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Review

2009–2023 Bibliometric analysis of the clinical value of graphene quantum dots in glioblastoma treatment

Jingyan Zhu[1,2,3] · **Xiaoqing Li**[2,3] · **Zhenhua Lin**[1,2,3] · **Linzhuo Qu**[1,2,3] · **Hongjian Guan**[1,2,3]

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Abstract
Glioblastoma (GBM) is the most common primary brain tumour in adults and poses a serious health risk. Graphene quantum dots (GQDs) are zero-dimensional crystalline discs de-rived from two-dimensional graphene, which contribution of GQDs in the treatment of GBM and the great potential for future development. In this study, the Web of Science database was applied to search 462 relevant papers published between 2009 and 2023, and analyzed using VOS viewer and CiteSpace software tools. This analysis aims to provide researchers with insights into the current state of applications and to facilitate a clearer understanding of potential pathways and directions for future research in this field. Our study showed a continuous increase in the number of papers about GQDs in the treatment of GBM. In the field for more than a decade, GQDs has been a research priority in drug delivery due to their excellent optical and chemical properties. It is reasonable to believe that the use of GQDs for drug delivery for the treatment of GBM will be-come one of the extremely important research topics in the future.

Keywords Graphene quantum dots · Glioblastoma · Drug delivery · Visualized analysis · Clinical value

1 Introduction

Among central nervous system (CNS) tumours, glioblastoma (GBM) accounts for almost half of all primary malignancies [1]. Due to the highly infiltrative nature of gli-oblastoma cells and their possible origin in specific functional areas of the brain, patients cannot usually be treated by surgical resection [2]. Therefore, the therapeutic options for off GBM still need to be further developed. Despite some improvements in treatments and outcomes over the past decades, little has been achieved to improve patient survival [1]. This is due to the presence of the congenital blood–brain barrier (BBB) and the blood-cerebrospinal fluid barrier that impedes drug delivery, thus improving the effi-ciency of drug delivery to the GBM is key to improving patient prognosis [3].

The potential non-invasive cancer treatment technique was discovered through the integration of physics and medicine, which is the combination of photothermal therapy (PTT) and photodynamic therapy (PDT) (Fig. 1). PTT involves the conversion of light energy into heat by photothermal agents, leading to selective tumor cell destruction. On the other hand, PDT utilizes photosensitizers that generate cytotoxic reactive oxygen species under specific wavelengths of light, inducing tumor cell apoptosis. PTT and PDT can be used as stand-alone therapies, guided by multimodal imaging, or in combination with existing drugs for improving the efficiency of drug transport to the GBM. And they can also be used for the treatment of

✉ Hongjian Guan, hjguan@ybu.edu.cn | [1]Department of Neurology, Yanbian University Hospital, Yanji 133000, China. [2]Key Laboratory of Pathobiology (Yanbian University), State Ethnic Affairs Commission, Yanji 133000, China. [3]Department of Pathology, Yanbian University, Yanji 133000, China.

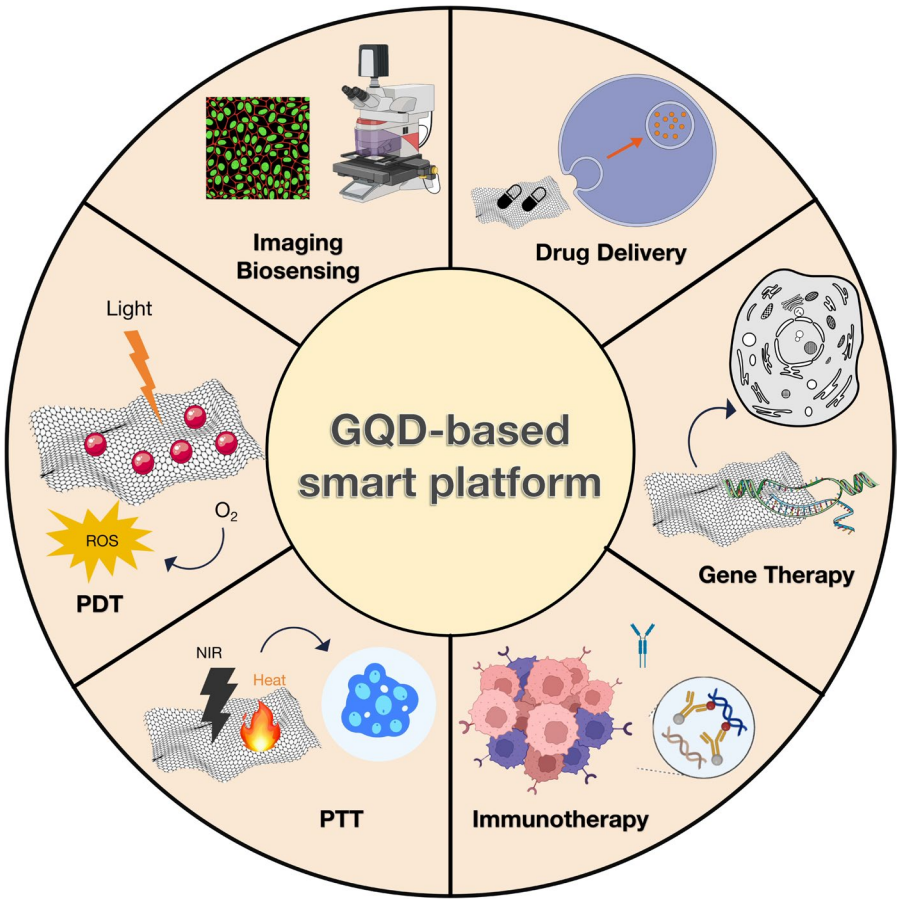

Fig. 1 Schematic of applications of graphene-based materials in GBM diagnosis and therapy

cancer metastasis. However, PTT- and PDT-based therapies still have shortcomings, and therefore continued exploration to find new disciplinary intersections remains a top priority in the treatment of GBM. A large number of previous studies have confirmed the potential of nanoparticle (NPs)-based approaches to overcome the limita-tions imposed by the pathophysiological characteristics of solid tumours. Enabling the development of multifunctional systems using nanoparticles to assist in the diagnosis and treatment of cancer has been possible and has already been applied in the clinic [4]. Among various types of NPs, quantum dots (QDs) are nanoscale semiconductor crystals with unique optical and targeting properties [5]. Graphene quantum dots (GQDs), which are zero-dimensional crystalline discs derived from two-dimensional graphene, show great potential for drug-targeted delivery and treatment of tumours due to their special optical and chemical properties. We therefore tried to summaries its potential applications and possibilities in aiding drug delivery as well as in the treatment of GEM.

Our study aims to provide a detailed scientometric analysis of the use of NPs and GQDs in GBM therapy. Using quantitative methods, specifically CiteSpace and VOSviewer, we seek to elucidate the active role of GQDs in helping to improve the ef-ficiency of GBM-targeted drug delivery as well as in the treatment of GBM. This com-prehensive, real-time assessment will highlight emerging themes in these studies to investigate developments in the field and indicate future directions regarding the treatment of GBM.

2 Materials and methods

2.1 Browse and search

Web of Science is a crucial database for accessing global academic information. It can rapidly identify high-impact papers, reveal research directions that domestic and foreign authorities focus on, and expose the trend of subject development. A search was conducted in the WOS core database for literature related to the use of nanomaterials in GBM from 2009 to 2023. The search formula used was as follows: TS = ("nano material" OR "nanostructured material" OR "nanostructured"

OR "nanotechnology" OR "nanomedi-cine" OR "nanocarrier" OR "quantum dots" OR "graphene") AND TS = ("lower grade glioma" OR "glioblastoma").

2.2 Screening procedures

The inclusion criteria are as follows: (1) the full text of the available papers focused on the diagnosis and treatment of nanomaterials in GBM; (2) the papers were written in English; (3) only articles and reviews were permitted; (4) the papers were sourced from the WOS Social Science Citation Index (SSCI) and the Science Citation Index Expanded (SCI-E) databases; and (5) the timeframe was from 2009 to 2023. The study's inclusion criteria were as follows: The following criteria were excluded: (1) This paper will focus on nanomaterials that are not related to GBM diagnosis and treatment. (2) This study will consider all types of publications, including reports, theses, and conference abstracts.

2.3 Data analytics

The publications and citations were exported as plain text for bibliometric analysis and visualization. VOSviewer (version 1.6.19) and CiteSpace (version 6.2) were used for visualisations. Line graphs were generated using GraphPad Prism (version 9.5.1) to display the number of publications, citations, and h-index per year. To create visual graphs analyzing the most prolific/collaborative countries, institutions, authors, co-cited journals, and co-occurring keywords, use VOSviewer.

Construct keyword timeline charts and keyword bursts using CiteSpace. Each dot on the visualization chart represents a country, institution, author, or journal, which are clustered into different groups depending on their collaboration [6]. The size of the dots depends on the number of publications. Link strength (LS) is represented by the thickness of the lines connecting the nodes and reflects the strength of collaboration between them [7]. Total Link strength (TLS) indicates the overall level of collaboration between the node [8]. During the keyword analysis, we excluded several irrelevant keywords and merged those with similar meanings to provide a better perspective. The graph generated by CiteSpace indicates significant and reasonable clustering, with a modularity value (*q*-value) greater than 0.3 and an average silhouette value (*s*-value) greater than 0.7.

3 Results

3.1 Selection and characterization of literature

A search for keywords related to GBM and nanomaterials in the Web of Science database retrieved a total of 462 papers. The first stage of selection did not involve any exclusion of articles based on type restrictions. Next, we conducted a screening of 462 publications published between 2008 and 2023 for our study. The number of publications peaked in 2021 with 78 publications, which accounted for 17.14% of the total publications (Fig. 2A). The data indicate a steady increase in the yearly publication count, suggesting a rising interest in GBM research and nanomaterials (Fig. 2B). The highest cited year was 2020 with 1,269 citations (Fig. 2C). The number of publications has steadily increased from 2009 to 2023. The annual H-index increased from 2 in 2008 to 20 in 2020 (Fig. 2D). Country/region and institutional analysis of publications.

3.2 Country/region and institutional analysis of publications

VOSviewer analysis shows that a total of 62 countries/regions have cooperated in this area (Fig. 3A). India had the most robust international cooperation network (TLS = 84) and cooperated most closely with the Saudi Arabia (LS = 65). The country with the highest centrality is USA (0.60), followed by PRC (0.31) and India (0.24). USA (6.95) has the highest burst strength next to Belgium (3.21). Next, we analyzed the top 10 productive countries/regions in terms of number of publications, total citations, and H-index. PRC published the most papers (98, 28.12%), followed by USA (96, 43.92%) and India (47, 13.96%). In addition, USA has the highest number of citations (4216) and highest H-index (34) (Fig. 3B).

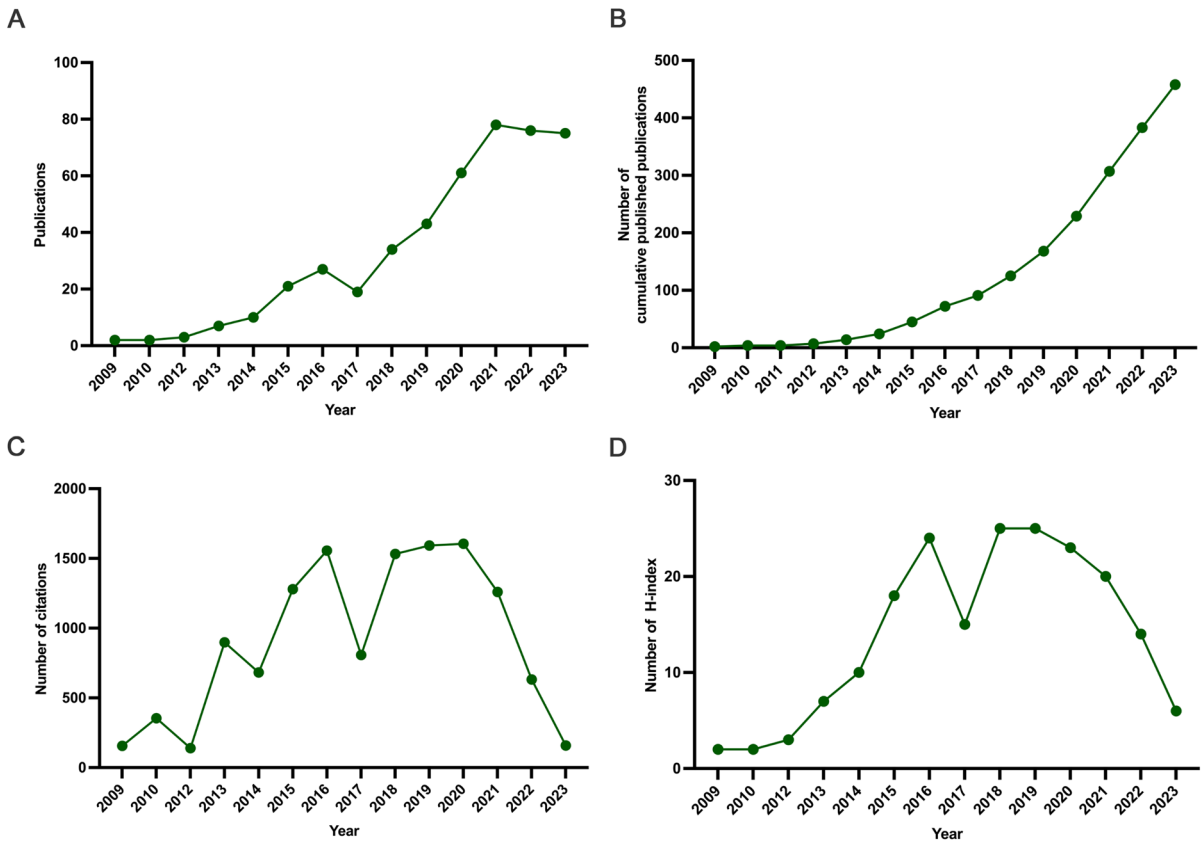

Fig. 2 Publication trends in research on the use of nanomaterials for therapy of GBM. **A** Number of papers. **B** Cumulative number of papers; publication rate and index trend line for the 15-year pe-riod from 2009 to 2023. **C** Total number of citations of publications. **D** H-index values for publications

3.3 Analyzing the authors of publications

The network of inter-authors and collaborative relationships is shown in Fig. 3C. In this study, we examined the top ten contributors in terms of posting volume. The highest number of posts is Shi Bingyang (15), followed by Wierzbicki Mateusz (14) (Fig. 3D). Four of these ten highly productive writers are from Poland. They have made a prominent and outstanding contribution to the field.

3.4 Institutional analysis of publications

The institutional collaboration network diagram is shown in Fig. 4A, which contains 99 institutions. Tehran University of Medical Sciences has the strongest total connectivity strength (TLS = 43). Figure 4B shows the top 10 most productive institutions. The highest number of published papers was from Centre National De La Recherche Scientifique Cnrs (25), next to Institut National De La Sante Et De La Recherche Medicale Inserm (22). Institut National De La Sante Et De La Recherche Medicale Inserm had the highest total number of citations (728) and the highest h-index (14). The top two places in terms of number of publications are both French research organisations.

3.5 Analysis of the publication journal

For this study we selected the top ten most productive journals from communication network diagram (Fig. 4C). The most partnerships with other journals is Journal of con-trolled release (TLS = 151,680). Top 3 journals with the most published research in the field are International Journal of Pharmaceutics, Pharmaceutics and Journal of controlled re-lease. The

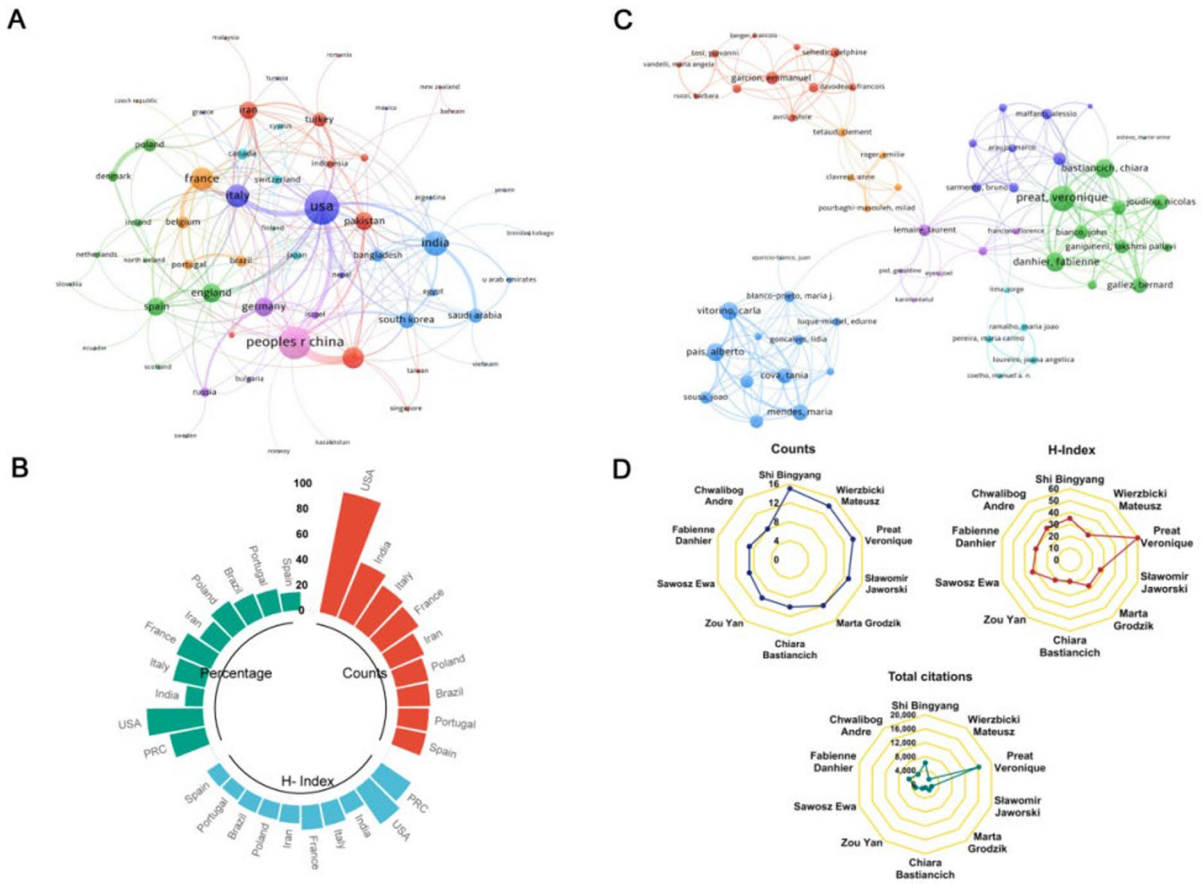

Fig. 3 **A**, **B** The map displays the coauthor ship network between countries. **C** The map displays the coauthor ship network of institutions. **D** Top 10 authors with the most publications

most cited is International Journal of Nanomedicine, which has the highest H-index (Fig. 4D). Furthermore, the Impact Factor (IF) of journal is a crucial parameter for assessing its worth and that of its published works. International Journal of Pharmaceutics has the highest IF (15.00) and JCR category (Q1).

3.6 Analysis of the most cited articles

Table 1 shows the top 10 most cited articles to date and the information associated with them, which we will examine in the next section. Six of these ten studies were from the United States, two were from Belgium, and the other two were from China and Italy. Specifically, a study entitle "Spherical Nucleic Acid Nanoparticle Conjugates as an RNAi-Based Therapy for Glioblastoma", written by Jensen and Samuel A, published in Science Translational Medicine of the USA in 2013 was cited 435 times, making it the most cited publication in the field.

3.7 For the study of keywords and research hotspots

Keyword co-occurrence analysis is a widely used method for identifying popular research topics [9]. The division of all keywords into 4 clusters in Fig. 5A. As shown in Fig. 5B, terms in purple indicate that their average publication year is in 2016 and earlier, while terms in bright yellow indicate that their average publication year is after 2021. "quantum dots" and "resistance" were the main focus in the early days. Keywords such as "immunotherapy"and "nanomaterials" and "anticancer activity" will not start to attract widespread attention until after 2021.

The largest clusters are in green and include keywords like "drug-delivery" and "nanocarries" in GBM. The second cluster is in red and contains key words such as "nanotechnology", "graphene" and "resistance". The third cluster is in blue and includes key words such as "cells", "in vitro" and "expression". The fourth cluster, in purple, contains keywords

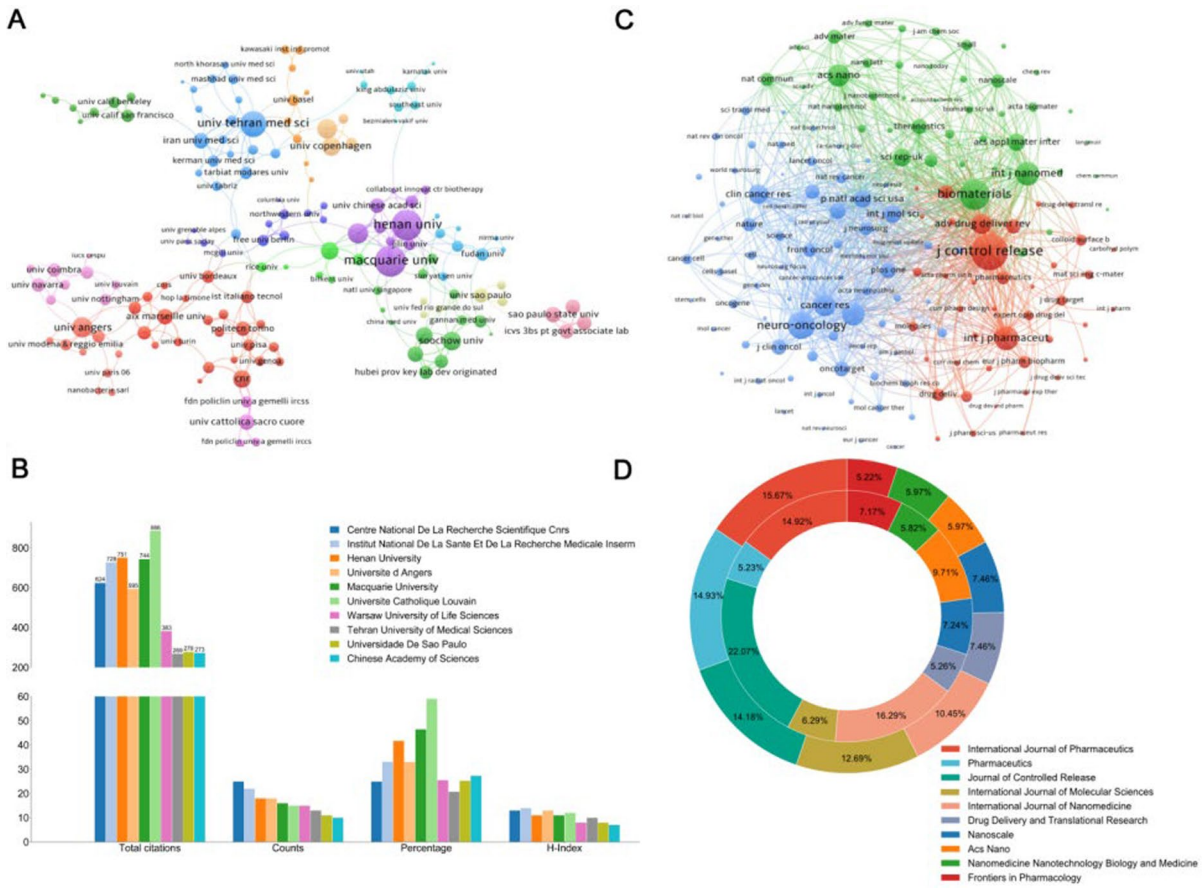

Fig. 4 Shows the results of the institutions and journals analysis on research hotspots. **A**, **B** The coau-thor ship network map and four groups of data of institutions. **C** The cocitation network map of journals. **D** The outer and inner layers of the circle indicate the number of journals in the top ten and the percentage of H-index

like "challenges" and "liposomes". Statistically, the keywords with the highest centrality are cancer (0.20) followed by blood brain barrier (0.11).

In addition, we have used CiteSpace to analyze the similarities and differences in the keywords over time. Keywords such as convection enhanced delivery and growth factor receptors were the main research hotspots up to 2009. Brain tumor and brain cancer continue to be topics of high interest in 2023 (Fig. 5C). The strength of the keyword bursts is another important indicator of the frontiers and hotspots of the study over time. The top ten keywords with the highest outbreak values are lipid nanocapsules (3.63), cancer (3.53), celluar uptake (3.48), in vivo (3.18), size (3.13), cancer stem cells (2.66), multiforme (2.44), growth factor receptor (2.43), convection enhanced delivery (2.43), nanotechnology (2.42) (Fig. 5D).

4 Discussion

4.1 Overview of the research area

In terms of the number of published articles, the research was at an early exploratory stage before 2009, and nanomaterials had not yet attracted extensive attention from scholars in the field of brain injury and GBM. Until 2013, the number of published papers on the application of nanomaterials in the treatment of GBM rose to more than ten. After 2017, the number of articles began to surge, and the role of nanomaterials in the treatment of GBM was widely found to be of concern.

The issuing countries are mainly concentrated in developed regions such as Europe and North America, and there are also a number of articles issued in Asian regions such as China and Japan. In addition, fast-growing developing countries

Table 1 Top 10 cited articles according to number of citations

Author	Title	Journal	Country	Institution	Year	Citation
Jensen, Samuel A	Spherical Nucleic Acid Nanoparticle Conjugates as an RNAi-Based Therapy for Glioblastoma	SCIENCE TRANSLATIONAL MEDICINE	USA	Northwestern Univ	2013	435
Hadjipanayis, Costas G	EGFRvIII Antibody-Conjugated Iron Oxide Nanoparticles for Magnetic Resonance Imaging-Guided Convection-Enhanced Delivery and Targeted Therapy of Glioblastoma	CANCER RESEARCH	USA	Emory Univ	2010	323
Zhou, Jiangbing	Highly penetrative, drug-loaded nanocarriers improve treatment of glioblastoma	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	USA	Yale Univ	2013	200
Zhao, Mengnan	Nanocarrier-based drug combination therapy for glioblastoma	THERANOSTICS	Belgium	Université catholique de Louvain	2020	180
Karim, Reatul	Nanocarriers for the treatment of glioblastoma multiforme: Current state-of-the-art	JOURNAL OF CONTROLLED RELEASE	Belgium	Univ Liege	2016	180
Guerrero-Cazares, Hugo	Biodegradable Polymeric Nanoparticles Show High Efficacy and Specificity at DNA Delivery to Human Glioblastoma in Vitro and in Vivo	ACS NANO	USA	Johns Hopkins Univ	2014	174
Kouri, Fotini M	miR-182 integrates apoptosis, growth, and differentiation programs in glioblastoma	GENES & DEVELOPMENT	USA	Northwestern Univ	2015	169
Hettiarachchi, Sajini D	Triple conjugated carbon dots as a nano-drug delivery model for glioblastoma brain tumors	NANOSCALE	USA	Univ Miami	2019	161
Zheng, Meng	ROS-Responsive Polymeric siRNA Nanomedicine Stabilized by Triple Interactions for the Robust Glioblastoma Combinational RNAi Therapy	ADVANCED MATERIALS	Peoples R China	Henan Univ	2019	146
Ciofani, Gianni	Folate Functionalized Boron Nitride Nanotubes and their Selective Uptake by Glioblastoma Multiforme Cells: Implications for their Use as Boron Carriers in Clinical Boron Neutron Capture Therapy	NANOSCALE RESEARCH LETTERS	Italy	Scuola Super Sant Anna	2009	143

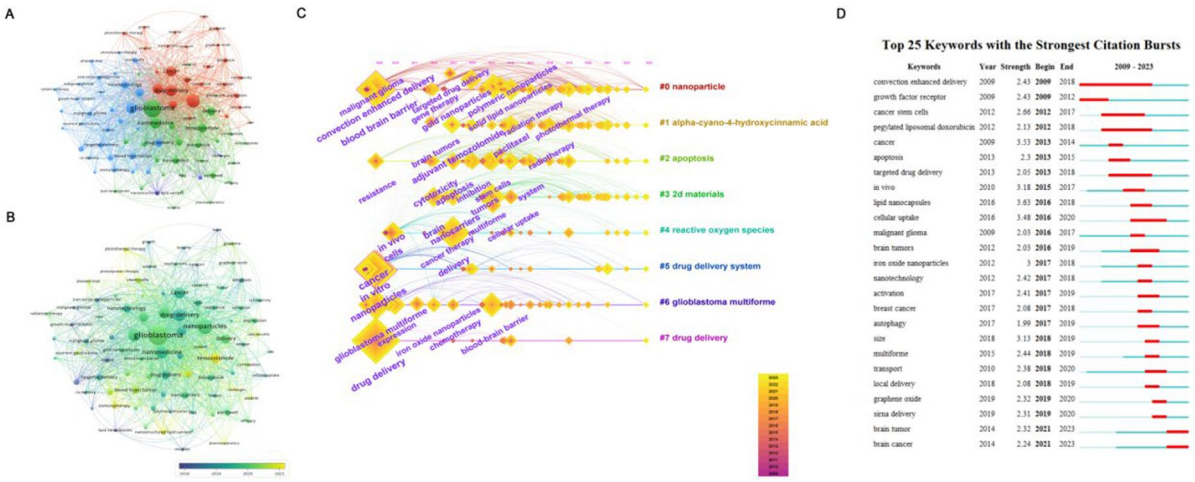

Fig. 5 Shows the results of the keyword analysis on research hotspots. **A**, **B** The keyword co-occurring network A and overlay B. **C** The timeline map shows the co-occurrence of keywords. **D** Top 25 keywords with the strongest citation bursts

such as India are also on the list. In terms of the number of papers published by each country, the United States occupies an absolute advantage, with the highest number of international cooperation, papers published and cited, and the highest h index, with a total of 96 papers, accounting for 43.92% of the total. The United States has a large population base and a large number of researchers and institutions in related fields, resulting in a high literature production. Among them, the efficacy of nanomedicines on GBM is a hot research topic in recent years. In terms of published articles, China follows the United States with a considerable centre position in the top ten countries, which indicates that China is also further ahead in the application of nanomaterials in GBM.

4.2 Overview of the publications

We analyzed the top 10 most cited publications. Highly cited studies are usually considered to be the most important and influential in the field. The most cited paper investigated the ability of spherical nucleic acids (SNA) to penetrate the blood–brain barrier and efficiently enter GBM cells for systemic drug delivery [10].Costas et al. demonstrated that Epidermal Growth Factor Receptor III (EGFRvIII) antibody-conjugated iron oxide nanoparticles can be employed for Magnetic Resonance Imaging (MRI)-guided convection-enhanced delivery, enabling targeted therapy for GBM [11].Fotini M Kouri et al. synthesised miR-182-based spherical nucleic acids (182-SNAs) that can penetrate the blood–brain/blood-tumour barrier (BBB/BTB) of orthotopic GBM xenografts and selectively diffuse into extravascular glioma parenchyma, thereby reducing the tumour burden and improving animal survival [12]. All of the above articles demonstrate the positive role of nanomaterials in assisting drug transport, helping drugs to cross the blood–brain barrier target as well as targeting GBM, as well as pointing the way for future research.

Furthermore, among the more relevant literature, we find Giordano Perini et al. re-porting that graphene quantum dots (GQDs) could be used as a suitable delivery and therapeutic strategy for the treatment of GBM, both directly destabilizing cell membranes and indirectly enhancing the efficacy of chemotherapeutic agents. Figure 6 shows the evaluation of the combined action of GQDs and doxorubicin (Dox), where a synergistic effect of both molecules on U87 cells can be observed in terms of the effect on cell viability [13]. Soma Yaswi et al.'s study [14] demonstrated that nano-targeted delivery systems not only improve the efficiency of the DNA alkylating agent temozolomide (TMZ) to cross the BBB with target specificity, but also reduce toxicity to healthy tissues.

4.3 Analysis of the thematic evolution of the research area

Absolutely, keywords in academic papers serve as a crucial navigational tool that allows readers, researchers, and database search algorithms to identify the topic and theme of a research study more accurately and quickly. Keywords make it easier to search for and locate articles in large databases. By using specific and relevant keywords, a paper can be more easily discovered by those interested in the particular area of research. From the keyword clustering analysis, keyword time zone map and keyword burst analysis, the researches between the nanomaterials and GBM before 2016 was at a

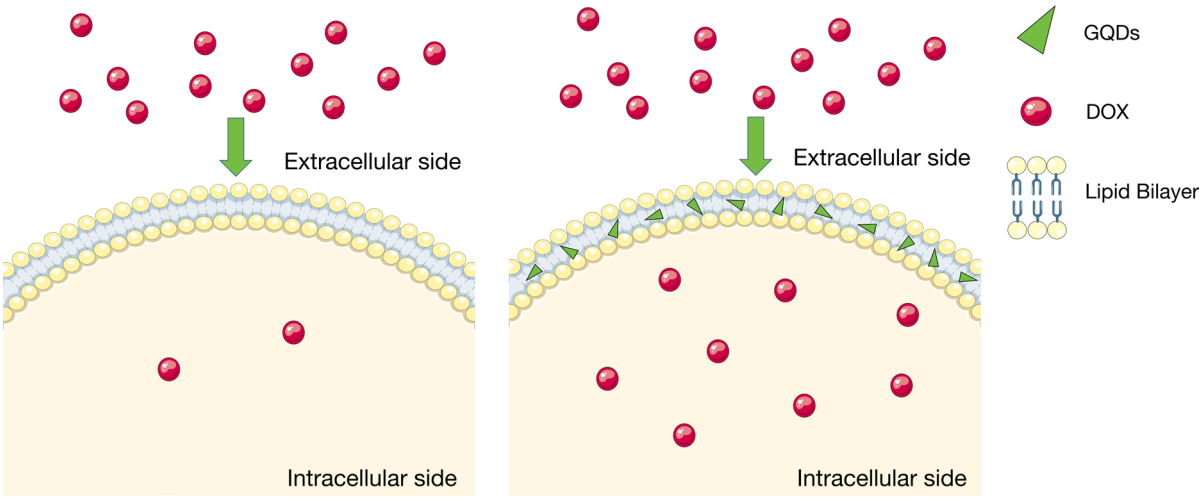

Fig. 6 When Dox approaches cells, its uptake increases with the increase in membrane per-meability. The amount of Dox uptake inside an untreated cell (left) is less than that of cells pretreated with COOH and Green-GQDs (right)

relatively macroscopic and superficial stage. "quantum dots" and "resistance" were the main focus in the early years. In the medium term (2018–2021), the research direction will be gradually extended to the level of drug delivery and therapeutics, and the role of nanomaterials in the diagnosis and treatment of GBM will be defined to some extent. NPs have been broadly used as drug carriers to deliver therapeutic agents to tumor sites for cancer treatment [15]. The review written by Foo discussed the state-of-the-art applications of graphene-based materials in GBM diagnosis and therapy [16]. Furthermore, NPs-based drug delivery systems have attracted research attention continuously, and have been widely applied in GBM therapy over the past years. Under magnetothermal stimulation, the functionalized nanoparticles were able to disintegrate the GBM spheroids and cause significant cell death, proving to be an excellent approach drugs for the treatment of GBM [17]. In recent years (2021–2023), a large number of studies have elucidated or characterised some nanomaterials that are closely related to the diagnosis and treatment of GBM. Keywords such as "anticancer activity" will not start to attract widespread attention until after 2021. With their small size, lamellar and aromatic-ring structure, GQDs tend to enter into the cell nucleus and interfere with DNA activity [18]. Zahra Kiani Nejad founds that GQDs affect the survival of MCF7 cancer cells and have anticancer activity by causing early apoptosis through nuclear fragmentation [19].

4.4 Inadequate and challenges

The research in this paper is limited by the WOSCC database, which can be com-bined with other software tools to analyze further the relevant research literature pub-lished in Sinomed, Pubmed, and other databases. Due to the limitations of current re-search, some nanomaterials closely related to GBM have not been studied in depth. Despite their potential applications in fields such as bioimaging, drug delivery, and sensors, the translation of GQDs into clinical practice has been hindered by several critical challenges. Among these, the lack of sufficient research into the fundamental properties of nanomaterials and the difficulties in achieving large-scale production of GQDs stand out as major obstacles.

One of the most pressing issues in GQD production is the inconsistency in size, shape, and functionalization. GQDs are typically synthesized through various methods, including chemical exfoliation, solution shearing, and electrochemical approaches. However, these methods often result in particles with variable dimensions, irregular shapes, and inadequate functionalization. Such inconsistencies significantly affect the performance of GQDs in applications requiring precise control over their properties. For instance, in bioimaging, the fluorescence intensity and stability of GQDs depend heavily on their size and surface chemistry. Any variation in these parameters can lead to unreliable results, limiting their utility in clinical diagnostics.

Another major challenge is the high cost and resource-intensive nature of GQD production. The synthesis of GQDs often involves multiple steps, including precursor preparation, purification, and functionalization, all of which require advanced equipment and expertise. Additionally, the energy-intensive processes and the use of expensive reagents contribute to the overall cost of production. These economic barriers make it difficult to scale up GQD manufacturing

to meet the demands of clinical applications. For example, while GQDs show great potential in drug delivery systems, their high production costs limit their accessibility for widespread use in therapeutic settings.

The combination of these challenges—research gaps, production inconsistencies, and high costs—has created a bottleneck in the clinical application of GQDs. To address these issues, further research is needed to develop scalable, cost-effective, and environmentally friendly synthesis methods. Additionally, efforts should be made to standardize the characterization and functionalization of GQDs to ensure their consistency and reliability. By overcoming these barriers, GQDs can unlock their full potential and pave the way for innovative solutions in medicine and technology.

5 Conclusions

The study selected papers from WOSCC from 2009 to 2023 on the combination of nanomaterials and GBM. Through bibliometric analysis, we have drawn the following conclusions: In the therapeutic area, GQDs can be used in combination with existing chemotherapeutic agents such as doxorubicin and temozolomide to penetrate the blood–brain barrier, carry drugs to reach the GBM lesions, improving drug delivery efficiency, and thus playing an effective role in cancer treatment. Besides, research combining GQDs and GBM has the potential to contribute to personalized medicine approaches. By tailoring GQDs to target specific genetic mutations or molecular profiles in GBM, therapies can be customized to individual patients, improving outcomes and re-ducing side effects. Moreover, GQDs have good biocompatibility and can act as potent tumor suppressors with anti-tumor activity, effectively targeting cancer cells. The in-tersection of GBM and GQDs research has opened up novel interdisciplinary approaches, particularly in the development of advanced therapeutic strategies that combine the biological insights from GBM research with the innovative material properties of GQDs. This includes potential applications in nanomedicine, where GQDs could be used for targeted drug delivery, imaging, and therapeutic interventions in GBM treatment.

In summary, the combined research on GBM and GQDs is having a profound impact on both the theoretical understanding and practical approaches to treating this deadly form of brain cancer. The advances in nanoparticle design, drug delivery systems, imaging technologies, and personalized medicine are contributing to a more targeted, effective, and less invasive treatment paradigm for GBM. We have reason to affirm the key role of GQDs in GBM therapy, which has great potential for development, possesses clinical value, and deserves further in-depth exploration. This may become an even more popular research topic in the future. In a word, this bibliometric study can help re-searchers discover the current status and emerging trends in GQDs and GBM.

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Author contributions ZJY and LXQ performed the literature search and collected the data. ZJY performed the statistical analysis and wrote the manuscript, and prepared Figs. 1, 2 and 3. LXQ and ZJY prepared Figs. 4, 5. QLZ and ZJY prepared Fig. 6. LZH and GHJ revised the manuscript. ZJY and GHJ designed the study and conceived and revised the manuscript. All authors contrib-uted to the article and approved the final manuscript.

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Data availability Data sharing is not applicable to this article, as no datasets were generated or analyzed in the current study.

Declarations

Conflict of interest The funders had no role in the design of the study; in the collection, anal-yses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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