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Review

Bibliometric and visualized analysis of hydrogels in organoids research

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A B S T R A C T

Over the past decades, there has been ongoing effort to develop complex biomimetic tissue engineering strategies for in vitro cultivation and maintenance of organoids. The defined hydrogels can create organoid models for various organs by changing their properties and various active molecules. An increasing number of researches has been done on the application of hydrogels in organoids, and a large number of articles have been published on the topic. Although there have been existing reviews describing the application of hydrogels in the field of organoids, there is still a lack of comprehensive studies summarizing and analyzing the overall research trends in this field. The citation can be used as an indicator of the scientific influence of an article in its field. This study aims to evaluate the application of hydrogels in organoids through bibliometric analysis, and to predict the hotspots and developing trends in this field.

Contents

Abbreviations: 3D, Three-dimensional; ECM, Extracellular matrix; BME, Basement membrane extracts; WoS, Web of science; TLS, Total link strength; IF, Impact factor.

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1. Introduction

The development of three-dimensional (3D) human organotypic models in vitro is a significant technological advancement [1,2]. Organoids, which are 3D cell aggregates formed from pluripotent stem cells through self-organization in a laboratory setting, partially replicate the developmental trajectory, tissue-specific structure, and function of natural organs [3–5]. This breakthrough has proven invaluable for disease modeling and the exploration of therapeutic approaches, particularly for diseases that are challenging to study using animal models or conventional monolayer cultures [6,7]. Organoid development bridges the gap between genetics and patient trials [8,9]. In vivo, the natural extracellular matrix (ECM) is a dynamic and complex microenvironment that provides bioactive factors, morphological guidance, and 3D support for the clusters of cells embedded in all tissues and organs [10]. The cultivation and maintenance of organoids in vitro typically involves embedding cell clusters within a matrix [11]. In common protocols, the process of organoid formation heavily relies on basement membrane extracts (BME), such as Matrigel [2,12]. However, these extracts are derived from tumor cell secretion, which leads to batch variations, high expenses, and safety concerns. Furthermore, several studies have explored the use of decellularized tissues' whole ECM as 3D scaffolds for cell and organoid cultures [13–16]. These scaffolds may provide a more suitable tissue-like environment, their results remain unstable due to the unclear chemical composition of the ECM [17]. Therefore, there is a significant demand for the development of organoid models using fully defined components to ensure reproducibility in organoid culture.

In this regard, the utilization of defined hydrogels presents a promising alternative to BME in organoid culture, aiming to mimic the ECM of different tissues [18]. By designing hydrogels with specific physical and chemical properties, researchers can simulate the in vivo niche of the target organ, thereby facilitating the growth and differentiation of cells within organoids [19]. This approach allows for the creation of organoid models representing various organs [20–23]. Moreover, the incorporation of growth factors, signaling molecules, and other bioactive substances into the hydrogel ECM enables precise control over the organoid microenvironment, thereby promoting their further development [24]. Over the past 20 years, hydrogels have been extensively utilized in the field of organoids, and the related literature reports have also increased exponentially.

Citations indeed serve as an important metric to gauge the scientific influence of an article within its field [25,26]. Bibliometric analysis, which involves quantifying the number of published papers, provides a valuable means to obtain an extensive overview of the literature, comprehend the knowledge structure of a particular topic, and identify research frontiers or popular areas of focus [27,28]. Furthermore, bibliometric analysis allows for comparisons of research status across different countries, institutions, authors, or journals using database data, thereby facilitating a better understanding and visualization of trends in scientific publications [29].

The objective of the study was to conduct a bibliometric analysis to examine the utilization and advancements of hydrogels in the field of organoids. By employing bibliometrics, the study aimed to present an overview of the current research progress, identify hot topics, and highlight emerging trends in this field. The findings of the analysis would provide guidance to new researchers, enabling them to gain a better understanding of potential research interests and directions for their future investigations.

2. Materials and methods

2.1. Search methods

A bibliometric study was conducted to evaluate the publication trends and find the insight of publications on “Organoids”. A title search of “Organoids” was carried out on both well-known databases, SCOPUS and Web of Science (WoS), to select the preferred database for data collection. The number of documents on SCOPUS was 22,592 which was less than the number of documents with the same search on WoS (27,244 records). WoS is the most appropriate influential, extensive, and trustworthy database for literature retrieval and analysis [30].

On July 30, 2023, the WoS Core Collection database was used to identify documents on organoids and hydrogels. To ensure the breadth of the search scope, the search terms were constantly filtered. Finally the keywords were established: TOPIC=(organoids OR organoid) AND TOPIC = (hydrogel OR hydrogels) AND Language = English AND Document type= (Article OR Review) AND Time span = 1985 to 2023.

2.2. Data extraction and analyzes

The data was exported to Microsoft Excel 2016 and EndNote to identify duplicates. The number of citations, authors, institutions, published journals and countries are recorded. 628 documents were exported as plain text files and BibTex files then imported into the VOS viewer software 1.6.16 (Van Eck and Waltman, Leiden University, Leiden, The Netherlands) and HistCite Pro 2.1 (http://www.histcite.com) software, and bibliometric analysis was performed using the Bibliometrix-package (http://www.bibliometrix.org/) of R software (4.1.0). VOS viewer software was used for keywords, journals, and countries network visualization analysis. Co-occurrence represents how often a term or reference has been mentioned over a period of time. Bibliometrix-package was used for science mapping.

This study primarily concentrated on description rather than statistical analysis. The metrics provided, such as the number and ratio (%) of each metric, aim to depict the distribution and changing patterns in different years, nations, institutions, journals, and authors.

3. Results

In total, 668 publications were retrieved, including 450 articles, 181 review articles, 28 meeting abstracts, and other types of papers.

As document types such as meeting abstracts, book chapters and other publications do not share the same citation rates, only document types that included original articles and reviews (628 publications) were included in the following analysis. As shown in Table 1, we can find that there are three main types of hydrogels in the organoids field: Natural Polymer, Synthetic Polymer and bio-hybrid hydrogels. The latter builds upon the former and makes improvements to cater to diverse requirements. Hydrogels based on natural polymers are composed of naturally derived components, including alginate, chitosan, hyaluronic acid and collagen. The common synthetic polymers that have been reported include Poly(ethylene glycol) (PEG)-Based Hydrogels, Poly(acrylamide) (PAM)-Based Hydrogel, Polyisocyanopeptides (PIC)-Based Hydrogels, Poly(vinyl alcohol) (PVA) based thermogels. The coupling of synthetic polymers and natural ECM components produces bio-hybrid hydrogels, including Photopolymerized Hydrogels, Enzyme-Mediated Polymerized Hydrogels, Click Chemistry Crosslinked Hydrogels. Then, we analyzed the growth of the obtained publications according to the publication year. As shown in Fig. 1a, there was a significant surge in the number of published papers after 2016, coinciding with a consistent upward trend in early citations. However, it was observed that the number of citations started to decline after 2020. More than 40 countries and regions worldwide were actively carrying out research on the application of hydrogels in the field of organoids. The top 15 countries or regions with the most publications were shown in Fig. 1b. Out of all the countries, two countries have produced over 100 documents. Researchers from USA contributed the largest number of publications and had the highest H-index ($n = 261$, $H = 54$) in this field. China ($n = 115$, $H = 24$) and England ($n = 48$, $H = 18$) ranked second and third, respectively. In terms of average citation ranking, Switzerland has risen to the first place with an average of 67 citations per record. Regarding the most productive institutions, 960 institutions around the world were involved in the field. As shown in Fig. 1c, Wake Forest University and Harvard University were in the first and second place, in terms of the number of papers published in this field, with 30 and 27 papers published, respectively. Moreover, the H-indexes of these two institutions significantly surpassed those of other institutions, reaching 19 and 20, respectively.

3.1. Analysis of countries

Fig. 2a gave a geographic distribution picture of the number of authors affiliated with the country of publication. The intensity of blue in the figure was proportional to the number of affiliated authors in each country. Each blue color indicated the number of authors involved. Blue was the darkest in America. The United States and China were two core research powers in the field. Fig. 2b Co-occurrence analysis showed the number of joint papers published by the top countries on the application of hydrogels in the field of organoids. Along with Figs. 1b and 2a—a complete picture of the academic performance of leading countries could be observed. The size of the circle represents the number of articles published by the country, and the larger the circle, the higher the country's contribution to co-authorship. The thicker the lines between the two countries, the closer the cooperation exist between the two countries. The USA seemed to be the central country for any published document because there were so many scientific links between the USA and other countries. The USA and China cooperated the most in scientific production, followed by South Korea.

3.2. Analysis of authors

There were a total number of 3340 researchers publishing their scientific accomplishments on the application of hydrogels in the field of organoids from 2003 to 2023. This fact means there are 10.00 authors and 6.68 co-authors per document in our analysis collection. Fig. 3 showed the most relevant authors' production over time from 2015 to 2023. The bubble size was related to the number of documents published during the years. Skardal A (22 articles) had published the most articles in the field. The red line signifies the author's timeline. Meanwhile, Skardal A and Singh A had the most protracted timeline compared to other authors. The bubble color intensity was also related to the total citations per

Table 1
Characteristics of hydrogel materials in organoid culture.

	Biomaterial components	Differences	Similarities
Natural Polymer	Alginate	High biodegradability, excellent biocompatibility and simple gelation process	Good biocompatibility, bio-absorbability with controllable, low stability, poor mechanical properties, and rapid degradation
	Chitosan	Natural antibacterial properties, and non-toxic degradation by-products	
	Hyaluronic Acid	Good injectability, antioxidant properties and inhibits inflammatory factors	
	Collagen	Low immunogenicity and unique self-assembling fibril-forming properties	
Synthetic Polymer	Poly(ethylene glycol) (PEG)-Based Hydrogels	Well-defined, highly uniform architecture, tenability, lower cost and long-term stability	Strong mechanical properties, stimulus responsive and high regulation, but poor biocompatibilityand toxic degradation products,
	Poly(acrylamide) (PAM)-Based Hydrogel	Temperature responsive cell culture, bioinert, hydrophilic and electroneutral	
	Polyisocyanopeptides (PIC)-Based Hydrogels	Good stability, thermo-sensitive properties, rapid and reversible extraction of cells	
	Poly(vinyl alcohol) (PVA) based thermogels	Superior biocompatibility and controllable physical properties	
Biohybrid hydrogels	Photopolymerized Hydrogels	Rapid curing and high controllability	High-performance hydrogels, functional diversity, but high difficulty in production and limited material selection
	Enzyme-Mediated Polymerized Hydrogels	Reversibility and biological activity regulation	
	Click Chemistry Crosslinked Hydrogels	Easy, robust, modular, give high yields, work at mild conditions and only generate inoffensive byproducts in a reliable way	

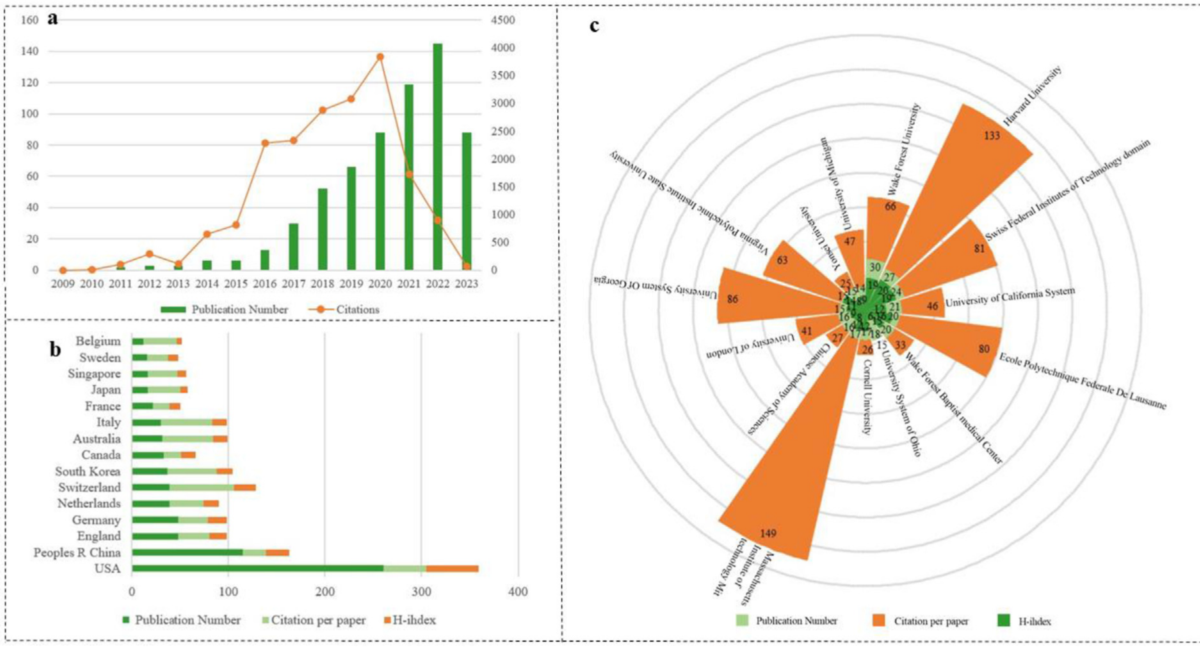

Fig. 1. (a) The annual publication and citation growth of literature regarding hydrogels for organoids applications, (b) The most contributing countries in the hydrogels-based organoids area, (c) The most contributing institutes in the hydrogels-based organoids area.

year. Lutole MP was the author with the most total citations per year in the field in 2016. Since 2020, several authors had published more than three highly cited papers.

3.3. Analysis of sources

As shown in Table 2, the leading journal was Biomaterials (n = 42; 17.4%, IF = 14), followed by Acta Biomaterialia (n = 22; 9.4%, IF = 9.7), and Biofabrication (n = 21; 9.0%, IF = 9) as described in Table 1.

Further, through co-occurrence network analysis, the minimum number of citations of a source was set at 270. Of the 3935 sources, only 31 sources met the threshold. The Biomaterials was the leading source with highest total link strength (TLS) 145420 (citations = 2818), followed by Nature (TLS = 76992, citations = 1477), and Acta Biomaterialia (TLS = 56925, citations = 971). The strongest link (10209) was between Biomaterials and Acta Biomaterialia (Fig. 4a). Two clusters of sources were identified by this analysis. Cluster 1, green color, included 15 journals closely in terms of scope. The Biomaterials was in the core of this cluster. Cluster 2, red color, included 16 sources and Nature was in the core. The area of the red color in Fig. 4b indicated active sources that having the highest rate of co-citation (i.e., Biomaterials).

3.4. Analysis of keywords

The keyword analysis is one of the most important indicators of bibliometrics. Three-field plots were created to give a general view of the articles' keywords referring to the application of hydrogels in organoids. Fig. 5 showed the relationship among top keywords, top authors and top journals. As shown in Fig. 5, Liu H, Skardal A, Lutolf MP, Zhang Y, Singh A, Liu Y, Chen Y, Soker S, Wang Y, and Li Y had used almost every top keyword in their publications. The top relevant keywords such as organoids, tissue engineering, hydrogels, organoid, hydrogel, biomaterials, bioprinting and extracellular matrix were the most frequently used keywords. While, regenerative medicine, stem cells, 3D bioprinting and 3D culture were mostly the top journal articles' keywords.

Further, Co-occurrence analysis found that the relationship of items based on the number of publications in which they occur together. The co-occurrence network analysis tool was used to set the minimum number of occurrences to 10. Of the 2803 keywords, 108 met the threshold. The keyword “hydrogels” (total link strength 939) appeared most, with 178 cooccurrences, followed by organoids (occurrences = 165, TLS = 838), and in-vitro (occurrences = 145, TLS = 760) (Fig. 6a).

To analyze the evolution of research topics over time, the highest frequency keywords were examined using VOS viewer (Fig. 6b). The colors in the figure indicate the chronological appearance of the keywords, with blue indicating early appearance and yellow representing later stages. In the initial phase of hydrogels-applied organoids research, the focus was primarily on “tissue engineering and expression”. However, recent trends suggested a growing interest in research on biomaterials, 3D bioprinting and biofabrication clusters, indicating that these areas may receive significant attention in the future.

4. Discussion

The global innovation in organoids technologies has now entered an exponential growth phase [31]. Over the past decades, there has been ongoing effort to develop complex biomimetic tissue engineering strategies for in vitro cultivation and maintenance of organoids [2,32]. The defined hydrogels can create organoid models for various organs by changing their properties and various active molecules [20–23]. Because to the increasing research on hydrogels and organoids in recent years, researchers who have just entered the field will face increasing difficulties in understanding the future direction. Different from review or meta-analysis, bibliometric analysis uses visualization software such as VOS viewer, Bibliometrix and HistCite to comprehensively analyze the current literature, more intuitively grasp the development trend, and predict future research hotspots [29,33]. These technologies are

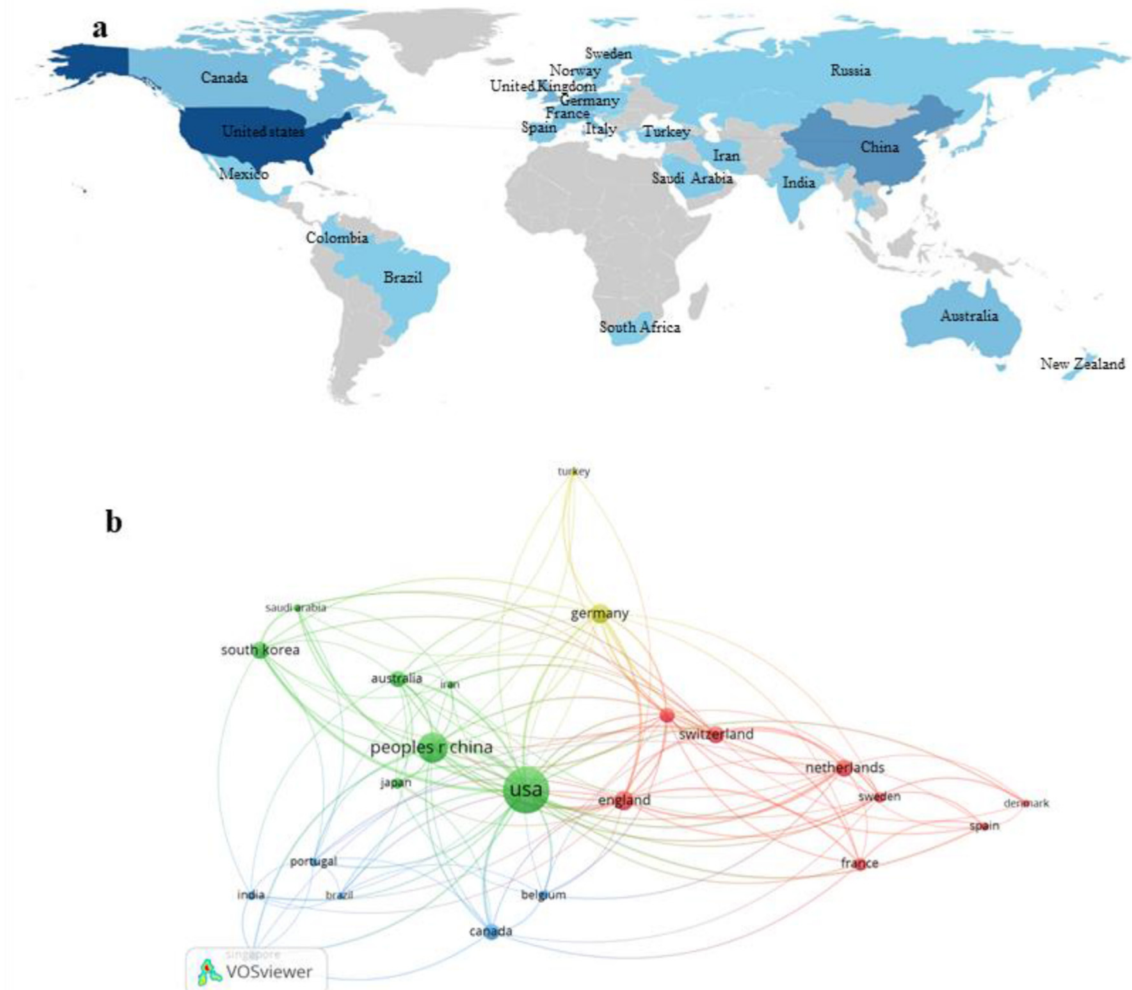

Fig. 2. (a) Country's scientific production world map of hydrogels for organoids research field (blue color intensity: the number of authors affiliated with each country, grey color: non-related country), (b) Country collaboration Network visualization map of hydrogels for organoids research field.

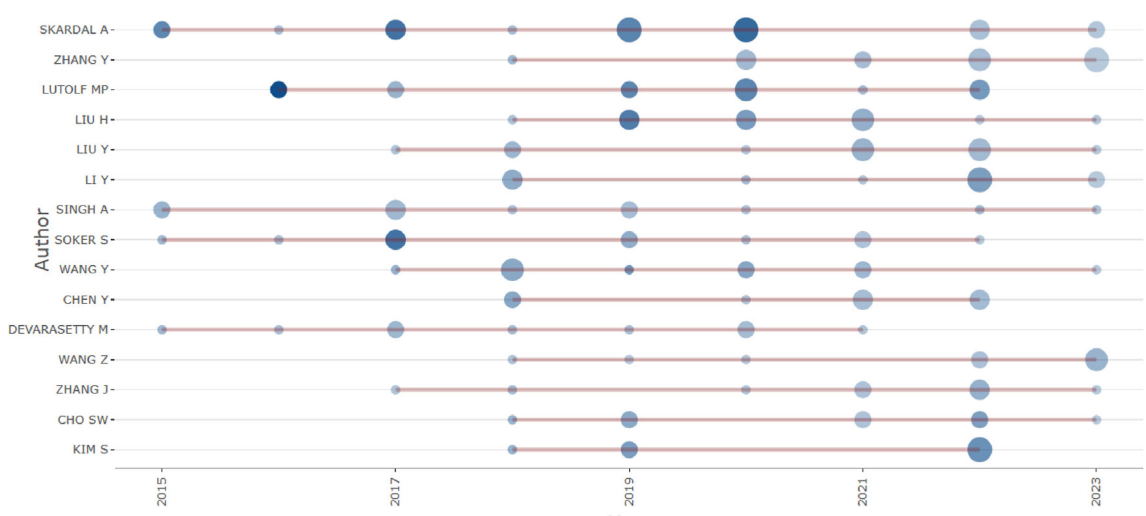

Fig. 3. Top 15 most relevant authors' production on hydrogels for organoids research field from 2015 to 2023 (red line: the author's timeline, bubble size: the number of publications, bubble color intensity: total citations per year).

Table 2
Top-10 leading journals of hydrogels in organoids research.

Ranking	Journals	Records	Percentage (%)	IF(2023)	Quartile
1	Biomaterials	41	17.4	14	1
2	Acta Biomaterialia	22	9.4	9.7	1
3	Biofabrication	21	9.0	9	1
4	Advanced Healthcare Materials	20	8.5	10	1
5	Frontiers in Bioengineering and Biotechnology	20	8.5	5.7	1
6	Advanced Materials	19	8.1	29.4	1
7	Advanced Functional Materials	18	7.7	19	1
8	Advanced Science	14	6.0	15.1	1
9	International Journal of Molecular Sciences	12	5.1	5.6	1
10	Acs Biomaterials Science & Engineering	11	4.7	5.8	2

IF, impact factor.

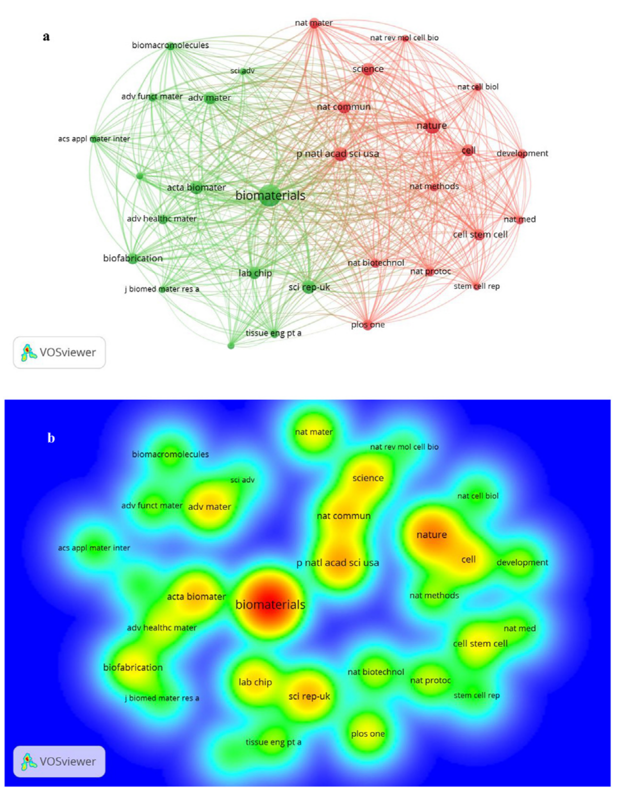

Fig. 4. Visualization mapping of co-citation cited sources. (a) The citation network visualization map of sources. A minimum of 270 documents per journal was fixed. Of the 3935 sources, 31 meet the threshold, (b) Density visualization map.

extensively utilized across various scientific domains, ranging from micro (institutional level) to macro (global level), allowing for both qualitative and quantitative evaluation [34]. This study is the first bibliometric analysis that specifically focuses on hydrogels, organoids, and visual maps. The findings of this study offered valuable insights into organizing and maximizing research output on the application of hydrogels in the field of organoids. Additionally, they shed light on the development trends within this field and provided a better understanding of its future path.

In the present study, a total of 628 documents on organoids and hydrogels were analyzed (Table 2). Hydrogel is utilized as a scaffold in organoid culture to facilitate cell growth, proliferation, and differentiation. These natural hydrogels are very rich, showing good biocompatibility, bio-absorbability with controllable and rapid degradation. However, their limitations include low stability, poor mechanical properties and rapid degradation. Due to the complexity and variability of natural matrices, chemically defined synthetic hydrogels are gaining popularity. At present, numerous studies have concentrated on developing biologically inspired synthetic materials as replacements for tissue-derived ECM to enable consistent, repeatable, and clinically relevant organoid culture programs. The coupling of synthetic polymers and natural ECM components produces biohybrid hydrogels. These hydrogels have the potential to minimize the disadvantages of pure natural and synthetic hydrogels while combining their advantages. The result should be a series of high-performance hydrogels, but there are still few studies on high difficulty in production and limited material selection. Due to their inherent advantages, synthetic polymer-biohybrid hydrogels have become a prevalent component in organoid scaffolds with the emergence of tissue engineering.

The rapid growth in the number of publications since 2016 suggested that with the development of technology, more and more research were devoted to this field. However, citations began to decline after 2020. It is widely recognized that the publication date has a significant impact on the number of citations. Older studies often tend to have higher citation counts, whereas recently published articles require more time to gain widespread recognition and citations [35]. Articles from recent years need more time to cite.

The H-index represents the highest number of publications and citations achieved by a particular institution, country, or individual. A higher H-index value indicates a greater number of both publications and total citations for that entity [36]. The H-index of the top-15 institutions ranged from 6 "University System of Ohio" to 20 "Harvard University". Among the top 15 research institutions that published the most articles in this field, they were affiliated with the USA (10), Switzerland (2), China (1), England (1), and South Korea (1), indicating that the level of research in North America, Europe, and Asia may be high. Notably, although the number of articles coming out of Massachusetts Institute of technology Mit puts it only in ninth place, its citations per article have reached the highest value of 149, indicating that its papers have a high academic influence in the field. To obtain a more comprehensive evaluation of the most influential institutions in the field, it is reasonable to consider multiple key indicators such as H-index, total citations, and citation per paper.

A total of 48 countries have been involved in hydrogels and organoids research, however, only two of these countries have published more than 100 papers. The distribution of research output among countries and regions were significantly unequal. Except for China, the top 10 countries were all developed countries, highlighting a research gap betwe6en developed and developing countries in this field. Due to their robust economic support and advanced science and technology, developed countries have played a significant role in promoting the development of hydrogels in organoid research and have published numerous related papers. In contrast, progress in developing countries has been comparatively

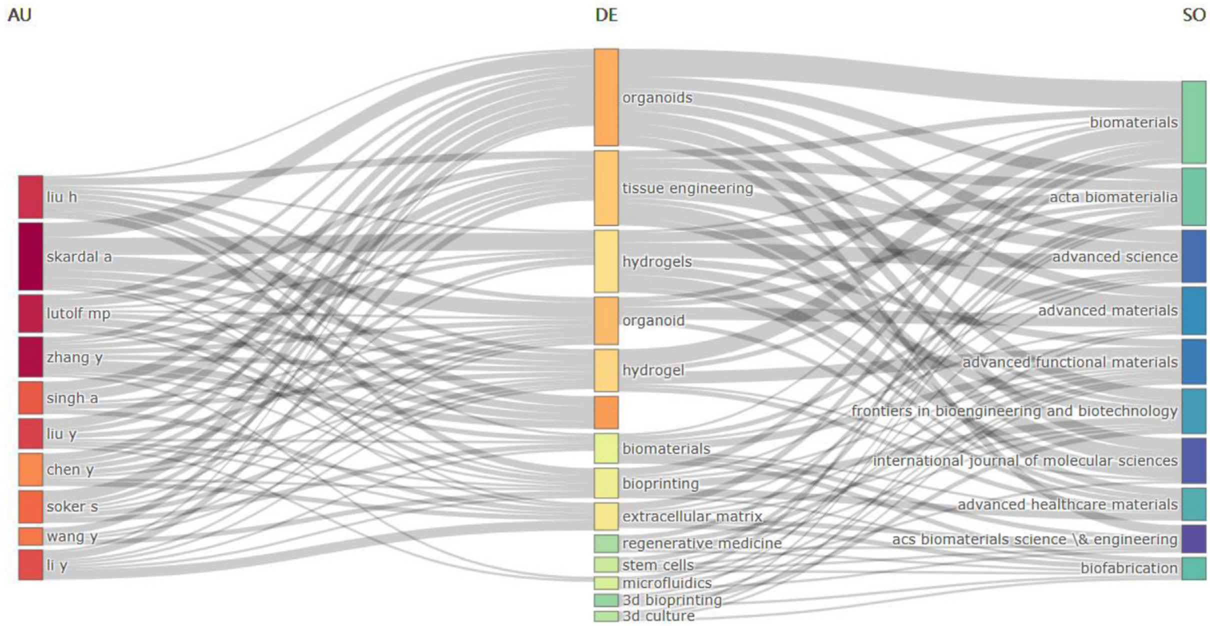

Fig. 5. Three-fields plot for the relationship among top keywords (the middle field), top authors (the left field) and top journals (the right field) in hydrogels for organoids publications.

slower. However, developing countries can seek collaboration with nations possessing greater knowledge in organoid research to expedite their own growth. The accumulation of information, the complexity of research, and the need for specialization necessitate increased international cooperation [33]. Based on the above analysis, we analyzed international cooperation, and built a network visualization map of co-authorship country. TLS is a sign of close cooperation [37]. There were significant differences in the degree of cooperation between different countries. The USA was the focus of research in this field, with the closest cooperation with China. Both China and the USA had made significant contributions to the research on hydrogels and organoids, showcasing a combination of high quality and quantity of work. By intensifying international cooperation and fostering the exchange of ideas, technical expertise, and even financial aid, publications in the field can become more comprehensive, reputable, and of high quality [38].

Among the multi-author papers, the most prolific authors in hydrogels and Organoids research were from USA (Skardal A). Moreover, we found that the author has been focusing on this hot topic, continuing to publish articles. By analyzing the lead authors in this field, we can identify the primary contributors and look for opportunities for further cooperation.

The JCR category and impact factor (IF) are effective indicators for assessing the quality of journals [29]. The IF of the top-10 journal ranged from 5.6 “International Journal of Molecular Sciences” to 29.4 “Advanced Materials”, of which ninth journals were placed in Quartile 1 (Q1) and 1 in Quartile 2 (Q2). This finding indicated that the authors targeted top journals, as the majority of publications on hydrogels and organoids were published in influential and well-known journals. Furthermore, it was also discovered that the number of articles published in Biomaterials far surpassed those published in the second-ranking journal. This observation, coupled with the journal network visualization map and density map, highlights the significant authoritative standing of Biomaterials in the field, indicating its pivotal role in guiding research. These results align with Bradford's law, as deviating from the core journals will result in a decrease in citation frequency for researchers [39]. It is anticipated that in the future, the aforementioned journals will continue to publish an increasing number of papers on the application of hydrogels in the field of organoids.

The keyword analysis is one of the most important indicators of bibliometrics [30]. The three-field plots allow us to quickly discover the keywords most commonly used by each top author and is ideal for finding topics and themes for articles published in top journals in order to provide guidance for submission to specific journals. The most common keywords in the keyword visualization were hydrogels and organoids, indicating that these topics will still be research hotspots in the future. We utilized VOSviewer to color-code the keywords based on the average publication year, as depicted in Fig. 6b. This analysis enables a visual differentiation of the occurrence of keywords, thereby highlighting patterns, evolutionary progressions, and emerging research domains [40]. It was evident that the research emphasis on hydrogels and organoids field has shifted from one pillar to another over the years. Earlier research primarily concentrated on tissue engineering methods and expressions. With the development of defining hydrogels, more and more research is focusing on biomaterials with different properties and more precise 3D bioprinting.

4.1. Limitation

While bibliometrics is a commonly used approach for evaluating the impact of articles, our current research still has several limitations. First, our study specifically focused on English language articles, which may result in the exclusion of relevant studies published in other languages [41]. Second, while older research may attract higher citation counts, it was possible that these older articles may not keep up with the current research trends or hot topics in the field [42]. Finally, self-citation, including authors citing their own publications and selectively citing articles from journals they intend to publish in, might be one of the causes for a large number of citations [34,43]. Despite these limitations, bibliometric

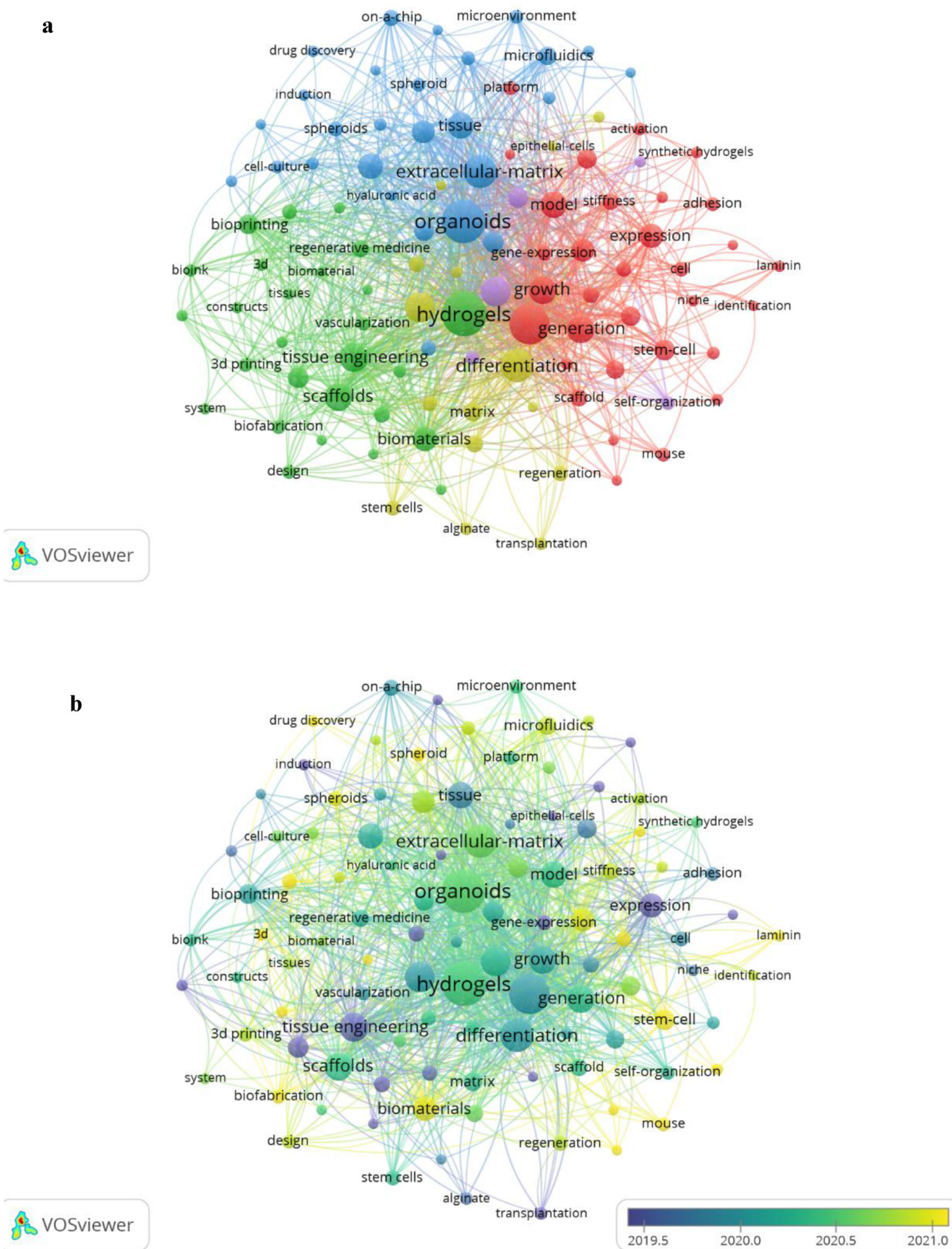

Fig. 6. Keyword analysis. (A) Network visualization map showing cluster analysis of keywords associated with hydrogels for organoids field. The larger the circle is, the words are used more frequently. The curves between the nodes represent the co-occurrence of the two keywords. (B) Network visualization map showing the changing trend of keyword over time. Colors are assigned according to the average year in which keywords appeared in articles. The blue node represents the keywords appearing earlier than the yellow node.

analysis remains a crucial tool for quantifying the number of articles in various disciplines and offering a comprehensive overview of the literature. Our study is the first bibliometric analysis and visualization of hydrogels and organoids, and can also track the research trends and latest hot spots of hydrogels in organoids.

5. Conclusions

Bibliometric analysis employs mathematical and statistical methods to assess scholarly outputs. This study represents the first bibliometric analysis focusing on research and visualization mapping of the application of hydrogels in the field of organoids. It provides comprehensive insights into published literature and offers an overall perspective on the research landscape. Biomaterials, Acta Biomaterialia, and Biofabrication are identified as the most relevant journals in hydrogels and organoids research field. The USA has consistently been at the forefront of this field and will continue to do so in the foreseeable future. It is essential to enhance scientific research collaboration, and developing countries should actively foster close cooperation with the USA and other developed nations. Furthermore, the focus of research in this field is gradually shifting from tissue engineering methods to more mature biomaterial hydrogels with different properties and more accurate 3D bioprinting.

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Author contributions

Jia-bo Wang, Jie Wu: Protocol/project development, Data analysis, Manuscript writing.

Jian Zhang, Ke-yan Zhu, Bo Meng, Sheng Yang, and Yu Zhang: Data collection or management, Data analysis.

Hua Sun, Wenjie Zhao, Li-an Guan, Hai-bo Feng and Qing Peng: Assist in the literature searching based on WOS, Data analysis.

Ye-dong Yang, Liang Zhang: Protocol/project development, Data analysis, Manuscript editing.

All the authors are agreed and approved the final manuscript for publication.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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