCC is continuously evolving. The two countries with the highest publication output in this field are China and the United States. China has emerged as the country contributing most to the field in terms of volume, while the United States stands out for the impact of its individual publications. The top contributing institution is the Chinese Academy of Sciences, and five of the top people in this field of nanomaterials and HCC are Jie Tian, Dan Shao, Robert J Lee, Xiaolong Liu, and Wei Wang. The research hotspot in nanomaterials is the use of nanoparticles for drug delivery, with a greater tendency toward targeted chemotherapeutic applications. The frontier trends are the development of nanomaterial-based therapies targeting the tumor microenvironment and photodynamic therapy.

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Author Contributions

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

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Disclosure

The authors declare that they have no competing interests.

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