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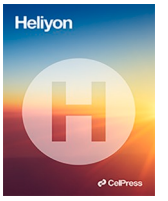

Review article

Knowledge mapping of nano drug delivery systems across blood - Brain barrier from 1996 to 2022: A bibliometric analysis

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ABSTRACT

Background: The blood-brain barrier (BBB) is a natural physiological barrier that protects the central nervous system from foreign substances and limits the delivery of drugs to the brain. Nanotechnology has opened up new possibilities for drug delivery in the brain. Over several decades, various Nanoparticle Drug Delivery Systems (NDDS) that can cross the BBB have been developed for targeted delivery in the brain. To gain a comprehensive understanding of the current research hotspots and trends of NDDS across the BBB, this paper employs bibliometric analysis of articles published in the core database of Web of Science (WOS) from 1996 to 2022.
Method: A search for relevant research literature on NDDS that can cross the BBB was conducted in the Web of Science database, covering the period from 1996 to 2022. The Bibliometrix R-4.0 software package was used to analyze data related to the countries of publication, research institutions, journals, citations, and keywords. The analysis aimed to identify the co-occurrence of keywords in the documents, including their titles and abstracts. Additionally, cooperative network analyses of authors, institutions, and countries of publication were conducted.
Results: A total of 436 articles were analyzed, originating from 174 journals and 13 books, with the majority published in Q1 and Q2 journals. Contributors from 53 countries or regions participated in the publication of these articles, with China, the United States, and India having the highest number of articles by correspondent authors, and China, the United States, and Germany being the most cited countries. Fudan University, Hacettepe University, and Sichuan University were the top three institutions with the most publications. Among the 436 articles analyzed, 1337 keywords and 1450 keywords plus were identified. Factor analysis grouped the keywords plus into two categories: drug delivery systems, polymeric nanoparticles, gold nanoparticles, transferrin, and others, and drug, delivery, efficiency, expression, and mechanism.
Conclusion: The research on NDDS that can cross the BBB is gradually receiving attention, and the recognition and cooperation in this field have increased.

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1. Introduction

The human brain is the most critical organ in the body, and injuries or illnesses affecting it can have a significant impact, including conditions like stroke, Alzheimer's disease, and Parkinson's disease [1–3]. The blood-brain barrier (BBB) restricts the entry of most drugs into the brain parenchyma, allowing only a few small molecule drugs to pass through the bloodstream [4]. The BBB plays a vital role in maintaining the stability of the central nervous system, consisting of brain microvascular endothelial cells, astrocytes, pericytes, and extracellular matrix [5]. As a highly selective permeability barrier, the BBB separates the central nervous system from the peripheral blood circulation, serving a dual purpose of providing necessary nutrition and oxygen to neurons and shielding the brain from toxins and pathogens while controlling the CNS microenvironment to maintain normal neuronal function [6,7]. However, it also blocks more than 98% of small molecule drugs and almost all macromolecular drugs, resulting in extremely low bioavailability of active ingredients in the brain [4]. Therefore, BBB permeability is the primary factor limiting drug penetration into the CNS [8].

Nanotechnology and its interdisciplinary research in biomedicine have led to the emergence of nanomedicine as a new research focus [9]. Nanomedicine involves the application of nanotechnology to enhance existing diagnosis and treatment technologies for improved patient outcomes [10]. By linking nanomaterials with biomolecules or structures, these materials can acquire additional functions. Compared to traditional materials, nanomaterials possess several advantages due to their small size and easily modifiable biological properties, including high solubility, strong targeting effect, extended tissue residence time, enhanced tumor tissue penetration and blood-brain barrier penetration, and high biocompatibility [11]. These properties make nanomedicine highly promising for a range of medical applications, including the diagnosis and treatment of heterogeneous diseases such as tumors, tissue engineering, biosensors, drug carriers, and other medical fields, particularly in drug delivery [11]. Biological nanotechnology has opened up a new avenue for drug delivery, with the development of various Nanoparticle Drug Delivery Systems (NDDS) over several decades. NDDS can be classified into carrier-based and carrier-free systems, depending on whether a carrier is necessary or not [12]. Nanoparticle Drug Delivery Systems (NDDS) can be categorized into organic carrier and inorganic carrier systems based on the type of carrier employed [13]. Organic nanocarriers such as polymer nanoparticles, dendritic macromolecules, and liposomes, and inorganic nanocarriers such as gold nanoparticles, magnetic iron oxide nanoparticles, silica nanoparticles, and carbon nanotubes, are commonly used [14–17]. A wide range of NDDS options are available for targeted drug delivery. Research has demonstrated that NDDS can enhance drug pharmacokinetics and biodistribution, as well as improve drug bioavailability in the brain [18–20]. Therefore, using NDDS to promote drug penetration through the BBB without disrupting it is a promising strategy for preventing, diagnosing, and treating CNS diseases. In this study, we employed bibliometric methods to analyze articles related to BBB-crossing NDDS published in the Web of Science (WOS) core database between 1996 and 2022. We systematically summarized publication trends, research institutions, article citations, keywords, and other characteristics in this field.

2. Data and methodology

2.1. Data source

The information was sourced from the Web of Science (WOS) Core Library (http://webofscience.com) using the following search criteria: title keywords "Nanoparticle Drug Delivery System" and "Blood-Brain Barrier". The search time spanned from the inception of the database until November 18, 2022. We limited the search to English-language articles and only included documents classified as articles. The retrieval was conducted on November 18, 2022.

The search formula is as follows:

#1 Nanoparticle Drug Delivery System (All Fields).

#2 blood-brain barrier (All Fields).

#3 #1 AND #2.

2.2. Statistical methods

The bibliometrix [21] package was utilized to quantify and visualize the relevant literature on NDDS that can penetrate the BBB. The package's national function statistical method was used to count the number of papers published in a specific country or region. The highest cited country function was used to determine the number of citations published by authors in each country or region. The most relevant membership function was used to determine the number of papers published by each research institution. The WOS JCR query entry was employed to query the impact factor, category, and JCR partition results for each journal. The co-occurrence word network was used to analyze the results of keyword co-occurrence. Normalization was set to association, and the Clustering Algorithm was set to edge betweenness to remove unconnected points. The Factorial Analysis function in conceptual structure was used to analyze the results of keyword plus factor analysis. The method selected Multiple Correspondence Analysis, and the cluster was set to auto. Collaboration between authors and institutions was analyzed using the collaboration network. Data sets and triple tables were constructed by importing results from the bibliometric package into Excel software.

3. Results

3.1. Results of retrieved literature

A total of 733 articles were retrieved from the WOS database, including 436 articles, 282 review Articles, 24 book reviews, 21 proceeding Paper, 5 editorial Material and 3 early Access. After selecting Article, the title is imported into the software for analysis. The results show that 436 articles were published from 1996 to 2022. During these 26 years, the research of NDDS across BBB can be divided into two stages. The first stage was 1996–2008, during which the number of studies was stable and between 0 and 4 articles were published annually. The second phase is 2008–2022, and the number of studies in this one is increasing dramatically. The details are shown in Fig. 1.

3.2. Publication of articles in different journals

After analyzing the 436 articles, it was found that 17 of them were from books, and 7 were published in journals without impact factors. Out of the total, 436 articles were published in 174 journals and 13 books. The journal with the lowest impact factor was Critical Reviews in Biomedical Engineering (2021 IF: 0.292), while the journal with the highest impact factor was Advanced Materials (2021 IF: 32.086). Upon eliminating the books, the analysis was focused on the journals of 419 articles. The study revealed that the three categories with the largest number of articles were Chemistry, Multidisciplinary (78, 17.89%), Pharmacology & Pharmacy (67, 15.37%), and Engineering, Biomedical (35, 8.03%), as shown in Fig. 2A. These journals were categorized into quartiles 1 (Q1) to 4 (Q4) by the Journal Citation Reports, based on their impact factors in the WOS database. Most of these articles were published in Q1 journals (184,42.20%), Q2 journals (147,33.72%), Q3 journals (64,14.68%), as shown in Fig. 2B. Most of the articles were published in International journal of pharmaceutics (20,4.59%), Journal of controlled release (20,4.59%), Biomaterials (15,3.44%), as shown in Fig. 2C.

3.3. Articles published by countries and research institutions

Based on the corresponding author's country, 53 countries or regions participated in publishing the 436 articles. The top three countries with the highest number of articles published by corresponding authors are China (105, 24.08%), the United States (96, 22.02%), and India (29, 6.65%), as shown in Fig. 3A. The 436 articles were cited a total of 16 969 times. The results of the citation analysis by country show that the top three countries with the highest number of citations are China (5,139, 30.28%), the United States (4,112, 24.23%), and Germany (1,450, 9.54%), as shown in Fig. 3B. The analysis of research institutions reveals that the three institutions with the highest number of published articles are Fudan University (48, 11.01%), Hacettepe University (26, 5.96%), and Sichuan University (26, 5.96%), as shown in Fig. 3C.

3.4. Cooperation between countries and institutions

The analysis of collaboration among the 436 articles was conducted, revealing distinct regional patterns in research institution partnerships. Fudan University had close partnerships with Shanghai Jiaotong University and Nantong University, all located in mainland China. Chang Gung University and Chang Gung Memorial Hospital had strong ties and are both located in Taiwan, China. Johns Hopkins University and the University of Virginia had a close partnership and are both in the United States, as presented in Fig. 4A. National collaboration revealed that China and the United States, Australia, and other countries have strong partnerships. Germany and the UK, Russia, Switzerland, and other countries also have robust partnerships. Sweden and Norway collaborate closely as well, as shown in Fig. 4B.

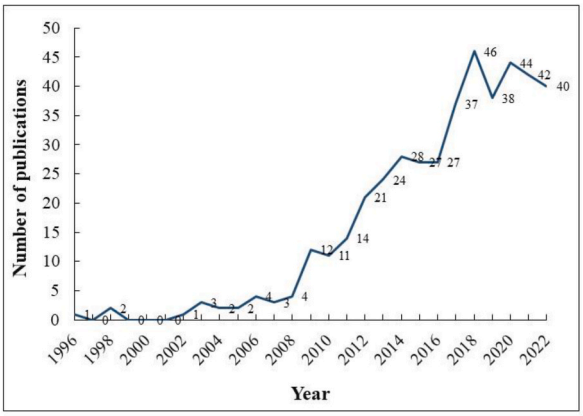

Fig. 1. Number of articles published per year from 1996 to 2022.

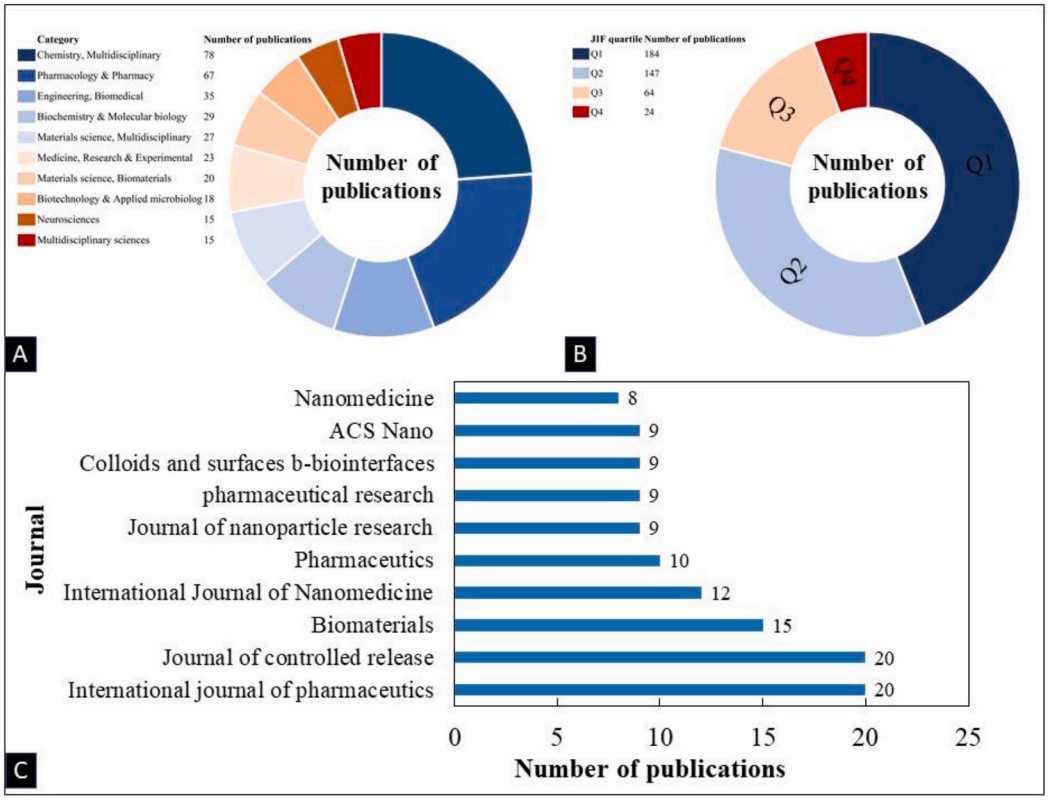

Fig. 2. A 10 categories with the most articles published; Fig. 2B The number of articles published in JCR Q1-Q4; Fig. 2C 10 journals with the most articles published.

3.5. Co-occurrence of keywords

The co-occurrence words of 436 articles were analyzed. The results showed that nanoparticles often appeared together with delivery and brain in the title of articles. Blood _ brain and barrier often appear together, as shown in Fig. 5A. Blood-brain and barrier often appear together in the abstracts of 436 articles. Nanoparticle often appears with Drug, Delivery, and System, as shown in Fig. 5B. Nanoparticles, Nanoparticle and blood-brain barrier often appear together in the keywords of 436 articles, as shown in Fig. 5C. In addition to the keywords added by the author himself, the WOS database will automatically add some supplementary keywords to the article, which are called Keywords plus. Blood-brain-barrier and Drug-delivery often appear together in Keywords plus of 436 articles, as shown in Fig. 5D.

3.6. Factor analysis results of keywords plus

The WOS database automatically adds Keywords Plus to articles as a way to increase the likelihood of articles being retrieved under related topics. These keywords consist of words or phrases frequently appearing in the titles of an article's references, but not in the article title itself. Out of the 436 articles analyzed in this study, 1337 keywords and 1450 Keywords Plus were identified. A factor analysis of these 1450 Keywords Plus revealed that they could be categorized into two clusters. The first cluster included words such as Drug delivery systems, polymeric nanoparticles, gold nanoparticles, and transferrin, while the second cluster included words such as drug, delivery, efficiency, expression, and mechanism. These clusters are depicted in Fig. 6.

3.7. The most cited papers

Out of the 436 articles that we analyzed, 14 did not have accessible full texts, 32 were not completely related to "blood-brain barrier" and "Nanoparticle Drug Delivery System", 17 were books, and 56 were reviews. Only 317 of them were actual research articles. The analysis of 317 research articles showed that the most cited articles were Jensen 's research papers published in Science Translational Medicine in 2013 [22]. In order to solve the problem that Glioblastoma multiforme (GBM) cannot target drug delivery, Jensen constructed an RNA interference (RNAi) NDDS (gold nanoparticle-based carrier) based on spherical nucleic acid (SNA) nanoparticle conjugates. The results showed that this targeted drug delivery system could effectively pass SNAs through the BBB and tumor barrier, and eventually spread to the entire heterogeneous glioma explants. The second most cited paper was a research paper by

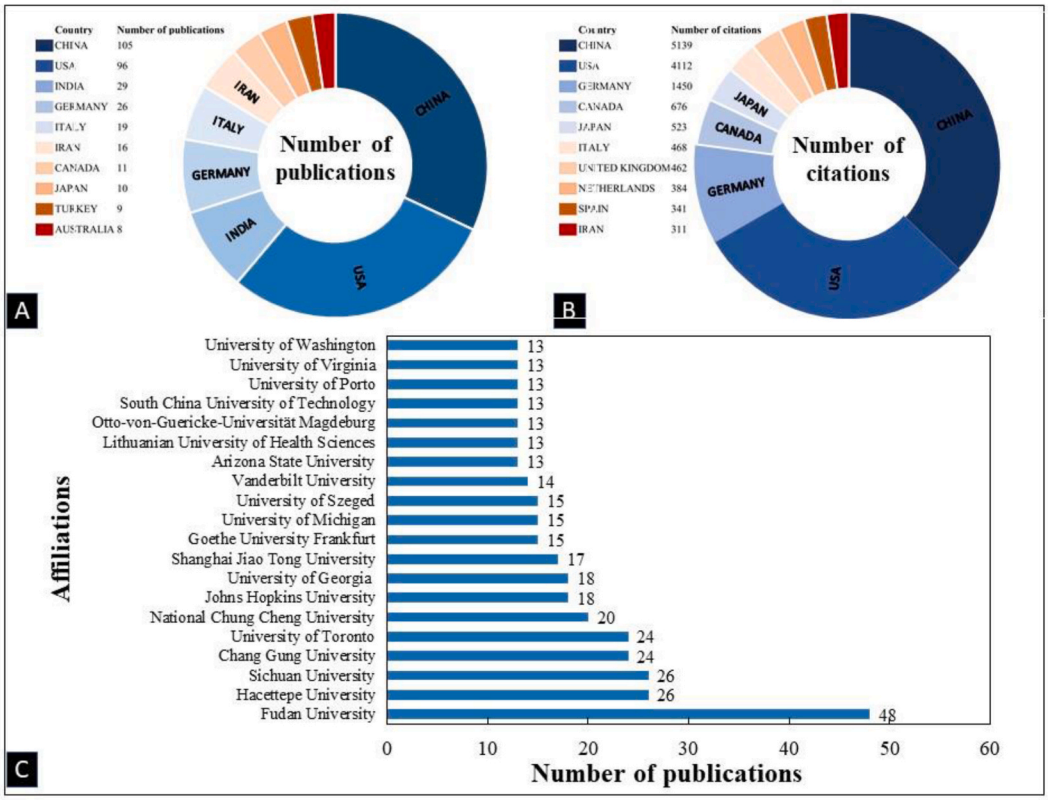

Fig. 3. A 10 countries with the highest number of articles published; Fig. 3B 10 countries with the most citations; Fig. 3C 20 research institutions with the largest number of published articles.

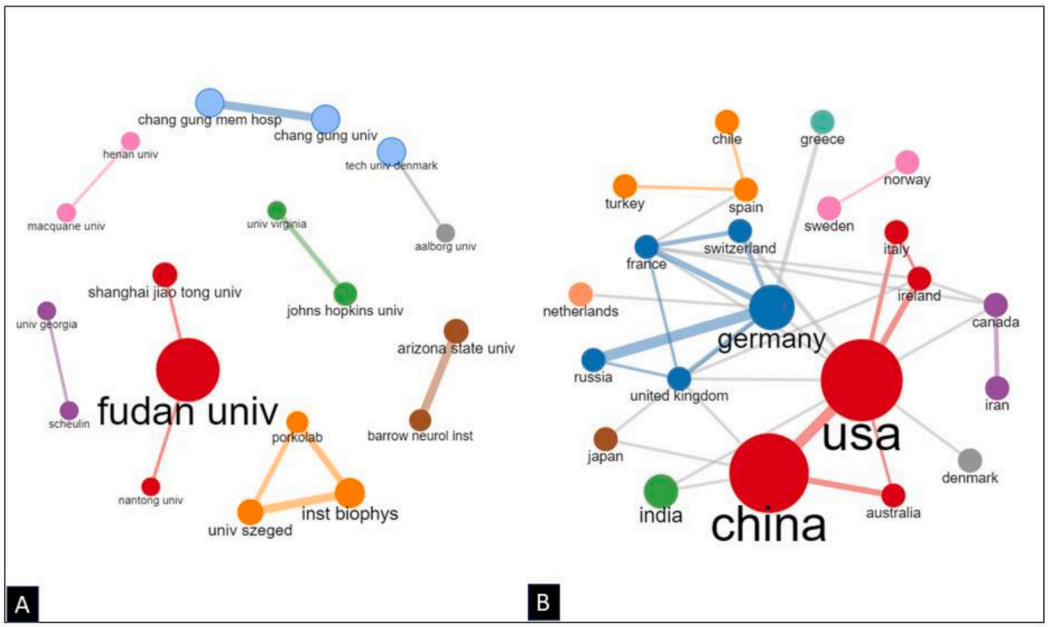

Fig. 4. A Collaboration network among research institutions; Fig. 4B Cooperation network between countries.

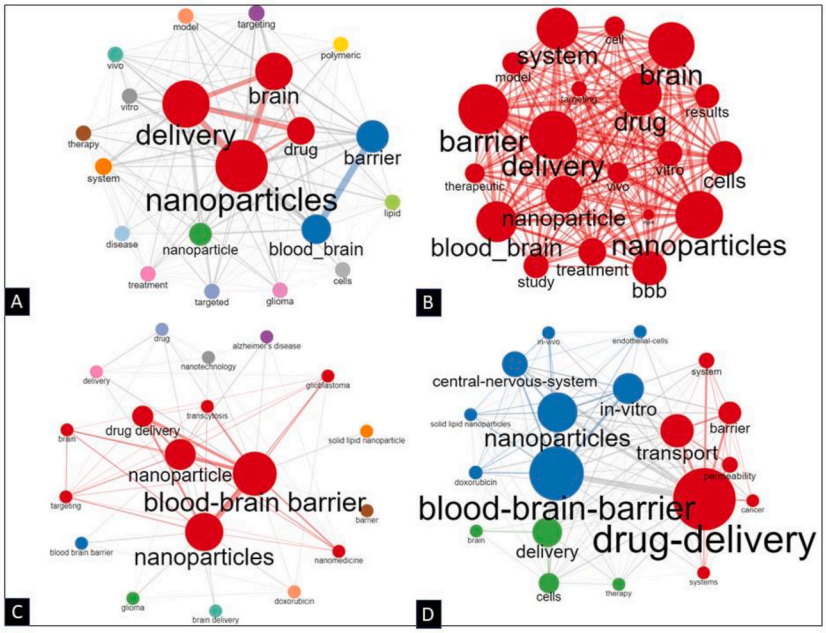

Fig. 5. A Co-word network of titles; Fig. 5B Co-word network appearing in the abstracts; Fig. 5C keyword co-occurrence network; Fig. 5D keywords plus co-occurrence network.

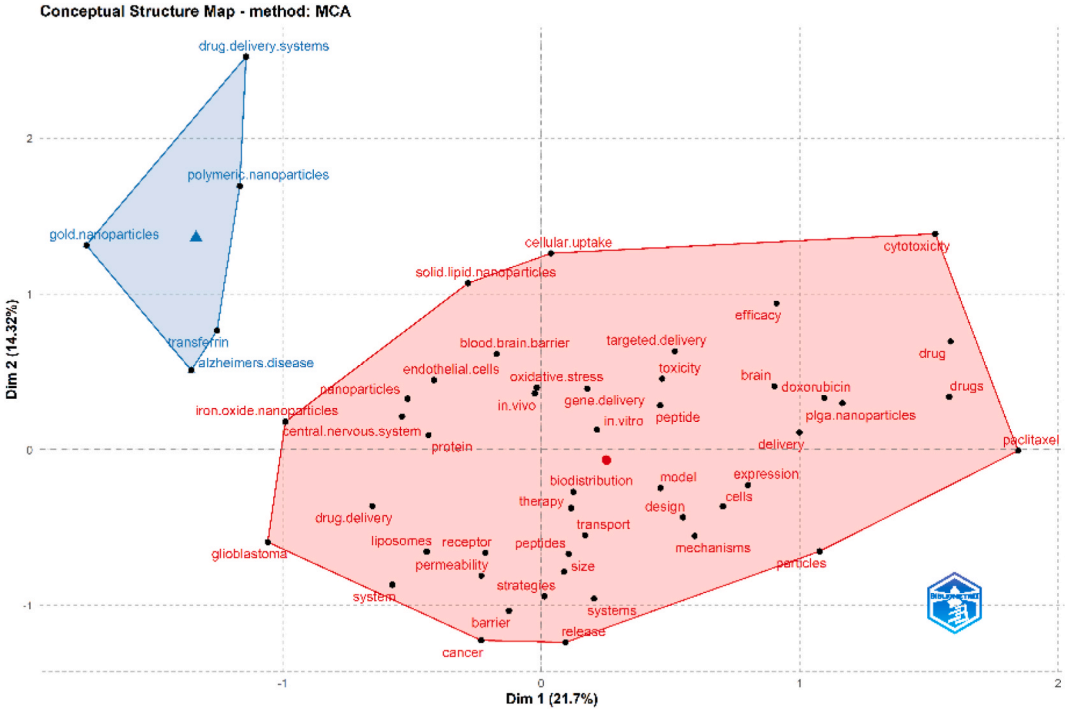

Fig. 6. Factor analysis results of keywords plus.

Kreuter published in Pharmaceutical Research in 2003 [23]. In order to clarify whether the mechanism of poly (butylcyanoacrylate) (PBCA) nanoparticle drug delivery system (based on liposome carrier) to deliver drugs to the brain is related to the toxic reaction of BBB, Kreuter compared the transport of dalargin across BBB by empty PBCA nanoparticles and polysorbate-80. The results showed that only dalargin pre-adsorbed on PBCA nanoparticles could cross the BBB [23]. The third most cited paper was Liu ‘s research paper published in The Proceedings of the National Academy of Sciences in 2010 [24]. To address the inability of magnetic nanoparticles

(MNPs) to cross the BBB, Liu characterized and evaluated therapeutic MNPs in vitro and in vivo using a combination of focused ultrasound and magnetic targeting, and used MRI to monitor and quantify their distribution in vivo. The results showed increased deposition of therapeutic MNPs in the brain with intact or damaged blood-brain barrier [24]. The details are shown in Table 1.

4. Discussion

The first article to introduce NDDS that could penetrate the BBB was published in 1996 by Schröder and Sabel in Brain Research [32]. They used polysorbate 80-coated polybutylcyanoacrylate nanoparticles to create targeted NDDS for the brain. This article garnered considerable attention upon its release. As per the WOS database, the article has been cited 114 times, while Baidu Academic Tips has cited it 331 times. For a while, the number of articles in this field remained stagnant, fluctuating between 0 and 4. It was not until 2008 that the number of articles began to increase gradually. These data suggest that the field of NDDS that can cross the BBB has been gaining more and more attention since 2008, with research in this area gradually heating up.

The Journal Citation Reports (JCR) database categorizes journals into various disciplines and assigns them to one of four quartiles based on their respective impact factors. Journals with impact factors in the top 25% are classified as Q1, those in the 25%–50% range as Q2, those in the 50%–75% range as Q3, and those in the 75%–100% range as Q4. Journals in Q1 and Q2 are highly influential and have a high citation frequency in their respective disciplines. This research shows that a majority of the 436 articles were published in Q1 journals (184, 42.20%) and Q2 journals (147, 33.72%). These results indicate a strong recognition of studies on NDDS that can cross the BBB. Furthermore, out of the 436 articles, 94 (21.56%) had an impact factor greater than 10 and 243 (55.73%) had an impact factor greater than 5, indicating that research in this field has significant influence.

A total of 53 countries or regions participated in the publication of 436 articles. The three countries with the most articles by correspondent authors are China, the United States and India. A total of 436 articles were cited 16 969 times. The three countries with the highest number of citations were China, the United States and Germany. The highest average number of citations per article was in China (48.94) and the United States (42.83), suggesting that China and the United States have greater influence in this area. The network suggests that China cooperates closely with the United States, which may be related to the fact that most Chinese researchers choose to study in the United States [33]. The research institutions that published the most articles were Fudan University, Hacettepe University and Sichuan University. Among them, Fudan University and Sichuan University are both from China. The number of papers published by these two universities is 74, accounting for 70.48% of the number of articles published in China. The institutional collaboration network suggests that research collaboration is often carried out between institutions in the same region, with fewer collaborations between cross-regional research institutions.

The results of co-word analysis showed that nanoparticles often appeared together with delivery and brain in titles, abstracts, keywords and keywords plus. Blood brain and barrier often appear together. These words highly coincide with our search terms ' Nanoparticle Drug Delivery System ' and ' blood-brain barrier '. This also suggests that the 436 articles included in this paper are highly related to the study of NDDS across BBB. The results of factor analysis of keyword plus show that keyword plus can be clustered into two categories. Drug delivery systems, polymeric nanoparticles, gold nanoparticles, transferrin and other words are clustered together. It is suggested that these articles focus more on NDDS research. Words such as drug, delivery, efficiency, expression and mechanism are clustered together. It is suggested that these articles focus more on the application of NDDS.

The advancement of NDDS that can cross the BBB holds significant importance for the diagnosis and treatment of diverse brain disorders. Nanoparticle drug carriers have garnered increasing attention in targeted brain disease therapy owing to their favorable stability, biocompatibility, degradability, safety, adaptable drug loading, controllable drug release, and surface modification features [34]. Nevertheless, there is still a substantial gap before practical clinical applications can be realized [34]. Although many nanomaterials have gained FDA approval or entered clinical trials, the clinical usage of nanomaterial-based brain drug delivery systems remains restricted. The primary reasons include: (1) further investigation is required for in vitro and in vivo models for BBB crossing [35]; (2) nanomaterial safety and side effects necessitate additional study [35]; (3) nanocarrier properties, such as surface properties, particle size, loading agents, and host materials, still necessitate further assessment for their BBB crossing impact [35]; (4) brain-targeted delivery efficiency is inadequate, and after intravenous administration, it is quickly phagocytosed by the reticuloendothelial system, leading to inadequate brain drug treatment concentrations and ineffective treatment outcomes [36]; and (5) nanocarrier degradation and biocompatibility challenges [36]. To address these challenges, it is worth exploring in-depth how functional modification can reduce nanocarrier toxicity while achieving rapid in vivo degradation while still maintaining a high therapeutic concentration at the target site. This is an area that requires further investigation in brain-targeted nano drug delivery systems. Despite less than 30 years of research, the development of NDDS that can cross the BBB has demonstrated substantial potential. In the future, more resources and expertise will certainly be invested in this field of research, and NDDS for crossing the BBB will continue to evolve towards stronger targeting, higher safety, and better efficacy.

5. Limitations

First, we only include articles from the Web of Science database. CNKI, Wanfang, VIP, PubMed and other databases have not been searched. Therefore, other published articles related to the research topic may be omitted. Secondly, we only made a preliminary summary of the research on NDDS that can cross BBB, and did not conduct in-depth analysis. Therefore, the guiding role of future research on NDDS that can cross BBB is limited.

Table 1
Top 10 most cited articles.

Reference	Types of research	Purpose	Conclusion	Total Citations
Jensen et al., 2013 [22]	Article	Preclinically evaluate an RNA interference (RNAi)–based nanomedicine platform, based on spherical nucleic acid (SNA) nanoparticle conjugates, to neutralize oncogene expression in Glioblastoma multiforme (GBM).	Silencing antiapoptotic signaling using SNAs represents a new approach for systemic RNAi therapy for GBM and possibly other lethal malignancies.	389
Kreuter et al., 2003 [23]	Article	Explore more fully the mechanism by which poly (butylcyanoacrylate) (PBCA) nanoparticles can deliver drugs to the brain.	The delivery of drugs to the brain by PBCA is not related to the destruction of the blood-brain barrier.	352
Liu et al., 2010 [24]	Article	This study combines focused ultrasound and magnetic targeting of nanoparticles as a synergistic delivery system for chemotherapeutic agents concurrent with MRI monitoring for treating CNS diseases.	The technique could be used in normal brains or in those with tumors, and significantly increased the deposition of therapeutic magnetic nanoparticles in brains with intact or compromised blood–brain barriers. Synergistic targeting and image monitoring are powerful techniques for the delivery of macromolecular chemotherapeutic agents into the CNS under the guidance of MRI.	306
Xin et al., 2011 [25]	Article	Dual-targeting nanoparticle drug delivery system was developed by conjugating Angiopep with PEG-PCL nanoparticles (ANG-NP) through bifunctional PEG to overcome the limitations of low transport of chemotherapeutics across the Blood-brain barrier (BBB) and poor penetration into tumor tissue.	Angiopep-conjugated PEG-PCL nanoparticles were prospective in dual-targeting drug delivery system for targeting therapy of brain glioma.	289
Hu et al., 2009 [26]	Article	The lactoferrin (Lf) conjugated poly (ethyleneglycol)-poly (lactide) nanoparticle (Lf-NP) was constructed in this paper as a novel biodegradable brain drug delivery system with evaluation of its in vitro and in vivo delivery properties.	Lf-NP is a promising brain drug delivery system with low toxicity.	285
Mathew et al., 2012 [27]	Article	Study on Anti - Alzheimer ' s Disease Effect of Curcumin Nanoparticles	Curcumin encapsulated-PLGA nanoparticles are able to destroy amyloid aggregates, exhibit anti-oxidative property and are non-cytotoxic. The encapsulation of the curcumin in PLGA does not destroy its inherent properties and so, the PLGA-curcumin nanoparticles can be used as a drug with multiple functions in treating Alzheimer's disease	257
Hynynen et al., 2006 [28]	Article	Explore the feasibility of using low-frequency magnetic resonance (MR) image-guided focused ultrasound as a noninvasive method for the temporary disruption of the blood-brain barrier (BBB) at targeted locations.	Low-frequency ultrasound bursts can induce local, reversible disruption of the blood-brain barrier without undesired long-term effects.	249
Ruan et al., 2015 [29]	Article	A gold nanoparticle-based delivery system was developed. The system, An-PEG-DOX-AuNPs, was loaded with doxorubicin (DOX) through hydrazone, an acid-responsive linker, and was functionalized with angiopep-2, a specific ligand of low density lipoprotein receptor-related protein-1 (LRP1), which could mediate the system to penetrate blood brain barrier and target to glioma cells.	An-PEG-DOX-AuNPs could specifically deliver and release doxorubicin in glioma and significantly expand the median survival time of glioma-bearing mice.	238
Gelperina et al., 2010 [30]	Article	Investigate the feasibility of drug delivery to the brain using the surfactant-coated PLGA nanoparticles.	Coating of drug-loaded PLGA nanoparticles with pharmaceutical surfactants such as poloxamer 188 and polysorbate 80 enables the delivery of drugs into the brain.	224
Schroeder et al., 1998 [31]	Article	The possibility of using dextran 70 000-stabilized and polysorbate 80-coated NPs for the delivery of two central analgesic peptides to the brain was compared with an alternative method using polysorbate 85-stabilized NPs.	The amitriptyline level was significantly enhanced in brain when the substance was adsorbed onto the NP and coated or when the particles were stabilized with polysorbate 85.	215

6. Conclusion

Although there are limitations in this study, this study has completely retrieved articles on NDDS that can cross BBB. The published articles on NDDS across BBB were sorted out. The characteristics of NDDS crossing BBB were discussed from the aspects of publication year, journal, country, institution, title, abstract, key word and highly cited paper. Therefore, this study still has some guidance.

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Authors' contributions

Determined the direction of the topic: Yihui Deng, Dayuan Zhong and Xueming Ou.
Literature search: Zhenyu Gan, Mengxue Zheng, Lan Li, Hui Cheng and Huanjie Li.
Data curation: Dayuan Zhong, Hongsheng Luo, Pingwen Liu and Deliang Liu.
Drafting of the manuscript: Dayuan Zhong and Xueming Ou.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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