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SCIENTOMETRICS

Nano-drug delivery systems integrated with low radiation doses for enhanced therapeutic efficacy in cancer treatment

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Abstract

BACKGROUND

Precision medicine is an emerging field that includes tumor-targeted delivery and tumor microenvironment. This review explores the synergistic potential of combining nano-drug delivery systems with low radiation doses to achieve optimized therapeutic outcomes, particularly in the context of cancer treatment. Nanoparticle-based drug carriers offer precise and targeted delivery, enhancing the therapeutic index of anticancer agents. The use of lower radiation doses has become a focus in radiation oncology to minimize off-target effects on healthy tissues in palliation treatment with high-target volume lesions.

AIM

To conduct a bibliometric review of nanomedicine and glioblastoma (GBM), all relevant studies from the last two decades were included.

METHODS

The search strategy comprised the keywords "nanomedicine "and "glioblastoma" in the title and/or abstract. All English-language documents from 1 January 2000 to 31 December 2023 were considered for the analysis. R code (version 4.2.0) with R Studio (version 2022.12.0-353) and the Bibliometrix package (version 4.0.1) were

used for the analysis. A total of 680 documents were collected.

RESULTS

We analyzed the bibliometric features of nanomedicine in glioma. With the limitations of the research, our analysis aims to highlight the increasing interest of researchers in the precision medicine field in GBM treatment and lead us to suggest further studies focusing on the association between nanomedicine and radiotherapy.

CONCLUSION

Due to the poor prognosis associated with GBM, new therapeutic approaches are necessary. There is an increasing interest in precision medicine, which includes nanomedicine and radiotherapy, for GBM treatment. This integration enhances the efficacy of targeted treatments and provides a promising avenue for reducing adverse effects, signifying a notable advancement in precision oncology.

Key Words: Nanomedicine; Nanoparticles; Drug-delivery; Radiotherapy; Combination therapy

Core Tip: Glioblastoma is a highly aggressive brain cancer, which main treatment consists of surgical resection or biopsy followed by radiotherapy and chemotherapy (STUPP protocol). Precision medicine is an emerging field that includes tumor-targeted delivery and tumor microenvironment. The integration of nano drug delivery systems with low radiation doses may offer a promising avenue for maximizing therapeutic efficacy and minimizing systemic toxicity.

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INTRODUCTION

Glioblastoma (GBM) continues to be one of the most formidable malignancies owing to its invasive proliferation and resistance to standard treatments[1-3]. Despite the STUPP procedure, which integrates radiation and chemotherapy, enhancing results, the blood-brain barrier (BBB) remains a continual impediment to efficient drug delivery[4-6]. Nanomedicine offers a promising strategy to circumvent the BBB and deliver medicines precisely, utilizing increased permeability and retention (EPR) effects in malignancies[7-9]. Furthermore, low-dose radiation has been examined to mitigate detrimental effects on healthy tissues, indicating a potentially synergistic strategy when integrated with targeted nanomedicine[10,11]. Accordingly, to improve the EPR effect, nanomaterials accumulate and retain in higher amounts in tumors than in healthy tissue due to the erratic and leaky vasculature and poor lymphatic drainage of the tumor tissue[5, 6]. Nano-drug delivery platforms, including liposomes, polymeric nanoparticles, and nanogels, are investigated for their ability to facilitate controlled drug release and improve the bioavailability of therapeutic agents. Liposomes, known for their biocompatibility and versatility, offer a promising avenue for precise drug delivery[12]. Polymeric nanoparticles, with their tunable properties, allow for controlled release kinetics[13]. Nanogels, characterized by their three-dimensional networks, exhibit the potential for sustained and targeted drug delivery[14]. The diverse range of nano-drug delivery systems with unique physicochemical properties underscores the multifaceted nature of precision nanomedicine[8,12-14]. Considering the tumor microenvironment (TME), precision nanomedicine strategies aim to address the challenges posed by the complex interactions within the TME[15]. Designed nanoparticles play a pivotal role in modulating the TME, enhancing drug penetration, reducing immunosuppression, and overall augmenting the effectiveness of both nanomedicine and radiotherapy within the intricate context of the TME[16].

Concurrently, advancements in radiation therapy planning and delivery techniques have enabled the exploration of lower radiation doses, seeking to strike a delicate balance between effective tumor control and reduced damage to surrounding healthy tissues[10]. The integration of nano-drug delivery systems with low radiation doses may offer a promising avenue for maximizing therapeutic efficacy and minimizing systemic toxicity[11]. Notwithstanding advancements in nanomedicine, deficiencies persist in comprehending the interactions between nano-drugs and low-dose radiotherapy within the TME. This review examines the possible synergy of different modalities, intending to build a basis for future research aimed at optimizing treatment effects while reducing systemic toxicity. This bibliometric analysis aims to highlight the increasing interest of researchers in the precision medicine field in glioblastoma treatment. It suggests evaluating the synergistic potential of combining nano-drug delivery systems with radiotherapy to optimize therapeutic outcomes in the treatment of GBM. The precision offered by nanoparticle-based drug carriers, ensuring targeted delivery, coupled with the focus on minimizing off-target effects through lower radiation doses, may represent a paradigm shift in the field of oncology[17,18].

MATERIALS AND METHODS

Data origin and search strategy

The Web of Science (WoS) electronic documents database was used as a data source (consulted in January 2024). Using the key words nanomedicine and GBM, the authors searched for records that included the same in their titles and abstracts.

Records published from 2000 to 2023 were included in this study. Papers not published in the English language were discarded. The entire metadata for the selected records was obtained in Bib TeX format. These records were then classified and assessed for relevance by Antonio Pontoriero and Paola Critelli. A total of 12 articles were retrieved. References used by these records in also searched for relevant documentation.

Data analysis

The analysis was carried out with R code (version4.2.0), R Studio (version 2022.12.0-353), and the Bibliometrix package (version 4.0.1)[19]. The "convert2df" function was used to extra data frames from the modified BibTeXfiles, subsequently utilizing the "biblioAnalysis" command and the "Summary ()" function from the Bibliometrix package. This facilitated an exploratory analysis, emphasizing critical attributes such as the annual publication count, growth rate, leading active countries, and their respective output based on the institution the publication lead is affiliated to, the most cited papers, and the most prominent journals.

The command "Biblioshiny ()" was engaged to further analyze sampled studies by converting them to a pictorial representation, a graphical user interface, and generating maps for national scientific cooperation, institutional collaboration networks, and a comprehensive co-occurrence network.

Keywords were evaluated using clustering analyses in machine learning, and trending topics were identified. The co-occurrence network of authors' keywords was examined using the walk trap clustering technique[7].

RESULTS

Publishing trend

A total of 680 publications about nanomedicine and GBM were collected from 2000 to 2024. Among them, 514 were articles (74%), 143reviews (20%), 9 editorial material (1%), 8 meeting abstracts (1%), 7 early access (1%), six book chapters (1%), 6 Proceeding Paper (1%), 4 Corrections (1%) and 2retractions (0%). Figure 1 shows the trend of the publications in the years for the period 2009-2023. Since 2009, an increase in the production of documents has been observed. The most productive year was 2021, with 88 articles, followed by 2021 and 2022, with 81 documents. In 2013, the highest mean of total citations per article and per year was observed (Supplementary Figure 1).

Countries and institutions distribution

A total of 680 publications from 8 countries and 10 institutions. The two main Countries that contributed to production are China and the United States, with 999 and 755 articles, respectively, followed by France (293 articles) and Italy (287 articles) (Figure 2, Supplementary Figure 2 and Table 1). The top ten countries in terms of publication volume are reported in Table 2. The highest number of publications was from China, with 999 articles. In Figure 3 and Supplementary Figure 3, we analyzed the relationship network among countries. Each vertex represents an item, and its size is proportional to the item's occurrence. Each cluster can be considered as a topical macro-area, and the colors represent the cluster to which each word belongs. China has a strong connection with the United States and Australia, and there is a clear tendency for European countries (blue) to collaborate. China, the United States, and Italy generated the greatest quantities of multi-national documents, characterized as publications with authors from a minimum of two countries. China and the United States were often the foremost contributors to single-country publications. In most cases, China and the United States participated in publications (Figure 4). Furthermore, the United States and China are the most cited countries, respectively, with 5878 and 4566 citations (Figure 5A). The principal institutions in terms of production were Johns Hopkins University, with 118 articles, followed by the University of Anger, with 58 articles (Figure 5B, Supplementary Figure 4).

Journal, citations, and local cited sources

The most relevant source is represented by the "*International Journal of Nanomedicine*" with 123 articles, followed by "*Nanomedicine*" and "*Nanomedicine Nanotechnology Biology and Medicine*" with 55 and 45 articles, respectively (Figure 5C). The most locally cited sources are *Journal Control Release and Biomaterial,* with 1725 and 1343 articles, respectively (Supplementary Figure 5). The core sources are represented by "The *International Journal of Nanomedicine*" *Nanomedicine* and *Nanomedicine Nanotechnology Biology and Medicine*" and "*Journal of Controlled Release*" (Figure 6). The source production over time revealed the "*International Journal of Nanomedicine*" as the principal source with increasing production from 2009 to 2024 (Figure 7). The most local global cited reference was "Radiotherapy plus concomitant and adjuvant temozolomide for GBM" with 146 followed by "Effects of radio therapy with concomitant and adjuvant temozolomide *vs* radio therapy alone on survival in GBM in a randomized phase III study: 5-yearanalysis of the EORTC-NCIC trial" with 52 citations (Supplementary Figure 6). The most global cited document was Jensen *et al*[8] with 432 citations followed by Graham *et al*[9] with 346 citations; the most local cited document was Ganipineni *et al*[20] with "Drug delivery challenges and future of chemotherapeutic nanomedicine for GBM treatment" obtaining with 28 citations

Table 1 Annual production of scientific publications on glioblastoma nanomedicine from 2009 to 2024, categorized by country[1]

Year	China	United States	France	Italy
2009	0	5	0	1
2010	0	16	5	4
2011	8	23	5	6
2012	32	31	11	18
2013	47	88	21	22
2014	51	126	36	36
2015	88	182	62	45
2016	114	254	80	53
2017	208	320	115	74
2018	304	428	132	85
2019	397	508	155	132
2020	519	600	178	176
2021	653	662	218	206
2022	815	724	250	240
2023	991	755	290	284
2024	999	755	293	287

[1]The data encompasses the overall document count per annum for China, the United States, France, Italy, and other leading generating nations.
The table depicts the evolution of research volume over time, with values reflecting the increasing influence and emphasis of specific countries in furthering the discipline.

Table 2 The 10 foremost countries ranked by publication volume in glioblastoma nanomedicine research[1]

Country	Number of documents
China	999
United States	755
France	293
Italy	287
Spain	162
South Korea	115
India	113
Australia	109

[1]The table illustrates the quantity of documents published by each nation, with China and the United States leading.
This distribution identifies the main contributors to research and emphasizes the regions most committed to nanomedicine applications for glioblastoma therapy

(Figure 8).

Keyword analysis

A total of 51 keywords were identified from documents. The main keyword's authors (right side) resulted in GBM, nanomedicine, nanoparticles, glioma, drug delivery, BBB, nanoparticles, GBM multiforme, brain tumors, cancer, temozolomide, nanotechnology, chemotherapy, delivery, radiotherapy, brain, targeted, brain cancer (Supplementary Figure 7). The top ten keywords are nanomedicine, GBM, nanoparticles, glioma drug delivery, BBB, cancer, and brain tumor, and are reported in Figure 9. Among the keywords used by authors, the top three are nanoparticles (8%), drug delivery (7%), and GBM (6%) (Figure 10). The keywords network (Figure 11) confirmed two different clusters and GBM, nanoparticle, and drug delivery are the principal words. In the period 2011–2023 a change in trend topics demonstrated an evolution of the research. The principal themes were "drug delivery" "GBM" and "*in vitro*". The trending topics developed from 2017

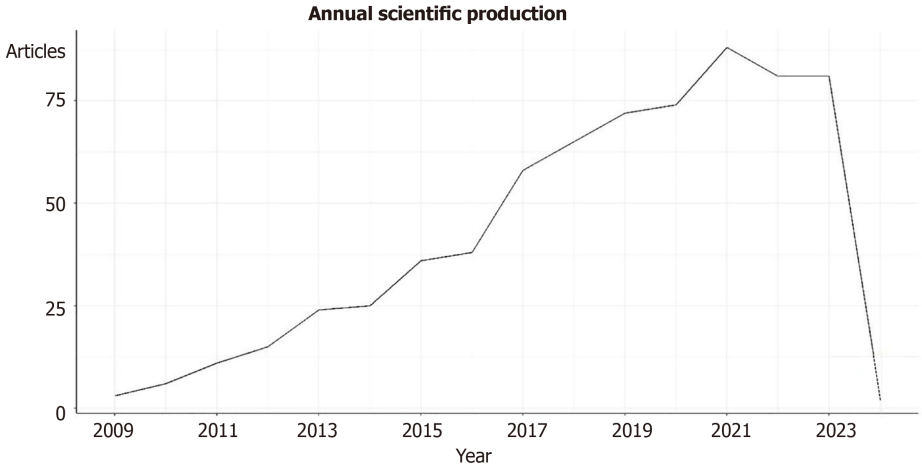

Figure 1 Annual trend of publications pertaining to nanomedicine uses for glioblastoma from 2009 to 2024. Each bar denotes the aggregate count of peer-reviewed articles, reviews, editorials, and conference papers published annually, as documented in the Web of Science database. The prevailing upward trend underscores a growing scientific interest and expenditure in research concerning nano-drug delivery systems integrated with low-dose radiation in oncology.

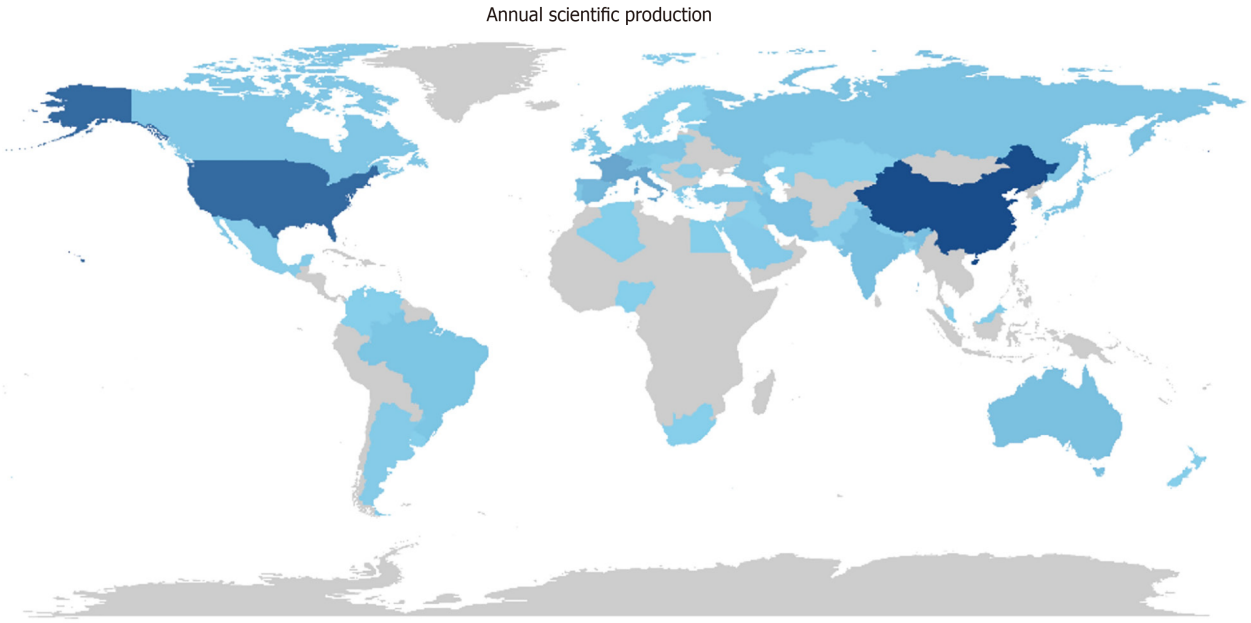

Figure 2 International partnership network among nations engaged in glioblastoma nanomedicine research. The dimensions of each node indicate the publishing volume of each country, whilst the lines depict the frequency of collaborative publications among nations. Color-coded clusters indicate regional collaboration patterns, with notable clusters demonstrating robust connections across China, the United States, and European countries. This figure illustrates the geographical diversity and collaboration intensity within the field.

to 2021, "nanoparticle" and "blood-barrier" saw their main development during 2017–2023. The most recent topic (2020-2023) regards "loaded liposomes" "blood" "loaded page nanoparticles" and "drug-delivery system" (Supplementary Figure 8). Figure 12 represents the evolution of the thematic areas and their relationships during the considered periods (2009-2016, 2017–2018, 2019–2020, 2021-2022, 2023-2024). Several niches appeared in 2009-2016. Among them, "nanotubes", "glioma", "toxicity", "hyperthermia", "angiogenesis", "target delivery", "glioblastoma", "cytotoxicity" and "micelles" in 2017-2018 emerged "nanomedicine", "magnetic hyperthermia", "gold nanoparticles", "microglia", "magnetic resonance imaging", "liposomes", "chemotherapy" and "inhibitor"; in 2019-2020 appeared "photodynamic therapy" while in 2021-22 appeared "barrier", "tumor microenvironment", "peptide" and "stem cells". The niches that have appeared in the last year are "blood barrier", "autophagy", "nanotechnology" and "combination therapy".

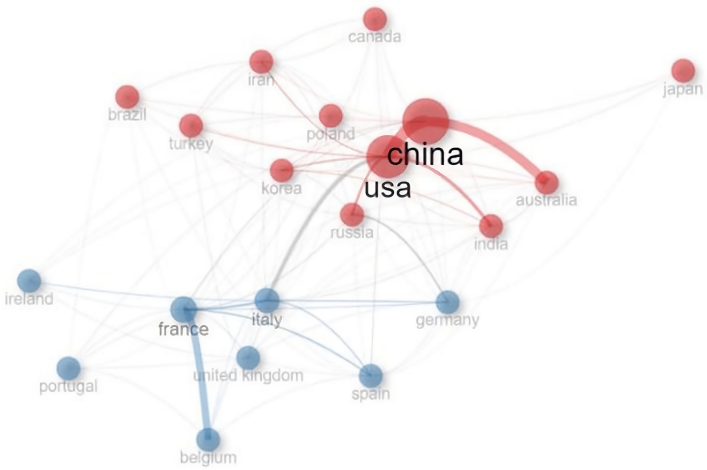

Figure 3 Collaboration network illustrating the global linkages among nations engaged in glioblastoma nanomedicine research. Node dimensions represent publishing quantities, whereas line thickness indicates the level of collaboration. Clusters signify regions of frequent international collaboration, with the United States and China serving as pivotal centers, promoting global research integration.

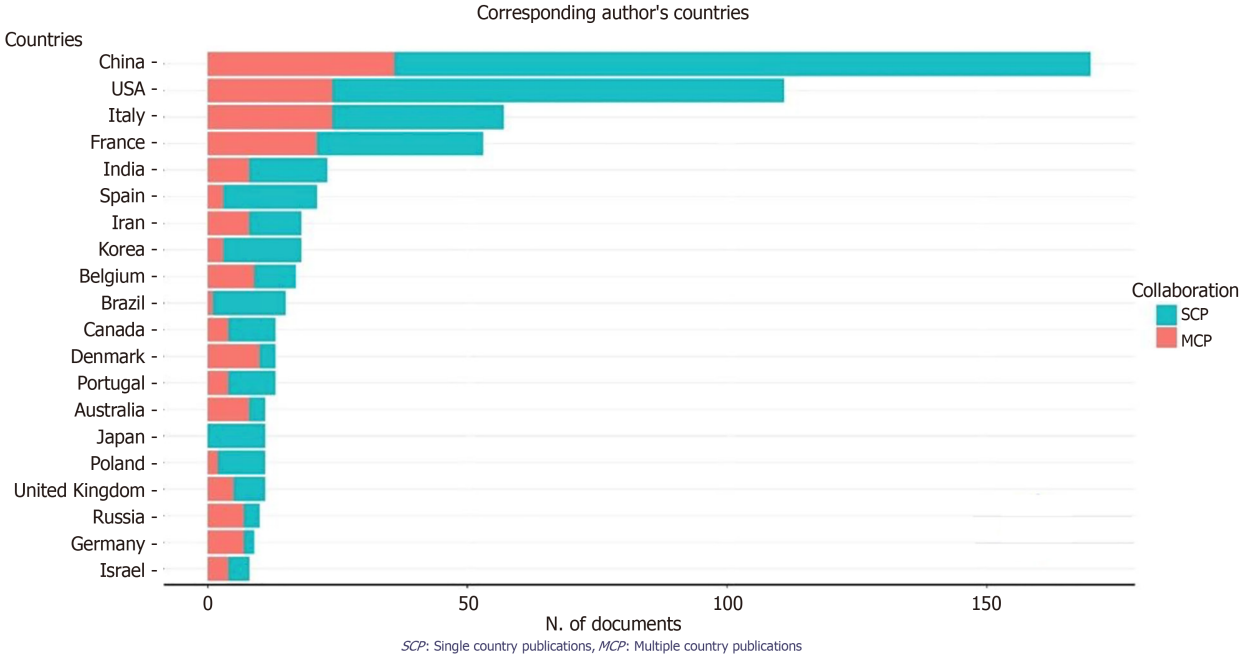

Figure 4 Illustration of the collaborative network among prominent institutes engaged in glioblastoma nanomedicine research. Each node signifies an institution, with node size denoting publication volume and edge thickness representing the frequency of inter-institutional collaboration. Distinct color coding signifies clusters of strongly networked universities, emphasizing important cooperation hubs and possible research synergies.

DISCUSSION

The quantity of publications is a vital indicator for evaluating the progression and trends in academic research on subjects over time. The speed of the publications in a specific period is important for assessing the trend of academic research. Our bibliometric research encompassed 680 documents published from 2000 to 2023 across 59 distinct nations. The annual volume of literature pertaining to nanomedicine and GBM has markedly escalated, reflecting an increasing interest in the adjunctive treatment of GBM. The works of Stupp *et al*[1,2] garnered the most citations (n = 146 and 52, respectively)[1,2].

Concerning countries and geographical distribution, the United States and China had the highest volume of publications and citations. The most efficient academic institution is situated in the United States (Johns Hopkins University). Italy has demonstrated a rise in document creation from 2009 to the present, ranking fourth (n = 287) after the United States, China, and France in output, and third in citation frequency. The primary cluster of involving the United States with Italy and India, as well as France with Belgium.

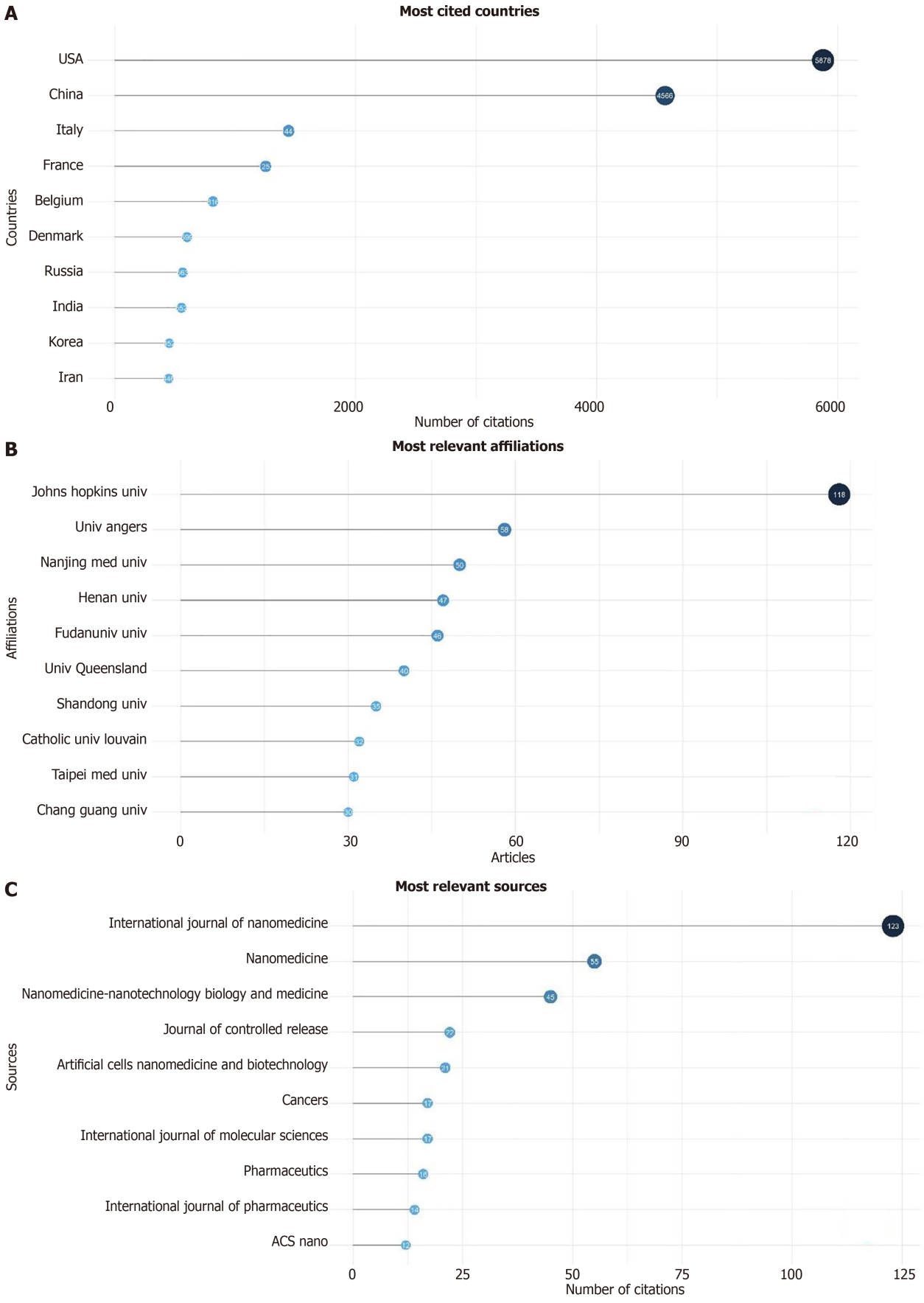

Figure 5 Glioblastoma nanomedicine research. A: A comparison illustration of the countries with the highest citations in glioblastoma nanomedicine research. Each bar illustrates a country's total citation count, offering insight into regional research influence and the acknowledgment of scholarly work performed by scholars in different nations. These graphic highlights the substantial contributions of the United States, China, and European countries to the subject; B: Graphical

depiction of significant institutions' contributions to glioblastoma nanomedicine research, ordered by publication volume. Each bar signifies an institution, such as Johns Hopkins University, illustrating the premier research organizations that propel innovation and discovery within this specialized domain; C: Journals classified by their publication volume in glioblastoma nanomedicine, in accordance with Bradford's Law. Journals are ranked based on the volume of published papers, with the '*International Journal of Nanomedicine*' at the forefront. The distribution highlights journals that function as important venues for the dissemination of research in nanomedicine applications for oncology.

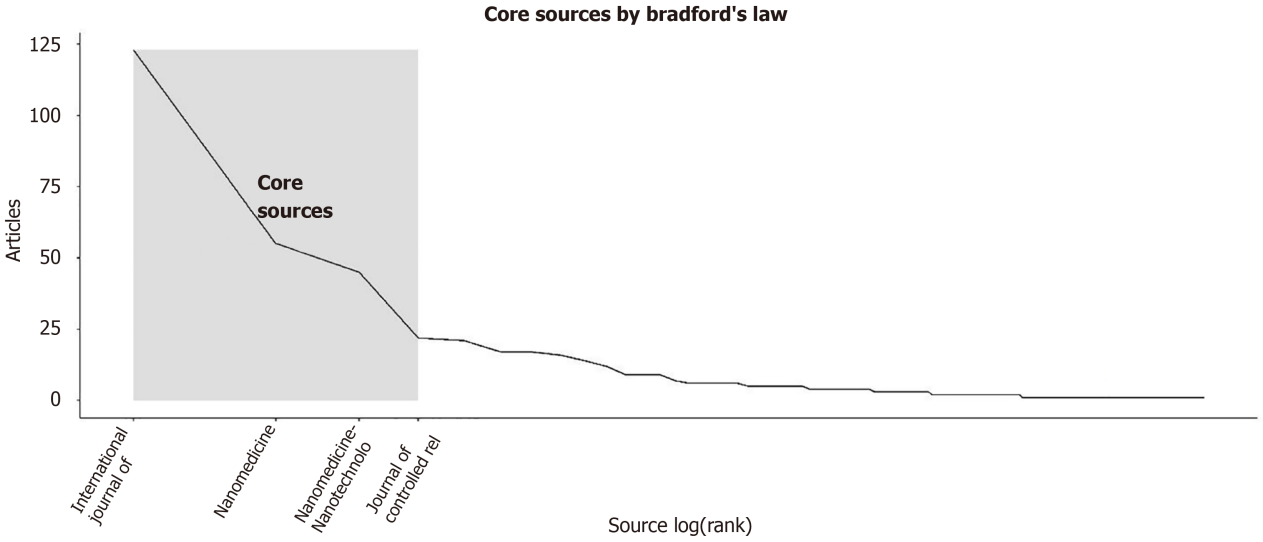

Figure 6 Co-occurrence network of important phrases in glioblastoma nanomedicine literature obtained from keyword analysis. The dimensions of the nodes reflect the frequency of each term, while the links denote co-occurrences in publications. The network identifies fundamental theme domains, such as medication delivery and blood-brain barrier methodologies, while highlighting the interconnectedness of new ideas in glioblastoma research.

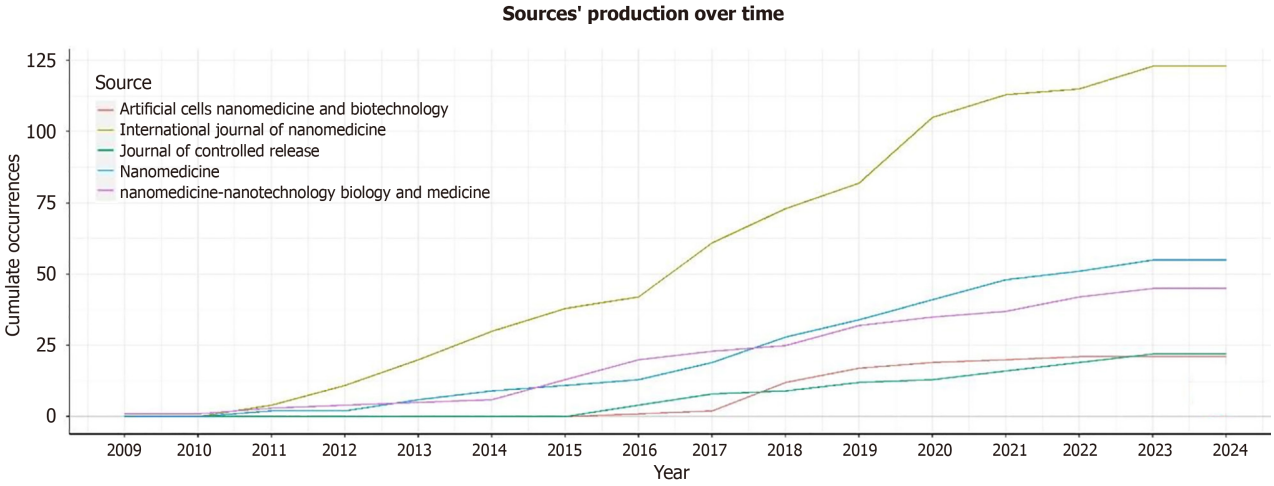

Figure 7 Sources' Production over time. The *International Journal of Nanomedicine* is the most representative.

An examination of the most referenced papers was conducted to ascertain the nature and significance of articles that have profoundly influenced scholarly literature in the field. The initial and most frequently referenced paper is regarded as the foundation of adjuvant therapy in GBM. A report by Stupp *et al*[1] published in 2005 shown that incorporating temozolomide with radiotherapy for newly diagnosed GBM yielded clinical benefits regarding survival and toxicity.

The evolution of precision medicine with the necessity of new therapeutic approaches introduces new treatment strategies over time. This progression is evident in the analysis of trend topics. From 2009 the main interest was focused on "nanotubes", "glioma", "toxicity", "hyperthermia", "angiogenesis", "target delivery", "glioblastoma", "cytotoxicity" and "micelles" while in the last 3 years, the principal collaboration transpired between the United States and China, succeeded by lesser clusters topics included "barrier", "tumor microenvironment", "peptide" and "stem cells" and "blood-barrier", "autophagy", "nanotechnology" and "combination therapy".

The cluster analysis results of the machine-learning-based revealed two main groupings of co-occurring words, highlighting the key areas of focus within the field and the interconnections between them.

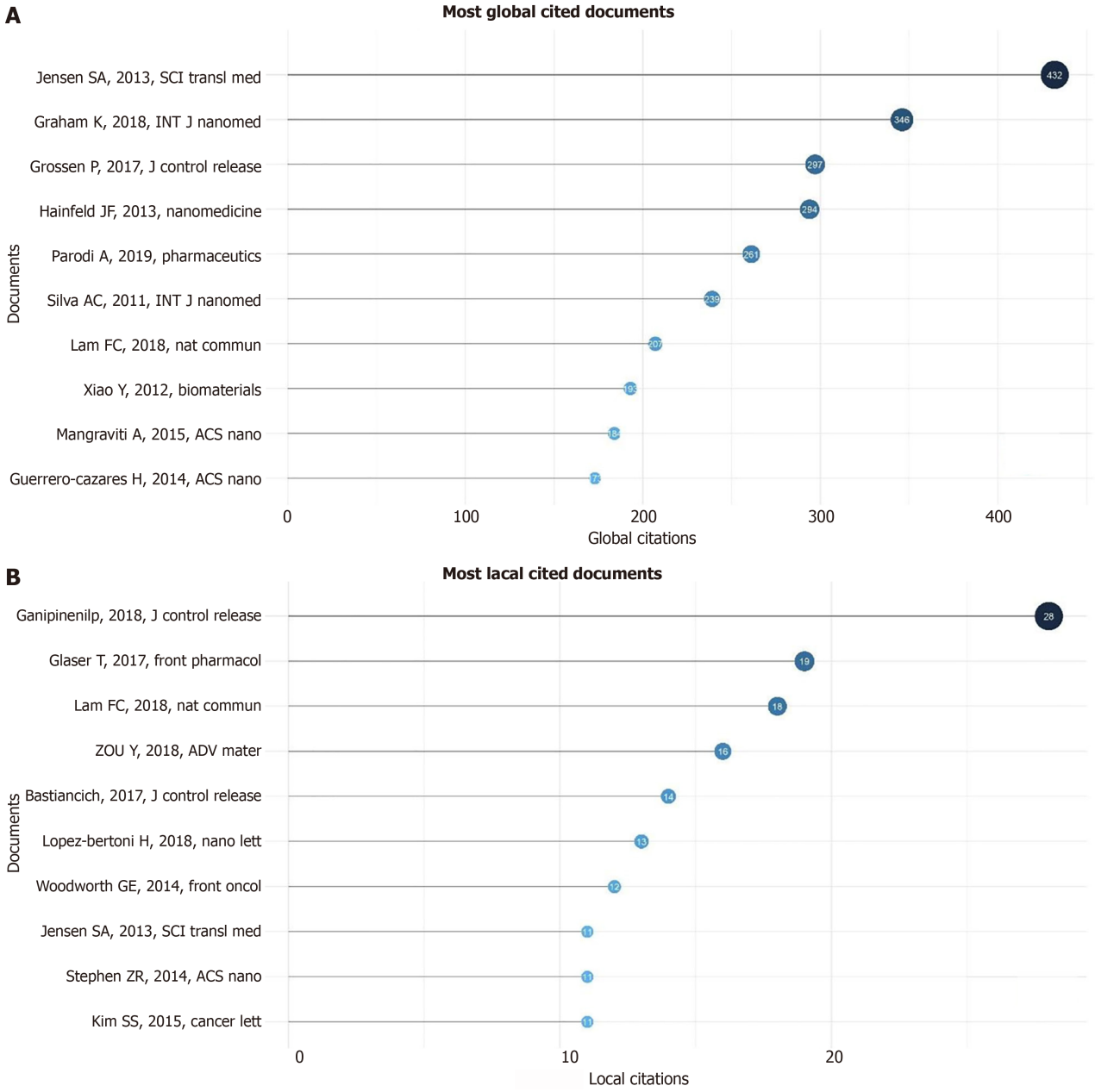

Figure 8 Most Cited Articles in Nanomedicine Pertaining to Glioblastoma Entries comprise article names, authors, publication years, and citation frequencies. These significant publications signify crucial developments, including the use of nanoparticles in drug transport and tumor-targeting mechanisms, that have influenced contemporary understanding and research directions in the field. The most Global cited document was Jensen *et al*[8] the most local cited document was Ganipineni *et al*[20]. A: Global cited document; B: Local cited document.

The first cluster, with nanoparticles as the main contributor, presents networks focused on systemic treatment as "temozolomide", "doxorubicin" and "paclitaxel". The second cluster, centered on "drug delivery" presents networks with the main mechanisms of actions such as "*in vitro*", "blood-brain barrier", "*in vivo*" and "receptor". Both clusters present a small network with "radiotherapy" terms, indicating the lack of studies that deepen the combination between "nanomedicine" and "radiotherapy" in the treatment of GBM.

The word "radiotherapy" occurs 43 times and represents only 2% of the words cited in the tree map among 680 documents. Furthermore, "radiotherapy" isn't present in the trend topic theme from 2009 to 2024. Recent literature data show that the different fractionations of radiation dose and low-dose radiotherapy can induce effects on the TME and support the delivery of drugs[10,11].

Radiotherapy and nanomedicine could be combined to enhance the overall effectiveness of cancer treatment. An association between radiotherapy and nanomedicine could determine the following. Increase tumor-targeting: Radiotherapy could modify the tumor environment, enhancing the EPR effect and improving the accumulation of nanoparticles[17]; enhance drug delivery: Radiotherapy induces a change in tumor physiology, making it more susceptible to drug penetration, improving, in turn, the overall therapeutic effect[17]; radio sensitivity: Nanomedicines have intrinsic radio-sensitizing properties; when combined with radiotherapy, they can improve the cancer sensitivity of therapeutic agents in response to specific stimuli, including radiation, providing a cell to radiation, leading to increased

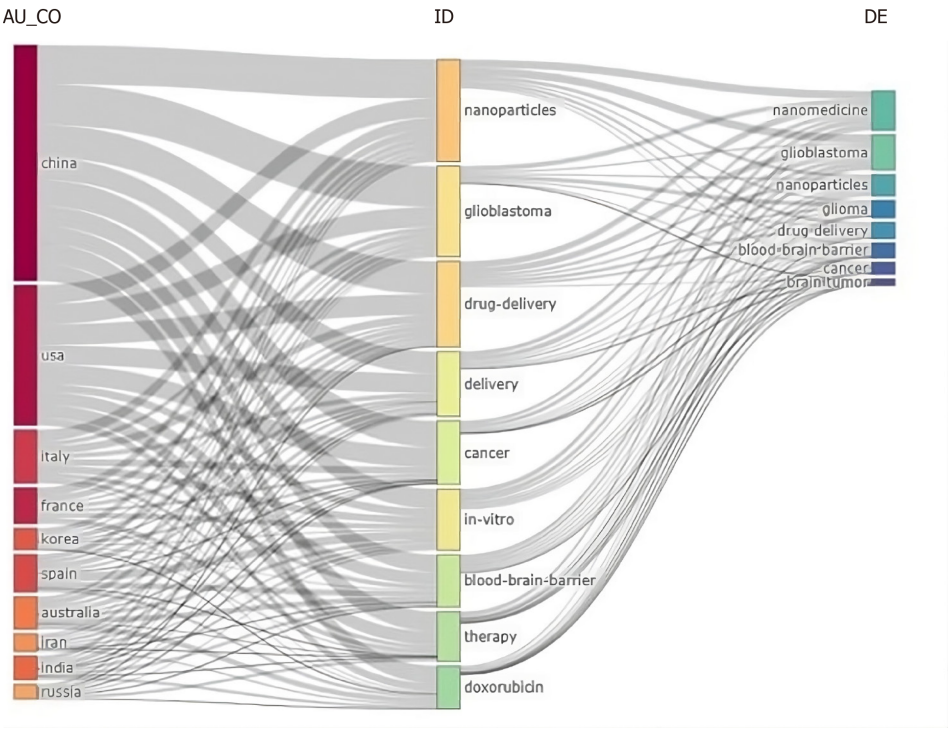

Figure 9 The top ten keywords (right side): Nanomedicine, glioblastoma, nanoparticles, glioma drug delivery, blood-brain barrier, cancer, and brain tumor.

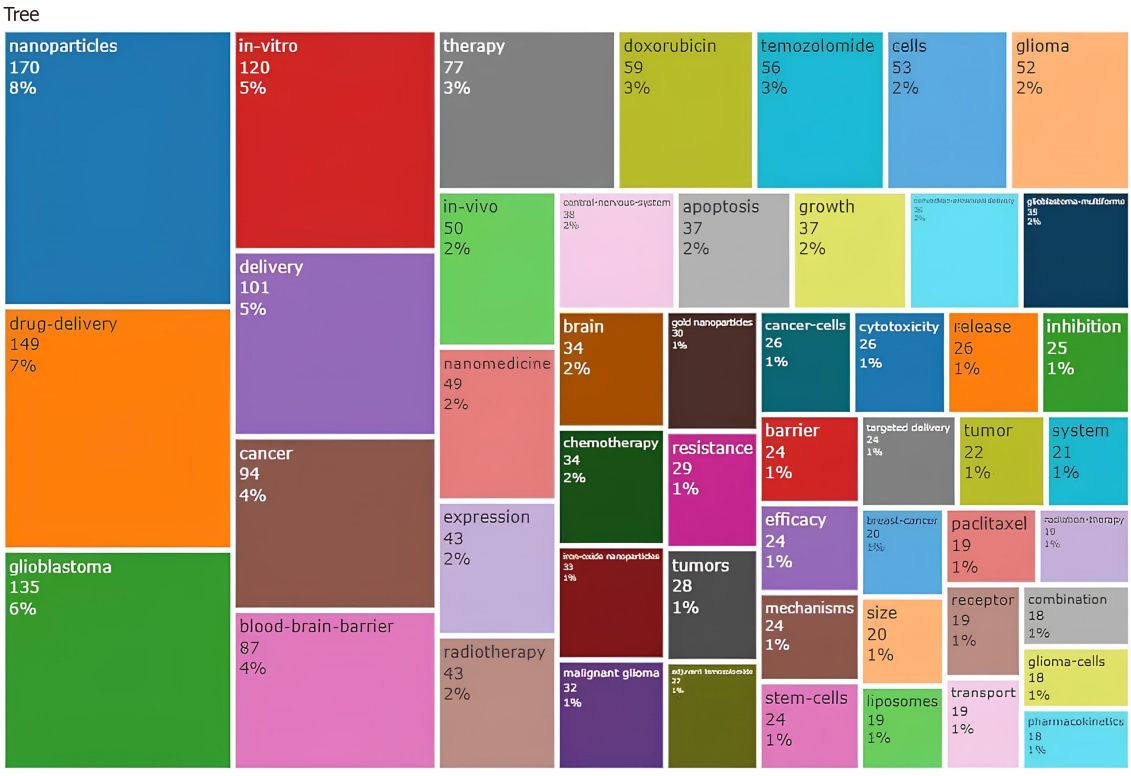

Figure 10 Treemap of keywords' occurrence. The top three are: Nanoparticles (8%), drug delivery (7%), and glioblastoma (6%).

cell death; low radiation doses could exploit this synergistic effect[18]; nanoparticles can serve as imaging agents to visualize tumors and monitor the response to radiotherapy. Real-time imaging can help guide the radiation treatment, ensuring accurate targeting. Additionally, nanoparticles can be planned to controlled and targeted drug release[19]; reduced side effects: By improving the specificity of drug delivery to tumor cells, the combination of radiotherapy and nanomedicine may help reduce systemic toxicity. This is particularly important in minimizing side effects associated with

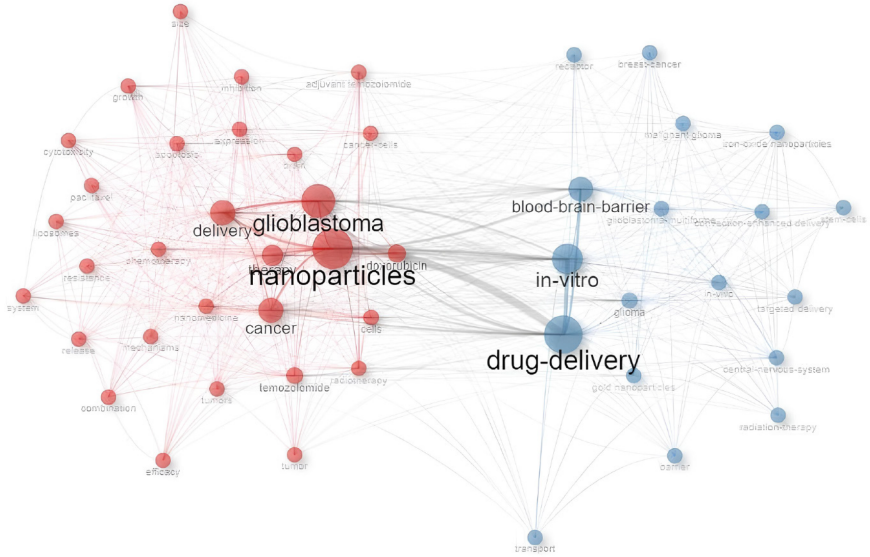

Figure 11 Keyword network analysis. Two different clusters are present glioblastoma, nanoparticle, and drug delivery.

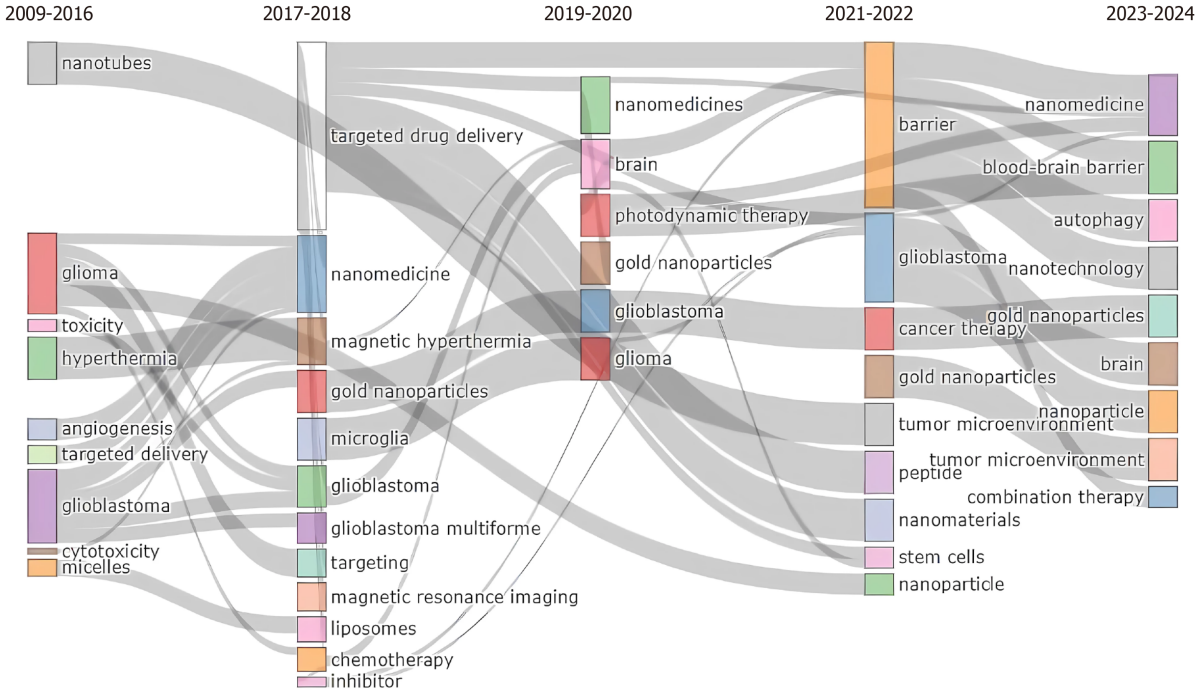

Figure 12 Progression of principal research themes in glioblastoma nanomedicine, spanning from 2009 to 2024. Keywords are monitored longitudinally, with theme clusters illustrating transitions in focal areas, such as 'nanotubes' in early years to 'tumor microenvironment' and 'stem cells' in contemporary research. This chart provides insights into the evolving nature of research goals, illustrating the field's advancement.

traditional chemotherapy, where healthy tissues can be affected[20]; overcoming treatment resistance: Nanoparticles can be engineered to overcome resistance mechanisms in cancer cells. By combining nanomedicine with radiotherapy, it may be possible to address different resistance pathways, improving the likelihood of treatment success[21]; personalized medicine: The combination of radiotherapy and nanomedicine permits a more personalized approach to cancer treatment. Tailoring the treatment strategy based on the individual characteristics of the patient and their tumor can optimize therapeutic outcomes[22].

Young researchers should concentrate on enhancing nanoparticle formulations to optimize the therapeutic index in GBM treatment. Research on low-dose radiation and its potential to augment the EPR effect and drug infiltration is also an interesting domain. Furthermore, interdisciplinary research on nanoparticle interactions in the TME may provide essential insights for clinical use.

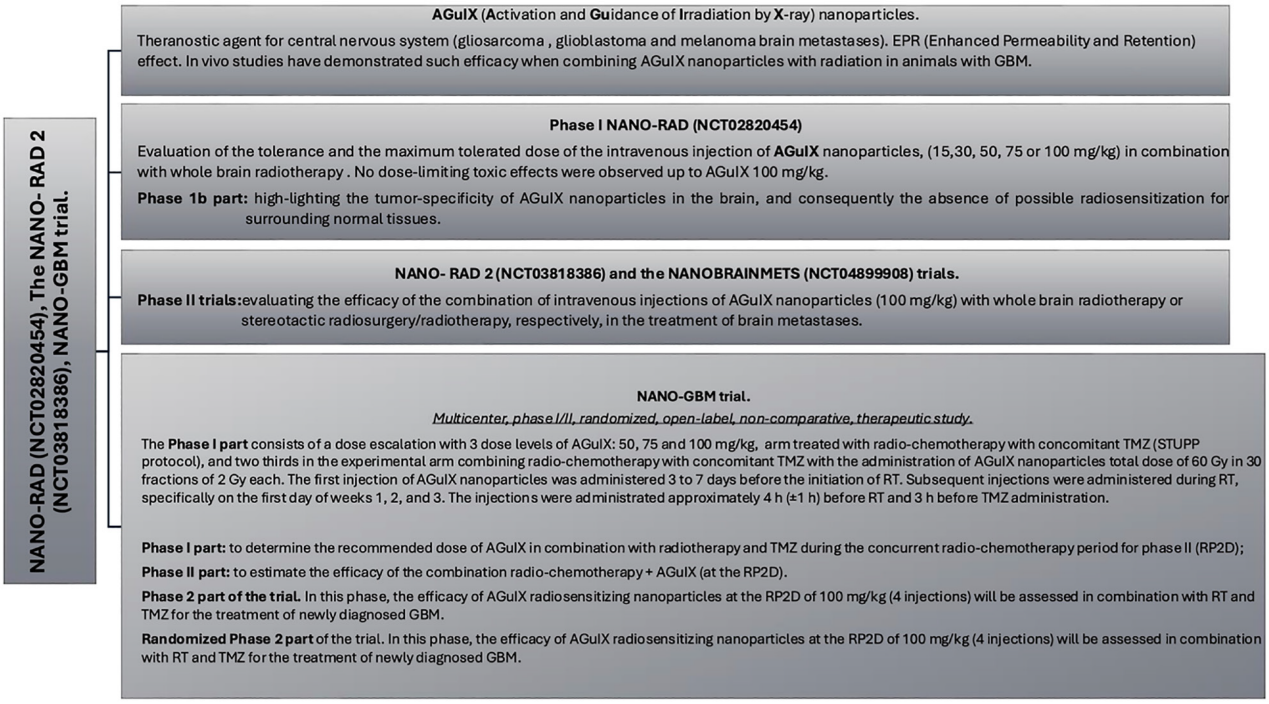

Figure 13 Nanomedicine clinical translation. Schematic evolution of the NANO-GBM trial[24] and various steps through other trials[25-28] for the first human application in newly diagnostic glioblastoma patients.

Research hotspots

The frequency of citations reflects the research hotspots and development trends about the discipline. The research hotspots and trends of nanomedicine in glioma were:

Nanomedicine platform RNA interference-based with nanoparticle conjugates of spherical nucleic acid: Jensen *et al*[8] assess, with 432 citations, a preclinical Nanomedicine platform RNA interference (RNAi)-based with nanoparticle conjugates of spherical nucleic acid (SNA) to inhibit oncogene expression in GBM. SNAs are gold nanoparticles covalently modified with arranged densely, strongly orientated small interfering RNA (Bcl2 L12) an effector caspase and p53 inhibitor that is overexpressed in GBM duplexes. The small nucleolar RNAs (SNAs) against of the oncoprotein Bcl2 Like12 compared to normal brain tissue and low-grade astrocytoma reduced endogenous Bcl2 L12 mRNA and protein levels. The sensitizing glioma cells to therapy-induced apoptosis by augmenting impediment to effective cancer therapy effector caspase and p53 activity. Consequently, inhibiting antiapoptotic signaling through SNAs constitutes a novel strategy for systemic RNAi therapy targeting GBM and maybe other fatal cancers.

Tumor hypoxia impairment to cancer therapy: The hyperbaric oxygen therapy, artificial hemoglobin, allosteric hemoglobin modifiers, hypoxia-activated prodrugs, and fluorocarbons (FCs) have been employed. Graham *et al*[9], with 346 citations, assess oxygen treatments utilizing liquid fluorocarbons, which may enhance the oxygen-carrying capacity of blood to mitigate tumor hypoxia. At present, a minimum of two pharmaceuticals are undergoing clinical trials aimed at reversing tumor hypoxia; one is intended to enhance oxygen permeability within tumor tissue, while the other utilizes a low boiling point fluorocarbon that delivers greater quantities of oxygen per gram than previously evaluated fluorocarbons.

The prominence of nanomedicine clinical translation: Biau *et al*[23] proposed the results of the first human use of the theragnostic nanoparticles based on a polysiloxane network surrounded by gadolinium chelates (AGuIX) with radiotherapy and chemotherapy in the newly diagnosed GBM (Figure 13)[24].

The data were derived from WOS only. Failure by reviewers to manually remove irrelevant publications can lead to selection bias[25-28].

CONCLUSION

We analyzed the bibliometric features of nanomedicine in glioma. A comprehensive analysis was conducted to evaluate the research hotspots in the nanomedicine field. Integrating nano-drug delivery systems with minimal radiation doses presents a revolutionary method for treating cancer, especially GBM. This review emphasizes notable progress in nanomedicine, underlines the effectiveness of targeted medication administration, and calls for additional research on the synergistic potential with low-dose radiation. This method enhances therapeutic efficacy while aiming to reduce systemic toxicity, indicating a promising direction in precision oncology. However, new therapeutic approaches are necessary due

to the poor prognosis associated with GBM. With the limitations of the research, our analysis aims are to highlight the increasing interest of researchers in the precision medicine field in GBM treatment and lead us to suggest further studies focusing on the association between nanomedicine and radiotherapy.

FOOTNOTES

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