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Research article

The evolution of isothermal amplification technology: A bibliometric study (2013–2022) ☆

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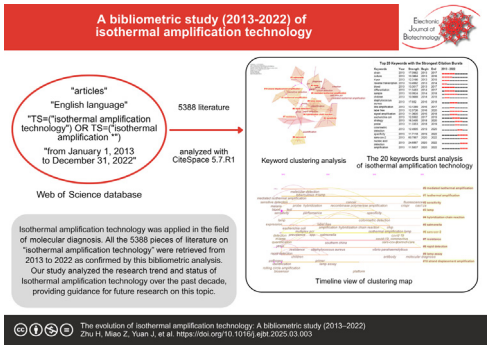
GRAPHICAL ABSTRACT

The evolution of isothermal amplification technology: A bibliometric study (2013–2022).



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ABSTRACT

Background: Isothermal amplification is a nucleic acid amplification technology (NAAT) that has contributed significantly to molecular diagnostics. The combination of NAAT with a suitable detection platform has improved sensitivity and specificity and enabled rapid disease diagnosis. A total of 5388 articles relating to isothermal amplification technology published from 2013 to 2022 were identified in the Web of Science Core Collection (WoSCC) database and subsequently analyzed with CiteSpace 5.7.R1 software. *Results:* The number of published articles on isothermal amplification technology steadily increased between 2013 and 2022. The disciplines included Chemistry, Science Technology Other Topics, Biotechnology Applied Microbiology, Microbiology, and Biochemistry Molecular Biology. The countries with the highest number of published articles were China, the United States, and Japan while the institutions with the highest number of published articles were the Chinese Academy of Sciences, the Chinese Academy of Agricultural Sciences, and Mahidol University. The high-frequency keywords included rapid detection, sensitivity, pathogen, *Escherichia coli*, probe, primer, and expression. Over

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(NAAT)
Trend analysis
Molecular

recent years, most research studies concerning isothermal amplification focused on its advantages, improvements, and applications. RCA, LAMP, RPA, and Cas technologies appeared sequentially from 2013 onward. The keyword "LAMP" exhibited the highest frequency (1222 times).
Conclusions: Our study described the research trends and the status of isothermal amplification technology over the past decade, providing guidance for future research in this field.
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1. Introduction

Isothermal amplification is a recently developed method for amplifying DNA performed under isothermal conditions. Its main advantages are ease of use and cost-effectiveness [1,2]. Employing this approach, a specific DNA template is amplified into millions of copies using Bst DNA Polymerase using an isothermal process [3,4,5,6,7]. This technology is mainly used in medical diagnostics, food safety assessment, and environmental monitoring [8,9].

Bibliometrics is an interdisciplinary science involving the quantitative analysis of knowledge carriers using mathematical and statistical methods, thus facilitating investigation, testing, and analysis in specific fields [10,11]. Detailed information on authors, keywords, references, institutions, and countries can be further used for performance analysis, enabling the evaluation of the development of a field [12].

The purpose of this study was to provide effective support for disease diagnosis through the use of rapid, sensitive, and specific isothermal amplification techniques while also addressing knowledge gaps in the bibliometric review of these topics. The main aims were to (1) summarize research on isothermal amplification technology from 2013 to 2022 in a global context, (2) examine key research topics and their characteristics, and (3) identify promising research directions by analyzing emerging trends in this field.

2. Methods

2.1. Data collection

The Web of Science Core Collection (Science Citation Index Expanded [SCIE]) database was used to search and retrieve published literature related to isothermal amplification technology. The advanced search option was adopted using the retrieval strategy of [TS= ("isothermal amplification technology") OR TS= ("isothermal amplification *")]. The time range of publication was set from January 1, 2013, to December 31, 2022. In all, 6629 documents were retrieved, including 5415 articles, 980 reviews, and 234 other types of publications. After filtering for original English language articles, 5388 publications were finally included.

2.2. Data analysis

CiteSpace5.7.R1 software was used to identify all the retrieved literature (named with download_x.txt), which was arranged in sequential order and in a fixed format. CiteSpace5.7.R1 software was also used for deduplication and further analysis. The time slicing was set from 2013 to 2022, the number of years per slice was set to 1, and the Top N was set to 50. The pruning parameters were set as Pathfinder, Pruning the merged network, and Pruning sliced networks. After setting the node types, a co-occurrence analysis regarding authors, countries, institutions, and keywords was conducted. Keyword clustering analysis, timeline views of keyword clusters, and keyword burst analysis were also carried out based on keyword co-occurrence analysis.

3. Results

3.1. Analysis of publication productivity

A total of 5388 articles on isothermal amplification technology published from 2013 to 2022 were retrieved from the WoSCC database. An average of 539 articles were published each year. The total number of articles published annually peaked at 861 in 2021 and bottomed out at 261 in 2013 (Table 1 and Fig. 1). Overall, the number of published papers related to isothermal amplification technology research increased steadily, while the number of citations displayed a more pronounced increase.

3.2. Disciplinary distribution of the articles

The disciplines covered in publications on isothermal amplification technology (2013 to 2022) retrieved from the WoSCC database were analyzed using CiteSpace 5.7.R1 software. The top five disciplines and the corresponding number of documents in the field of isothermal amplification technology are shown in Table 2 and Fig. 2, respectively. The disciplines included Chemistry, Science Technology Other Topics, Biotechnology Applied Microbiology, Microbiology, and Biochemistry Molecular Biology.

3.3. Analysis of countries and institutions

3.3.1. Analysis of countries

Using "Country" as the analysis node type in CiteSpace5.7.R1 software, a country analysis map was generated, which contained 267 network nodes, 232 connections, and had a density of 0.0065 (Fig. 3). The top three countries were CHINA, the USA, and JAPAN with 1620, 864, and 353 published papers, and their centrality values were 0.81, 0.66, and 0.1, respectively (Fig. 4 and Table 3).

Table 1
The total number of publications and citations in the field of isothermal amplification technology from 2013 to 2022.

Year	Total articles	Total citations
2013	261	146
2014	356	1045
2015	399	2340
2016	425	3627
2017	471	5313
2018	566	7710
2019	546	9304
2020	662	13,657
2021	861	19,912
2022	839	23,633

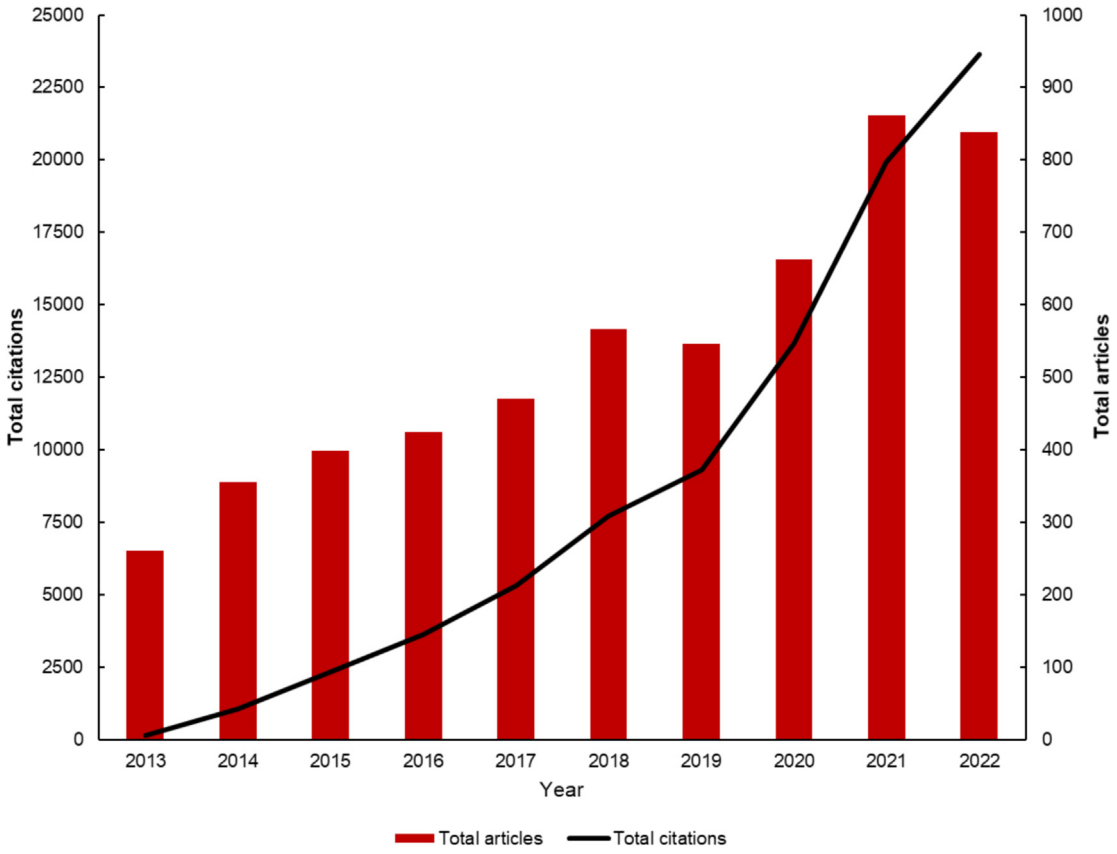

Fig. 1. The number of articles on isothermal amplification technology published from 2013 to 2022 and the number of related citations.

Table 2
The total number of documents for each of the top five disciplines covered in the field of isothermal amplification technology from 2013 to 2022.

Disciplines	Total number of papers for each discipline
Chemistry	1606
Science Technology Other Topics	961
Biotechnology Applied Microbiology	795
Microbiology	708
Biochemistry Molecular Biology	675

3.3.2. Analysis of institutions

Using "Institution" as the analysis node type in CiteSpace5.7.R1 software, an analysis map was generated, comprising 311 network nodes, 281 connections, and a density of 0.0058 (Fig. 5). The top three institutions in terms of the number of publications relating to isothermal amplification technology were the Chinese Acad. Sci., the Chinese Acad. Agr. Sci., and Mahidol Univ., with centralities of 0.1, 0.28, and 0.14, respectively. Regarding centrality, the top three institutions were the Chinese Acad. Agr. Sci. (0.28), Zhejiang Univ. (0.27), and Qingdao Univ. Sci. & Technol. (0.21), and the top 10 institutions were all from Asian countries (Fig. 6 and Table 4).

3.4. Keyword clustering analysis

The research topics relating to documents on isothermal amplification technology published in the last 10 years are shown in Fig. 7. The 10 keyword clusters obtained were as follows: #0 mediated isothermal amplification, #1 isothermal amplification, #2 sensitivity, #3 lamp, #4 hybridization chain reaction, #5 salmonella, #6 sars-cov-2, #7 resistance, #8 rapid detection, and #9 lamp assay. Topic #0, #1, #4, and #8 focused on the comprehensive understanding of the fundamental traits of isothermal amplification technology. Furthermore, Topics #2 and #7 examined how the isothermal amplification technology could achieve higher sensitivity compared to traditional methods. They also explored ways of optimizing the experimental procedures, highlighting the advantages of the method and facilitating its improvement. Topics #3 and #9 focused on the LAMP detection method. In addition, Topics #5 and #6 concentrated on species detection through the development of specific probes targeting bacteria and viruses, respectively.

3.5. Timeline view of the clustering map

The timeline view of the clustering map relating to isothermal amplification technology is shown in Fig. 8 and presents the research intervals for the various research contents. The year marked for a keyword in the timeline refers to when the keyword first emerged. RCA, LAMP, RPA, and Cas technologies appeared sequentially from 2013 onward. The term "COVID-19" appeared in 2020, with sensitivity and specificity being constant discussion points.

3.6. Keyword burst analysis

The 20 keywords with the strongest citation bursts relating to isothermal amplification technology are shown in Fig. 9. From 2013 to 2018, research was primarily concentrated on detection applications, such as for *Staphylococcus aureus* and *Escherichia coli*. Over time, new research hotspots appeared. Specifically, "specificity" emerged prominently in 2019, while SARS-CoV-2, nucleic

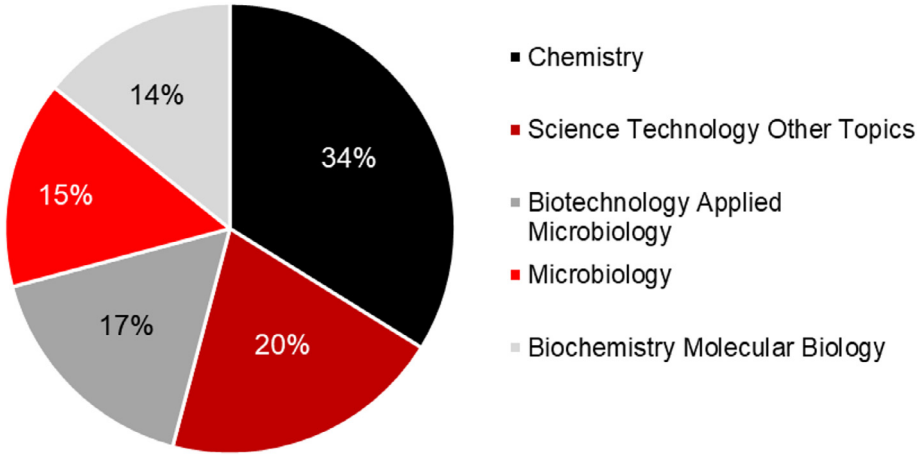

Fig. 2. The top five disciplines in the field of isothermal amplification technology from 2013 to 2022.

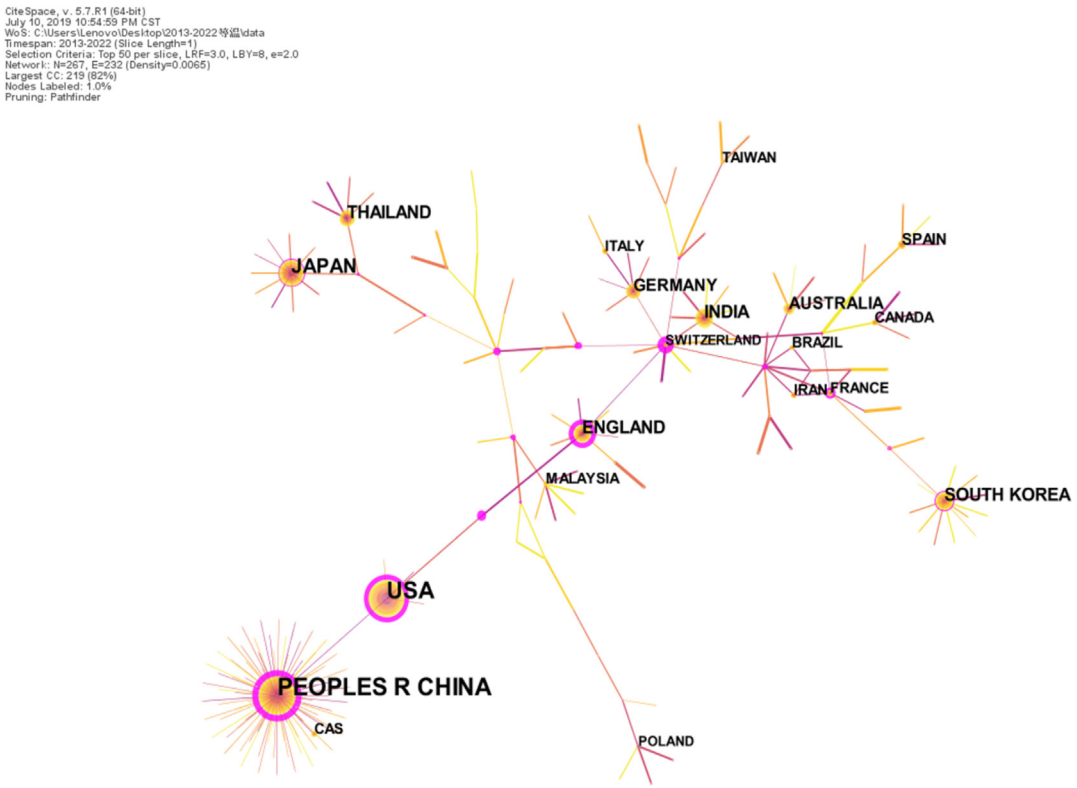

Fig. 3. Map of the main countries publishing on isothermal amplification technology. Centrality measures the importance of a node in a network structure and reflects the positional advantage of a country within the entire network of cooperation among countries. Compared with countries with low centrality, those with high centrality often play a more crucial role in aspects such as knowledge dissemination, resource integration, and cooperative exchanges. In the map, the diameter of the annual circle corresponds to the number of publications, while the extent of the purple area outside the annual circle represents centrality. The larger the purple area; the closer the cooperation of the country with other nations. The lines denote cooperation among countries, and the color of the lines indicates the publication time. Lighter coloring suggests a longer time interval since the initial publication. CAS: Chinese Academy of Sciences. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

acid detection, and amplification gained prominence in 2020, representing the new research directions for isothermal amplification technology. These shifts reflect the dynamic focus and demands within the field of isothermal amplification technology over time. In addition, "LAMP" was the most frequent keyword, with 1222 occurrences.

3.7. Citation analysis

From 2013 to 2022, the most cited literature (1514 times) was "CRISPR-Cas12a target binding unleashes indiscriminate single-stranded DNase activity" (Table 5). It was published in Science, which has an impact factor of 54.5 over the past 5 years. The

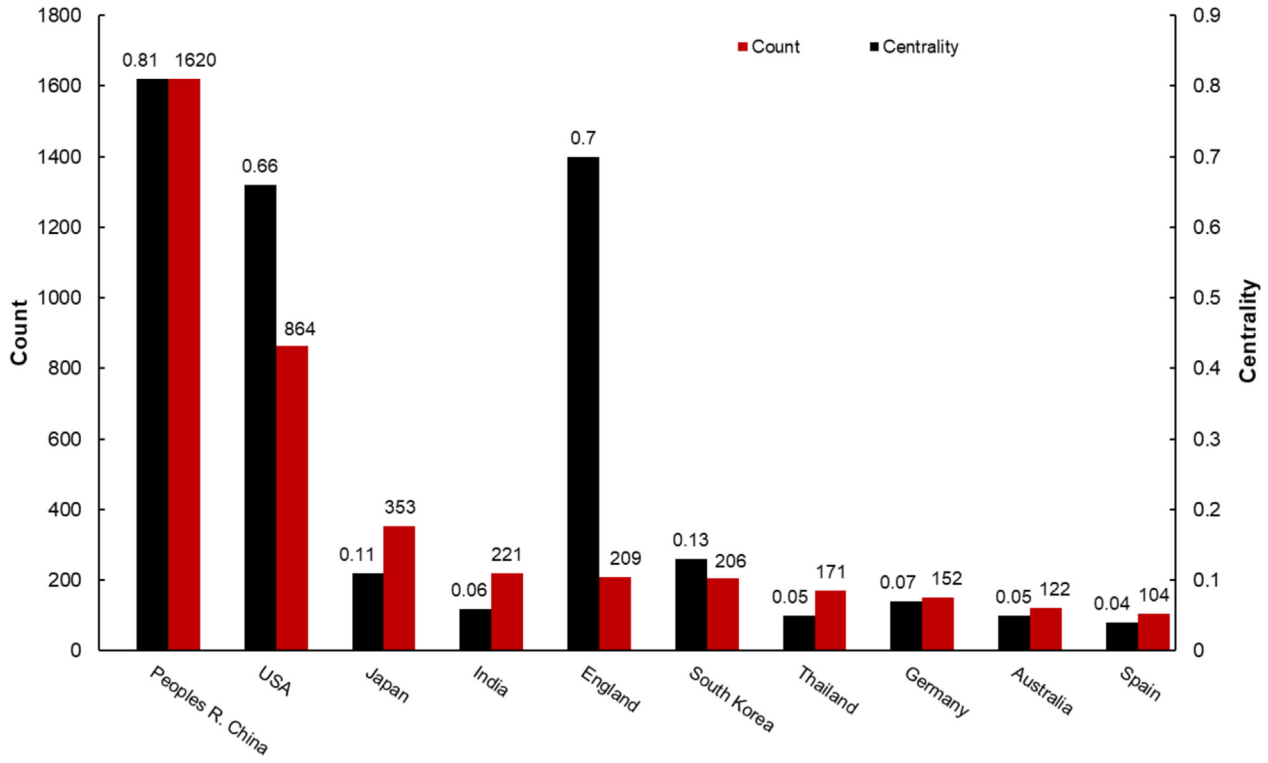

Fig. 4. The top 10 countries in the field of isothermal amplification technology research from 2013 to 2022.

Table 3
The top 10 countries in the field of isothermal amplification technology research from 2013 to 2022.

Rank	Country	Count	Centrality
1	Peoples R. China	1620	0.81
2	USA	864	0.66
3	Japan	353	0.11
4	India	221	0.06
5	England	209	0.70
6	South Korea	206	0.13
7	Thailand	171	0.05
8	Germany	152	0.07
9	Australia	122	0.05
10	Spain	104	0.04

second most frequently cited work (1139 times) was "Nucleic acid detection with CRISPR-Cas13a/C2c2", which was also published in Science.

4. Discussion

With the development of molecular technology, diagnostic approaches based on nucleic acid detection have been established and are widely employed in the laboratory detection of human diseases [2]. Both polymerase chain reaction (PCR) and quantitative real-time PCR (qPCR) show high sensitivity and specificity; however, they are time-consuming, and require a laboratory with thermal cycle control equipment. In comparison, nucleic acid isothermal amplification requires significantly shorter analysis time, while retaining high specificity and sensitivity [18].

Employing Citespace5.7.R1 software, we undertook an elaborate analysis of the keywords, countries, institutions, and authors for articles related to isothermal amplification technology published from 2013 to 2022. Using this strategy, we unveiled the research status of isothermal amplification technology worldwide and provided valuable guidelines for the selection of molecular detection technology.

We examined publication output, international and institutional cooperation, and keyword clustering regarding isothermal amplification technology from different perspectives. Over the past 10 years, 5388 articles were published on the subject of isothermal amplification technology, involving many fields, such as Chemistry, Microbiology, and Biotechnology Applied Microbiology (Fig. 2 and Table 2). The number of articles steadily increased, mainly in Asia, North America, and Europe, and there was relatively close international cooperation (Fig. 3 and Fig. 4). The number of articles published in China was significantly greater than that of other countries (Table 3), and included institutions such as the Chinese Acad. Sci., the Chinese Acad. Agr. Sci., Zhejiang Univ., and Mahidol Univ., among others (Fig. 5 and Fig. 6). These institutions demonstrated high publication output and close inter-agency collaboration (Fig. 5 and Table 4). The number of publications on isothermal amplification technology in China was nearly twice that of the United States (Fig. 4 and Table 3). Regarding the institutional analysis results, a preponderant majority (9 of the top 10) were Chinese institutions (Table 4). Considering that China is densely populated and thus has a huge demand for medical resources, molecular detection has become a commonly utilized method for disease screening. Isothermal amplification technology has emerged as a frontrunner in molecular detection owing to its outstanding speed and ease of operation. This has spurred a notable increase in the number of publications in this domain from China, with most of its universities and science academies actively involved in molecular testing research using isothermal amplification technology.

We found that the advantages, application, and performance improvement of isothermal amplification technology were the

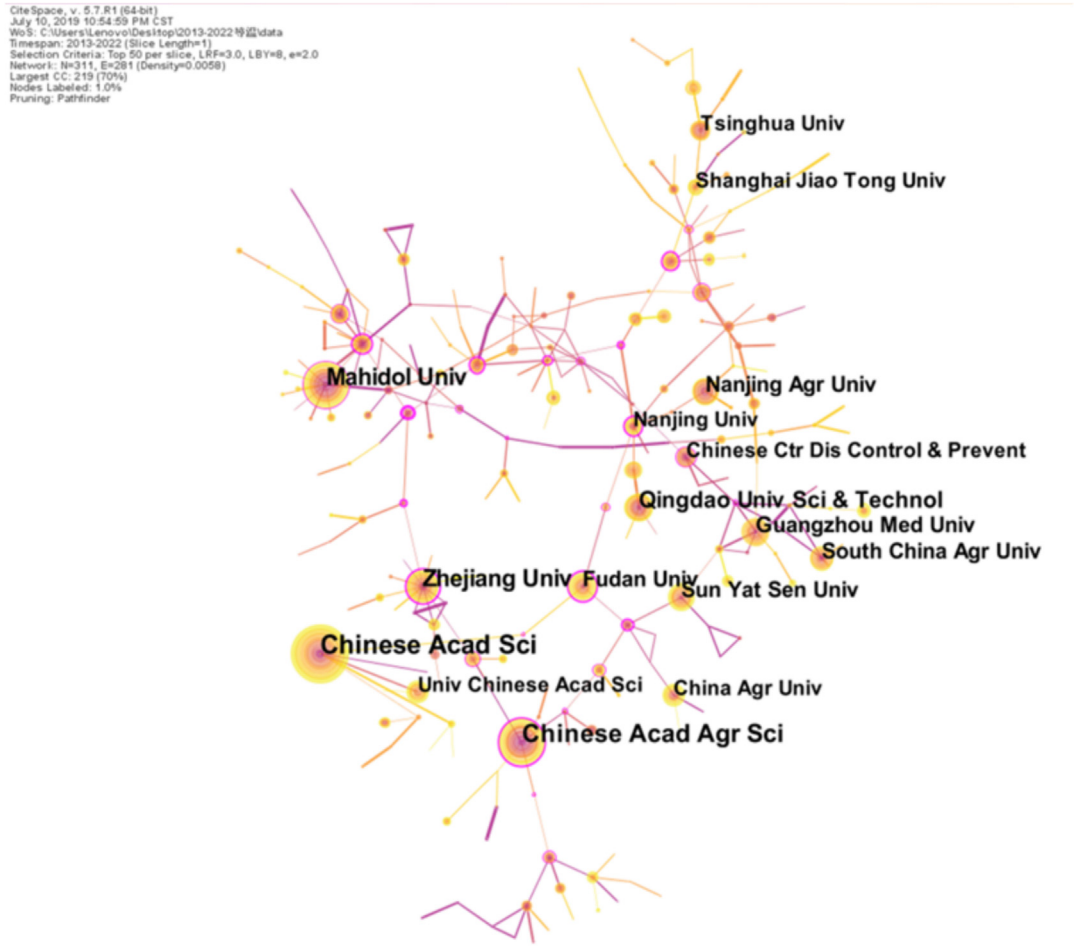

Fig. 5. Map of the main institutions that published papers on isothermal amplification technology (for the interpretation of the co-occurrence map, please see Fig. 3.).

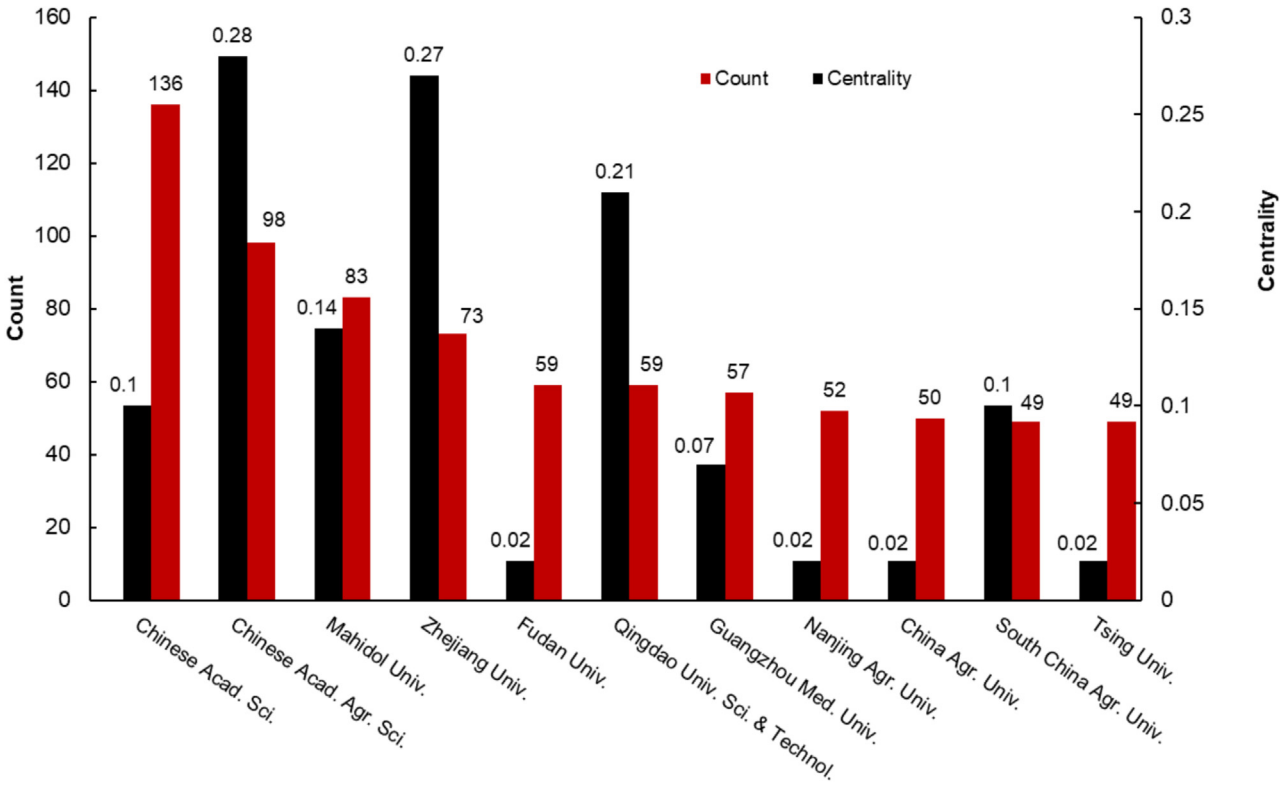

Fig. 6. The top 10 institutions in the field of isothermal amplification technology from 2013 to 2022.

main research direction from 2013 to 2022 (Fig. 7). Between 2013 and 2016, there was an emergence of keywords such as "rapid detection", "sensitivity", "pathogen", "*Escherichia coli*", "probe", "primer", and "expression" (Fig. 8). This highlighted the speed and sensitivity of isothermal amplification technology for the detection of pathogens during its developmental phase as well as the importance of probe and primer design for the sensitivity and specificity of this technology (Fig. 8). Since 2013, the keywords "Rolling Circle Amplification (RCA)", "LAMP", "Recombinase Polymerase Amplification (RPA)", and "CRISPR-associated (Cas) protein technology" emerged sequentially, and their principles are all based on isothermal amplification (Fig. 8). From 2016 to 2022, keywords such as "cancer" and "covid-19" appeared, indicating that isothermal amplification technology had been applied for the detection of different diseases (Fig. 8).

RCA is noted for its high sensitivity and selectivity in detection. In particular, amplification can be performed at a low temperature and without the requirement for an initial denaturation step; however, it requires optimally designed circular DNA or RNA templates [19,20,21]. LAMP has been widely used for point-of-care applications because of the short amplification time and because the results can be directly observed with the naked eyes. Nevertheless, non-specific amplification and primer-dimer formation remain limitations that require further improvement [22,23,24,25]. Characterized by its high sensitivity, the RPA assay does not require costly tools, a sophisticated laboratory, or the use of multiple primers, and can deliver results in less than 20 min. However, RPA is inhibited by high genomic DNA concentrations (20–100 ng/μL) in whole-blood samples [26]. Finally, while CRISPR-Cas technology is highly sensitive and specific, it is also time-consuming [27,28]. This shows that different isothermal amplification technologies have their pros and cons, and researchers are constantly exploring ways to optimize them. The content of the four most frequently cited publications in the field of isothermal amplification technology was related to CRISPR-Cas technology (Table 5), which is widely used for gene editing and molecular detection.

Table 4
The top 10 institutions in the field of isothermal amplification technology from 2013 to 2022.

Rank	Institution	Count	Centrality
1	Chinese Acad. Sci.	136	0.10
2	Chinese Acad. Agr. Sci.	98	0.28
3	Mahidol Univ.	83	0.14
4	Zhejiang Univ.	73	0.27
5	Fudan Univ.	59	0.02
6	Qingdao Univ. Sci. & Technol.	59	0.21
7	Guangzhou Med. Univ.	57	0.07
8	Nanjing Agr. Univ.	52	0.02
9	China Agr. Univ.	50	0.02
10	South China Agr. Univ.	49	0.10
10	Tsing Univ.	49	0.02

Keyword burst analysis showed that "specificity", "SARS-CoV-2", "nucleic acid detection", and "amplification" were the main research hotspots from 2019 to 2022 (Fig. 9). SARS-CoV-2 spread rapidly across the globe from 2019, eventually becoming a serious health concern worldwide [29,30]. The virus's ongoing evolution, characterized by the appearance of single nucleotide polymorphism (SNP) variants and numerous lineages, suggests that it may continue evolving for years or even decades [31,32,33]. Accordingly, exploring rapid detection methods and potential drug targets, undertaking clinical trials, and raising key research questions could provide new directions for the study of infectious pathogens such as SARS-CoV-2 [34].

With its ability to provide rapid results at a low cost, nucleic acid isothermal amplification technology has proven invaluable for point-of-care applications and fast inspections at ports during infectious disease diagnosis, enhancing the speed and accuracy of

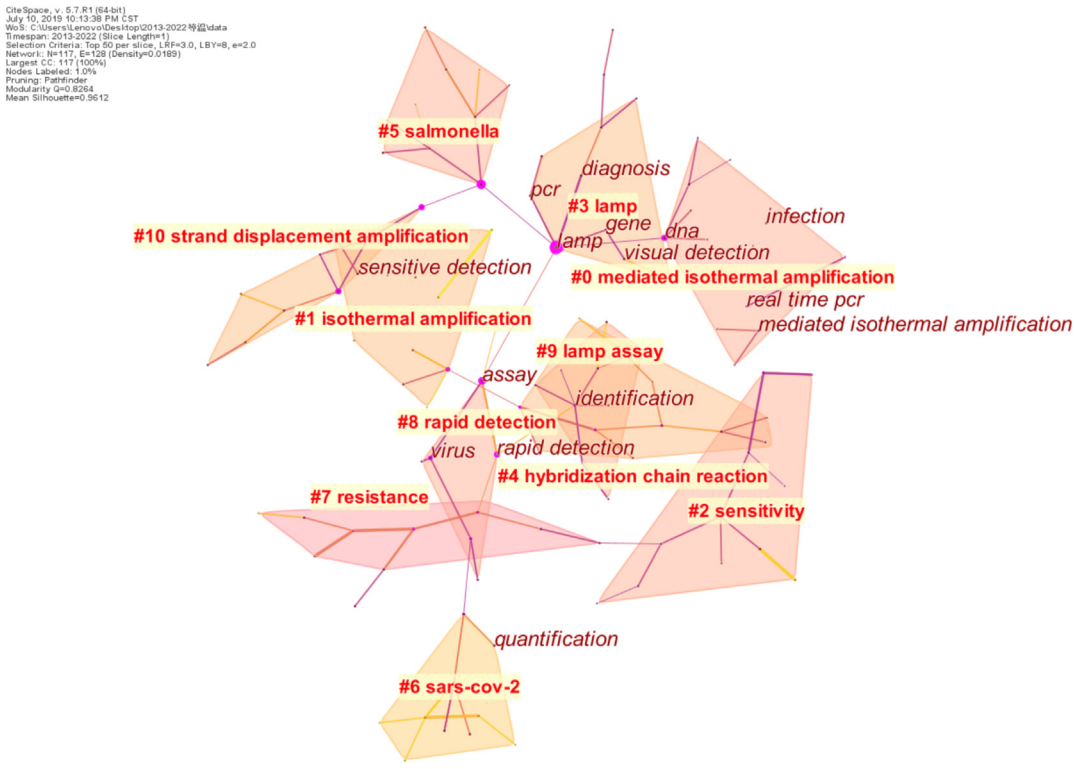

Fig. 7. Clustering map of high-frequency keywords on isothermal amplification technology.

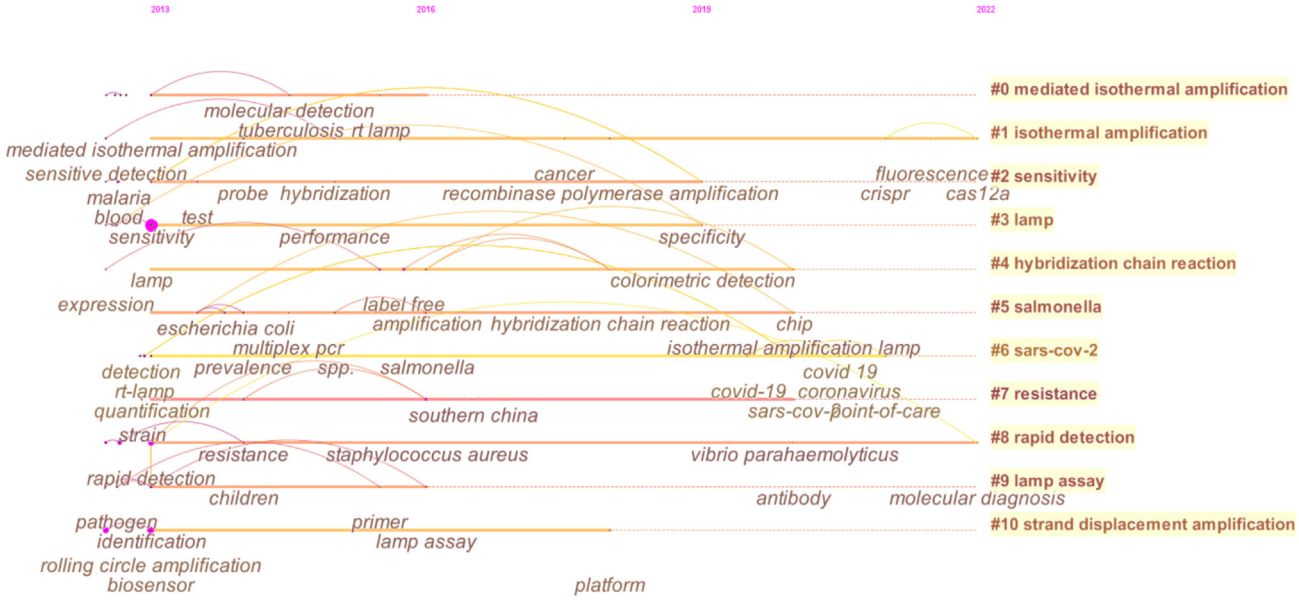

Fig. 8. Timeline view of the clustering map relating to isothermal amplification technology.

Top 20 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2013 - 2022
strain	2013	17.0982	2013	2017	
culture	2013	10.3884	2013	2016	
rt pcr	2013	12.3166	2013	2015	
reverse transcription	2013	13.4582	2013	2014	
blood	2013	13.3017	2013	2017	
differentiation	2013	11.3483	2014	2017	
sample	2013	10.9924	2014	2018	
children	2013	10.5688	2014	2015	
staphylococcus aureus	2013	17.652	2016	2018	
dna amplification	2013	13.1289	2016	2017	
label free	2013	12.5726	2016	2020	
signal amplification	2013	11.3605	2016	2018	
escherichia coli	2013	12.5582	2017	2019	
strategy	2013	16.3495	2018	2020	
probe	2013	11.3353	2018	2019	
colorimetric detection	2013	12.4995	2019	2020	
specificity	2013	11.7118	2019	2022	
sars-cov-2	2013	60.7567	2020	2022	
nucleic acid detection	2013	24.6567	2020	2022	
amplification	2013	11.5007	2020	2022	

Fig. 9. Burst analysis of the 20 most frequently occurring keywords relating to isothermal amplification technology. Begin and End denote the burst time of the keyword. Strength indicates the strength of the keyword's burst and its magnitude reflects the influence during that period.

detection to better combat the spread of diseases [35]. In conclusion, our study offered a preliminary exploration of the research status of isothermal amplification technology from 2013 to 2022 and explored future research directions through a network knowledge graph for isothermal amplification technology constructed using Citespace5.7.R1 software. Moreover, this bibliometric analysis also provides strong theoretical and data support for guiding future research.

Table 5
The top five publications in the field of isothermal amplification technology.

Rank	Title	Journal	Journal 5-year impact factor	Citations	Year	Corresponding author
1	CRISPR-Cas12a target binding unleashes indiscriminate single-stranded DNase activity [13]	SCIENCE	43.655	1514	2018	J.A. Doudna
2	Nucleic acid detection with CRISPR-Cas13a/C2c2 [14]	SCIENCE	40.627	1139	2017	J.J. Collins and F. Zhang
3	SHERLOCK: nucleic acid detection with CRISPR nucleases [15]	NATURE PROTOCOLS	13.563	539	2019	J.S. Gootenberg, O.O. Abudayyeh, and F. Zhang
4	CRISPR-Cas14 is now part of the artillery for gene editing and molecular diagnosis [16]	NANOMEDICINE-NANOTECHNOLOGY BIOLOGY AND MEDICINE	5.803	383	2019	G. Aquino Jarquin
5	A colorimetric RT-LAMP assay and LAMP-sequencing for detecting SARS-CoV-2 RNA in clinical samples [17]	SCIENCE TRANSLATIONAL MEDICINE	21.138	363	2020	M. Knop and S. Anders

CRediT authorship contribution statement

Hanting Zhu: Writing – review & editing, Visualization, Resources, Methodology, Investigation, Data curation, Writing – original draft. **Zhitong Miao:** Writing – review & editing, Validation, Software, Resources, Methodology, Investigation. **Junfei Yuan:** Validation, Software, Project administration, Methodology. **Wanying Xie:** Visualization, Software, Project administration. **Qiaoqiao Zhang:** Writing – review & editing, Writing – original draft, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kun Yang:** Writing – review & editing, Visualization, Validation, Supervision, Investigation, Formal analysis, Conceptualization, Writing – original draft.

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Declaration of competing interest

No potential conflict of interest was reported by the authors.

Supplementary material

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Data availability

Data will be made available on request.

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