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► **To cite this version:**

Xinyan He, Wen Wu, Yuchen Hu, Meiling Wu, Hong Li, et al.. Visualizing the global trends of peptides in wound healing through an in-depth bibliometric analysis. *International Wound Journal*, 2023, 10.1111/iwj.14575 . hal-04439892

HAL Id: hal-04439892

<https://hal.univ-lorraine.fr/hal-04439892>

Submitted on 5 Feb 2024

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Visualizing the global trends of peptides in wound healing through an in-depth bibliometric analysis

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Funding information

Chongqing Jiangjin District Science and Technology Project, Grant/Award Number: Y2022072; Chongqing Key Specialty of Clinical Pharmacy; Fundamental Research Funds for the Central Universities, Grant/Award Number: 2022CDJYGRH-017

Abstract

Wound healing is a complicated and multistage biological process for the repair of damaged/injured tissues, which requires intelligent designs to provide comprehensive and convenient treatment. Peptide-based wound dressings have received extensive attention for further development and application due to their excellent biocompatibility and multifunctionality. However, the current lack of intuitive analysis of the development trend and research hotspots of peptides applied in wound healing, as well as detailed elaboration of possible research hotspots, restricted obtaining a comprehensive understanding and development in this field. The present study analysed publications from the Web of Science (WOS) Core Collection database and visualized the hotspots and current trends of peptide research in wound healing. Data between January 1st, 2003, and December 31st, 2022, were collected and subjected to a bibliometric analysis. The countries, institutions, co-authorship, co-citation reference, and co-occurrence of keywords in this subject were examined using VOSviewer and CiteSpace. We provided an intuitive, timely, and logical overview of the development prospects and challenges of peptide application in wound healing and some solutions to the major obstacles, which will help researchers gain insights into the investigation of this promising field.

KEYWORDS

bibliometric analysis, peptide, research hotspots, visualisation, wound healing

Key Messages

- We conducted a comprehensive analysis of countries, institutions, authors, journals, co-occurrence of keywords, and co-citation references in this field from 2003 to 2022. Simultaneously, multiple visualisation results revealed the bibliometric characteristics of the field, including network visualisation maps, cluster analysis, timeline view, and citation bursts of the references and keywords, which were presented utilizing various scientific bibliometric tools.

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- In general, studies involved in the mechanism of peptides for wound healing and peptide-based drug delivery or biomaterials such as scaffolds are current research topics. Additionally, the top countries, institutions and researchers with the most production should enhance international cooperation, which will greatly benefit the development of this field.

1 | INTRODUCTION

Wound management is a major challenge worldwide, placing a huge health and financial burden on each nation's government.^{1,2} Chronic wounds, such as burns and diabetic wound healing, will lead to amputation in severe cases, and patients suffer greatly and live at risk.^{3,4} Therefore, increasing attention has been paid to wound dressing development.⁵ However, there is still a lack of precise targeted treatments for wound healing and an urgent need to find effective strategies.⁶ Wound repair process is complicated and multistage⁷ and typically involves four significant overlapping stages, including haemostasias, inflammation, proliferation and remodelling.^{8,9} However, wounds are associated with pre-existing conditions that may be triggered by external events, such as vascular disease, metabolic disorders, aging, smoking and immune suppression, which subsequently lead to chronic wounds.^{10,11} Chronic wounds are associated with persistent bacterial biofilm infection and vasculopathy, resulting in a prolonged inflammatory phase and longer healing cycles than normal wounds.^{12,13} The clinical treatments for chronic wounds include debridement, antibiotics, hypoglycemic and vasodilatory drugs, and the efficiency of the treatment is still limited and prone to drug resistance.^{14–16} Besides, some advanced biomaterials and technologies were developed in Lab for promoting chronic wound healing, such as carboxymethyl chitosan-based biomaterials^{17,18} and electrets.¹⁹ Unfortunately, the efficiency of the treatment is still limited and prone to drug resistance.

Peptide-based wound dressings have emerged to provide a new strategy for wound management.²⁰ Peptides exist widely in amphibians as well as in artificial designs, with various activities to promote wound healing,²¹ including, but are not limited to, antibiofilm, anti-inflammatory, haemostasis, and pro-proliferation properties.²² For instance, a variety of natural peptides (e.g., OA-GL12, RL-QN15, and Ot-WHP) are derived from skin secretions with the function of accelerating wound healing.⁷ Other natural peptides, such as epidermal growth factor and fibroblast growth factor,²³ could improve wound proliferation and tissue remodelling. In addition, antimicrobial peptides are another potential antibiotic and novel strategies in the treatment for wound healing.^{24,25} typical natural antimicrobial peptides from human skin (e.g., human β -defensin 3)

and bee venom (e.g., melittin). Even though natural peptides were multi-function and good biocompatibility, the poor stability and hemolytic toxicity limit the clinic application. To improve the therapeutic efficiency, large quantities of artificial peptides were designed and modified based on the natural peptides' derivative. For example, the cationic peptide-based hydrogels MARG1 have inherent antibacterial activity,²⁶ and conjugating peptide QK with RADA16 can effectively promote angiogenesis.²⁷ Additionally, the composition of peptides is closely related to the shape and biological function. Peptides have recognizable characteristics with a variety of sequences and structures, promising them various biological activities and different shapes. Generally, due to α -helix and β -sheet conformations, hydrophobic effect and electrostatic forces, the structure of self-assembly peptides including nanotubes, nanospheres, fibre bundles, and 3D network-nanofibers.⁷ Therefore, peptide-based molecules and drug delivery have also shown considerable potential for multimodal treatment due to their multifunctionality, good biocompatibility, various forms, and ease of design and synthesis during complicated wound processes.^{10,28,29} For instance, lots of bionic hydrogel constructed by self-assembly peptides for skin wound healing,³⁰ spinal cord regeneration³¹ and liver injury.³² Although various reviews have focused on the application of peptides in wound healing, there is a lack of comprehensive analysis to clarify the current trends and hotspots.¹⁶

Recently, an increasing number of researchers have studied the development process and structural relationship of scientific knowledge using bibliometric analysis,^{33,34} which is an interdisciplinary subject that can be utilized to conduct quantitative and qualitative analyses of scientific publications from related meta-data.^{35,36} To further understand the development of peptides in the wound healing treatment field, we comprehensively searched the relevant literature from the Web of Science (WOS) database. Then, these publications were visually bibliometrically analysed based on VOSviewer and CiteSpace in terms of sources, the contribution of journals, authors, co-citations, the cooccurrence of keywords, and the research trends. A flowchart describing the mining and analysis process for this topic is presented in Figure 1. Hence, the present study aimed to examine publication trends in peptide and wound healing and provide future research direction.

FIGURE 1 Scheme of mining and analysing data.

Data Collection	Data Collation	Data Analysis
Data Source	Exclusion criteria	Analysis Project
Web of Science Core Collection (SCI-Expanded & SSCI)	(1) Retraction or unpublished paper (2) Lack of basic information for bibliometric analysis	(1) Annual publication/citation analysis (2) Co-authorship analysis and collaboration map (3) Journal performance analysis (4) Co-occurrence and clustering analysis of keywords (5) Analysis of highly cited publication
Search Strategy	De-duplication	
TS= (peptides) AND TS= (wound healing) AND TS= (wound repaired) OR (peptides wound healing) OR (peptides wound repaired)	R-bibliometrix & Citespace	
Timespan	Data	
2003.01.01 to 2022.12.31	Data related to 3D printing in the drug research filed (n=3263)	
Publication Type		Analysis Tool
Article and Reviews		VOSviewer, Citespace, Bibliometrix R Package, Origin, excel, Tableau
Language		
English		

2 | MATERIALS AND METHODS

2.1 | Data source

The WOS database is the most frequently utilized database in bibliometric studies.³⁷ In this study, all data were sourced from the WOS and downloaded in plain text format. The search strategy that we used in the WOS database Core Collection, including Science Citation Index Expanded (SCI-Expanded) and Social Sciences Citation Index (SSCI), is as follows: TS = (peptides) AND TS = (wound healing) AND TS = (wound repaired) OR (peptides wound healing) OR (peptides wound repaired). After that, we screened target papers based on¹ Document type: “Article” and “Review,” excluded books, corrections, letters, conference materials, and retracted papers²; Publication date: January 1, 2003, to December 31, 2022³; Language: English. This work was completed on June 6, 2023. A flowchart describing the mining and analysis process for this topic is presented in Figure 1. Ultimately, a total of 3263 original articles and reviews met the criteria for inclusion in the analysis, and further visual analyses were performed.

2.2 | Bibliometric analysis

Bibliometric analysis methods were applied in this study. Bibliometric analysis is one of the most recent scientometric disciplines and can keep abreast of comprehensive research and technology via the qualitative and quantitative analysis of scientific publications from related

metadata such as abstracts, keywords, citations, and so forth.³⁸ The bibliometric mapping tool VOSviewer and citation visualisation analysis tool CiteSpace are used to visually represent the scientometric analysis results and facilitate visual interpretations, respectively. Additionally, R-bibliometrix was used to analyse the research trends.

CiteSpace is a Java-based bibliometric analysis tool that is widely utilized for the visual exploration of scientific literature and helps to discover research hotspots and future trends.^{39,40} Network visualisation in CiteSpace demonstrates how knowledge is managed, organized, and dispersed. In this study, we used CiteSpace (version 6.1. R4, Drexel University, Pennsylvania, United States) for countries/regions, references, and journal analyses. In addition, we investigated the citation burst of literature and keywords and conducted cluster analysis to reflect the recurrent new references and keywords. In addition, we created the time zone perspective to analyse research development over time. Another bibliometric analysis tool, VOSviewer, is usually utilized for creating and visualizing bibliometric maps, providing comprehensive and in-depth bibliometric analysis through graphical cross-linking maps and quantitative information based on the connection.³⁷ We mainly applied VOSviewer (version 1.6.19, Leiden University, Leiden, Netherlands) for institutional collaboration and co-authorship bibliometric analysis. Regarding the visualizing maps produced by those programs, each node corresponds to a specific parameter such as institutions or authors, and the node sizes are determined by weighing the attributes, such as the number of publications, frequency of occurrence, or the number of citations. The size of the node represents

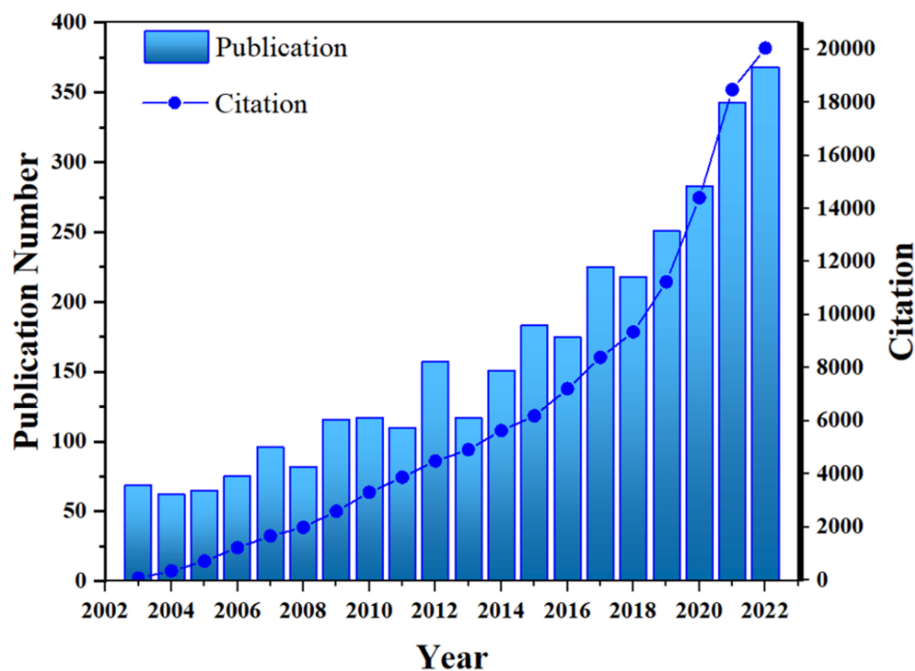


FIGURE 2 Global publication output and citation trend on peptide in wound healing from 2003 to 2022.

the count or frequency of the publications or citations. The links are depicted by the line connecting the node. The strength of the connections was assessed using the index of total link strength (TLS), which is the sum of the link strengths between each item. Research trends are shown by the clusters, which are distinguished using different colours.

3 | RESULTS

3.1 | Global trend in publication outputs

We obtained 2679 articles and 584 reviews meeting the inclusion and exclusion criteria from the WOS database in our bibliometric analysis. Figure 2 presents the past 20 years' worldwide trend in publications and total citations of peptide research in wound healing from 2003 to 2022. The number of published global articles showed a gradually increasing trend and steadily rose from 69 in 2003 to 368 in 2022, with a 26.67% annual growth rate. Especially beginning in 2018, there was a noticeable increase in the annual volume of publications. Accounting for approximately half of all publications between 2003 and 2022. In addition to the development of the number of publications, we also analysed the increase in the amount of cited information in Figure 2. All articles have been cited 134 740 times during the period from 2003 to 2022, with an average annual citation frequency of 6737 and 41.28 average citations per document. This rapid count of articles and citations in the peptide and wound healing field indicated that related research topics

are increasingly attractive, and more researchers prefer to focus on this exploration.

3.2 | Distribution of countries and regions

There were 81 countries or regions that contributed to publications in the field of peptide and wound healing. The distribution and the total number of publications are shown on the world map in Figure 3. According to the geographical distribution in the global articles' productivity map, North American countries (United States and Canada), Asian countries (such as China, Japan and South Korea), European countries (such as Germany, Italy and England), and Australia are actively involved in research in this field. Table 1 lists the top 10 countries/regions with high publication productivity related to this topic. The top 10 countries with the most articles are the United States (1008 records), China (762 records), Germany (213 records), Japan (200 records), Italy (179 records), South Korea (159 records), England (142 records), Canada (141 records), India (131 records), Australia (87 records), and Germany (213 records) respectively.

The annual publication numbers in these nations/regions throughout the period from 2003 to 2022 are presented in Figure 4A. Obviously, between 2003 and 2018, the United States consistently had the highest number of annual publications. However, China's annual publication volume gradually climbed after 2018 and began to overtake the United States as the country with the

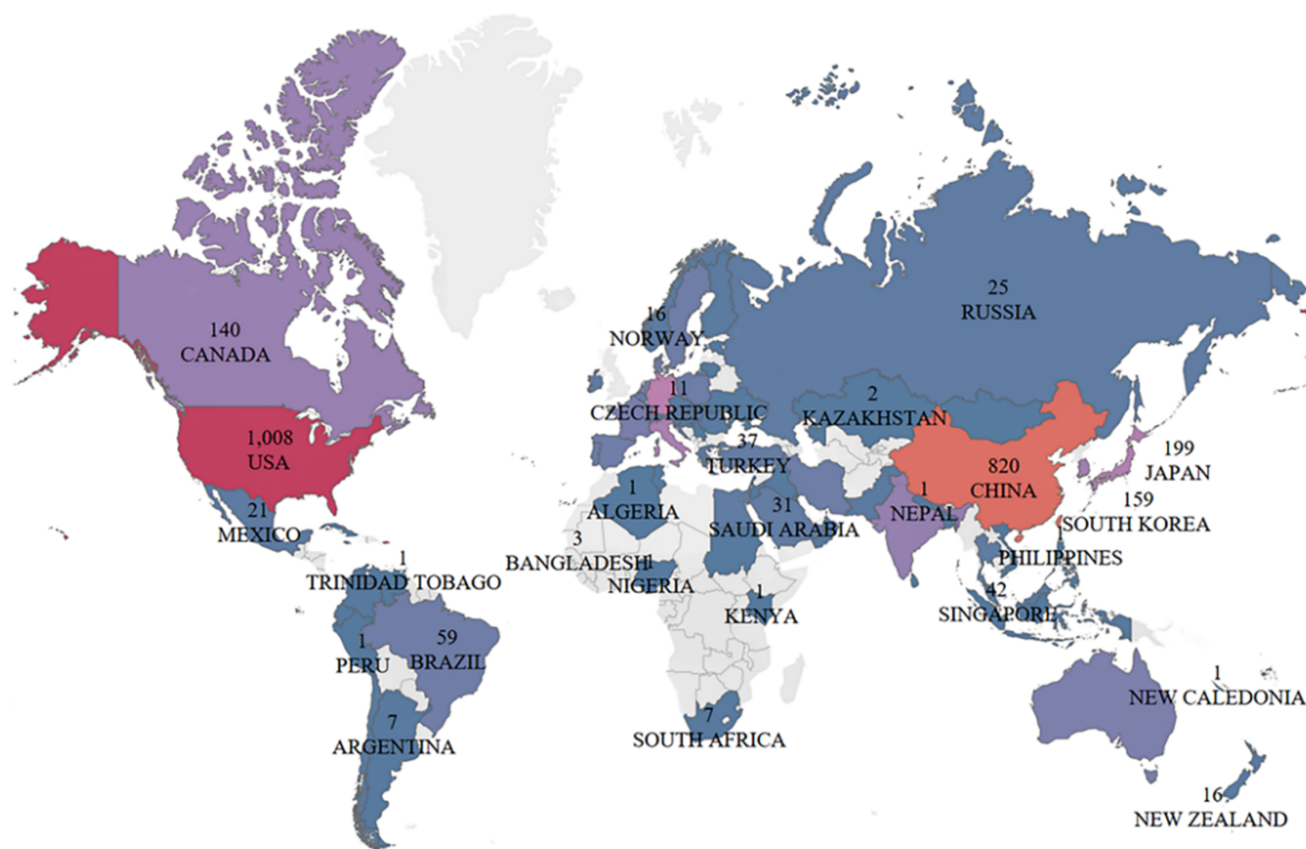


FIGURE 3 Interactive map based on the total publications of different countries/regions.

TABLE 1 The top 10 most productive countries/regions in peptides research in wound healing.

Rank	Country	Publications	Percentage	H-index	Total citations	Average citation per paper	Total link strength (TLS)
1	United States	1008	30.89	112	54 838	54.40	476
2	China	762	23.35	66	19 311	23.55	219
3	Germany	213	6.53	59	14 391	67.56	153
4	Japan	200	6.13	43	6975	34.88	85
5	Italy	179	5.49	48	8281	46.26	119
6	South Korea	159	4.87	34	3958	24.89	60
7	England	142	4.35	51	8420	59.30	148
8	Canada	141	4.32	50	11 074	78.54	102
9	India	131	4.02	30	3224	24.61	70
10	Australia	87	2.67	31	3451	39.67	74

highest annual number of publications. Figure 4B displays all countries with publication percentages related to peptides for wound healing. Clearly, the United States dominates the rankings based on records, followed by China and India. Among them, the total publication percentage of the United States and China reached 54.24%. When compared to the number of publications, citation

frequency is commonly considered a better indicator to evaluate the performance of scientific research. In contrast to output ranking, rankings based on citation characteristics fluctuate to variable degrees. For instance, when ranking by total citations, the United States received the most citations (54 838 times), followed by China (19 311 times) and Germany (14 391 times).

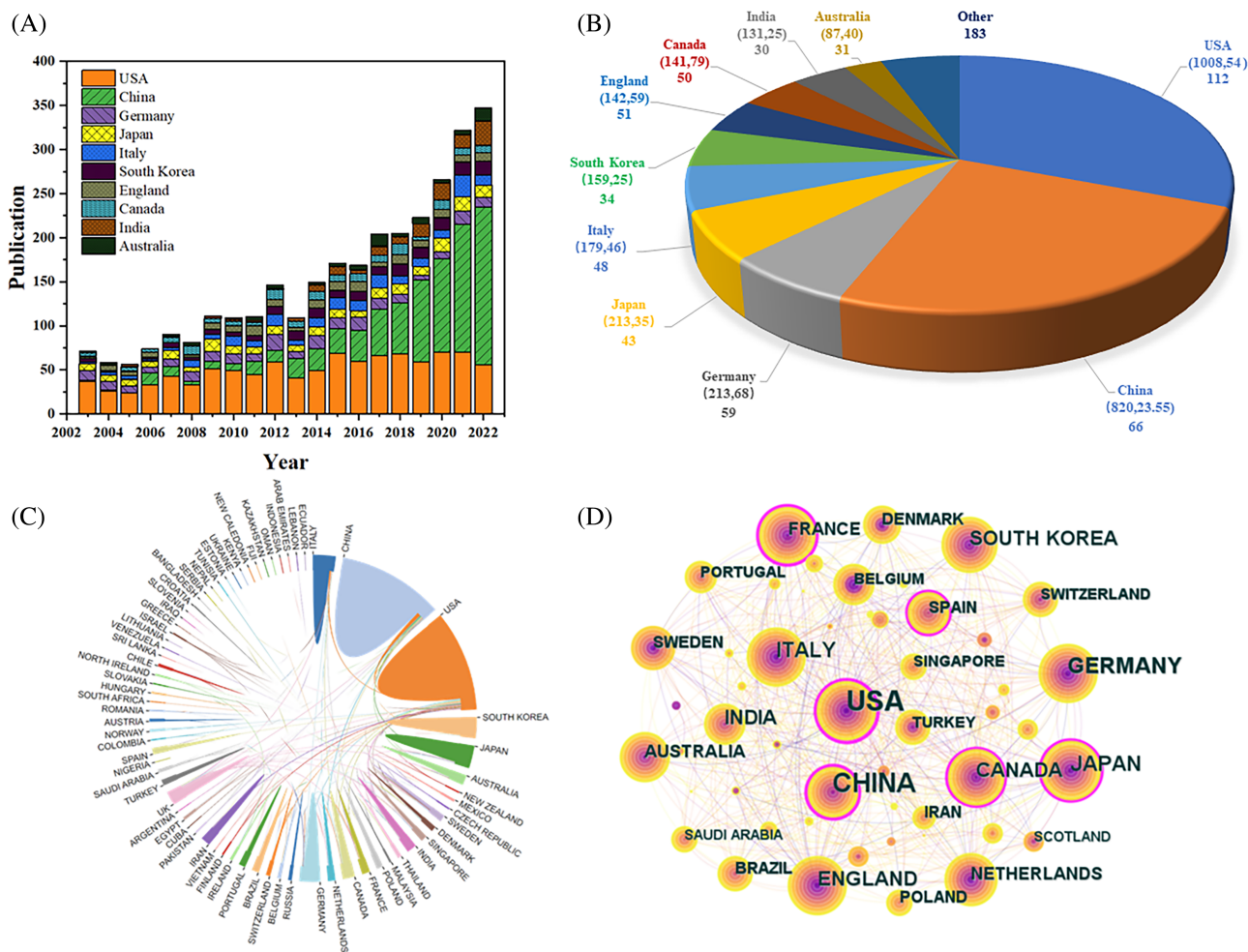


FIGURE 4 (A) The changing trend of the annual publication quantity in the top 10 countries/regions from 2003 to 2022; (B) Distribution of publications in countries/regions. The number in the brackets goes: (publication number, Average per item). The lowest number represents the h-index; (C) The international collaborations' visualisation map of countries/regions; (D) Network visualisation showing the relationship between countries.

However, when ranking by citations per item, Canada (79 citations) occupies an absolute leading position despite a relatively lower number of publications. In addition, the h-index, as a basic and effective indicator to measure academic achievement, is introduced to quantify the impact and performance of scientific research, with a higher h-index indicating a greater impact. As expected, the United States (112) and China⁶⁶ are the leading countries in terms of the h-index hierarchy. Hence, the comprehensive data of publication count, citation and h-index demonstrated the positive influence and importance of United States and China in peptides for wound healing treatment.

Figure 4C showed the international collaborations' visualisation map of countries/regions. And Figure 4D exhibited the relationship network between countries through visualisation map on CiteSpace. The size of the nodes represented the number of papers, and the line

thickness of the net showed cooperation strength. The network displayed that the United States with the most publications and had the strongest links with other countries. The index of TLS was used to assess the strength of the connections, reflecting the collaborative relationships throughout countries or institutions. From the visualisation network, the United States (TLS = 476) and China (TLS = 219) had the highest TLS and strongest international collaboration. Accordingly, the United States was the most influential in the field of peptide and wound healing based on publications.

3.3 | Contributions of institutions

In the field of peptide and wound healing, 1674 institutions contributed 3263 articles. According to the number of publications, Table 2 presents the top 10 producing

TABLE 2 The top 10 most productive institutions in peptides research on wound healing.

Rank	Institution	Country	Publications	Centrality	Sum of the Times Cited	Average Citations per Item	Total link strength (TLS)
1	Chinese Academy of Science	China	62	0.11	1990	32.10	90
2	Harvard University	United States	41	0.19	3884	94.73	58
3	Shanghai Jiao Tong University	China	36	0.04	1047	29.08	37
4	University of Michigan	United States	35	0.14	2432	69.49	43
5	University of California, San Diego	United States	34	0.17	4299	126.44	28
6	Zhejiang University	China	30	0.02	739	24.63	25
7	Shandong University	China	29	0.01	507	17.48	25
8	MIT	United States	28	0.05	2380	85.00	31
9	Seoul National University	Korean	26	0.04	619	23.81	13
10	University of Illinois	United States	26	0.01	608	23.38	17

institutions. Among them, the United States and China had the large bulk of the institutions engaged in scientific research related to this topic, and most articles were produced by the Chinese Academy of Sciences (62 items), Harvard University (41 items), Shang Hai Jiao Tong University (36 items), University of Michigan (35 items), University of California, San Diego (34 items), Zhejiang University (30 items), Shandong University (29 items), MIT (28 items), Seoul National University (26 items), and University of Illinois (26 items). The top 10 universities contributed 347 articles and 10.63% of the publications. There were significant fluctuations in the rankings of institutions based on citations and citations per paper; for instance, the University of California, San Diego, has the most citations and citations per document, despite having a relatively small number of publications.

Figure 5 visually displays the overlay visualisation map for investigating institutional collaboration produced by VOS viewer, including institutions with at least five publications, and the network map contains 222 nodes and 806 linkages. Each circle node denotes one institution, and the lines separating the circles signify collaboration among facilities. Thicker lines indicate closer collaboration, whereas different colours from green to yellow represent the change in publication time from 2003 to 2022. In the last 5 years, there was a significant increase in the number of articles published by Chinese research institutions. Moreover, the TLS reflected the strength of the connections between facilities. The

visualisation also showed that the Chinese Academy of Sciences (TLS = 62), Harvard University (TLS = 41), and Shang Hai Jiao Tong University (TLS = 36) are the top three institutions with the most publications and the highest TLS. Meanwhile, it is clear that the Chinese Academy of Sciences worked closely with numerous internal academic institutions and research facilities, such as Kunming Medical University, as well as with international organizations from the United States and other Asian nations.

3.4 | Author and co-cited author analysis

Concerning authors, a total of 17 302 writers contributed to 3263 articles in the field of peptide and wound healing. The top 10 most productive authors related to our topic published 147 articles with a total of 7621 citations, which are listed in Table 3. Separately, they are Wang, Ying (18 items), Yang, Xinwang (16 items), Tang, Jing (15 items), Gallo, Richard L (14 items), Gourdie, Robert G (14 items), Nishida, Teruo (14 items), Niyonsaba, Francois (14 items), Ogawa, Hideoki (14 items), Mangoni, Maria Luisa (13 items), Nusrat, Asma (13 items). The top three authors with the most papers contributed considerably to this area, and they are all from YunNan province, China. Meanwhile, the three writers Yang, Xinwang (TLS = 121), Wang, Ying (TLS = 116), and Tang, Jing (TLS = 94) had the strongest TLS, indicating their active

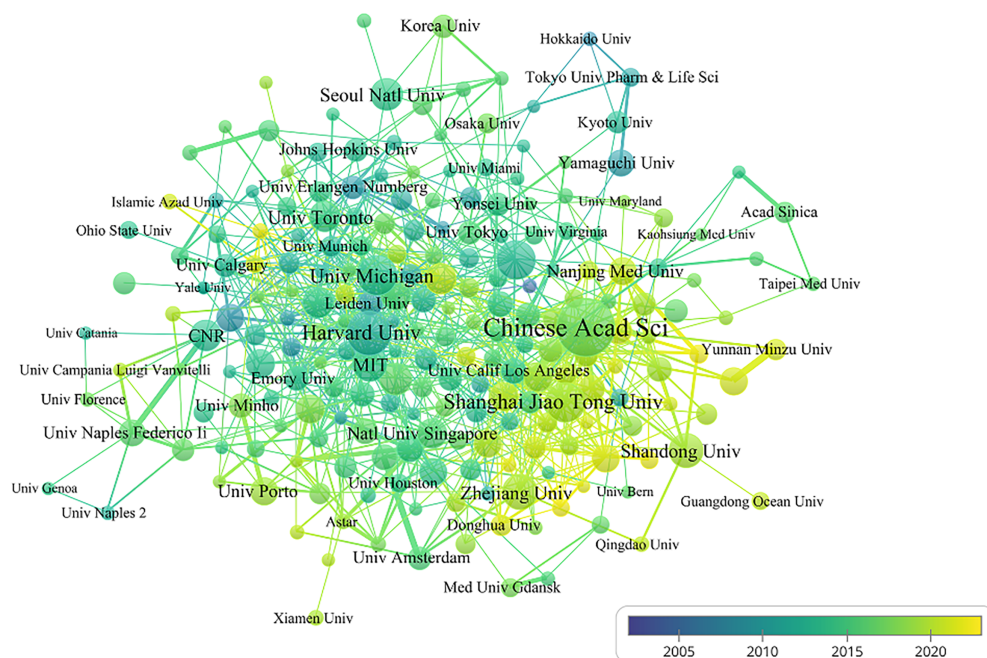


FIGURE 5 The institutions' collaboration overlay visualisation map from 2003 to 2022.

TABLE 3 The top 10 most productive authors in peptides research in wound healing.

Rank	Author	Institution	Publications	Total citations	Average citation per paper	Total link strength (TLS)
1	Wang, Ying	Yunnan Minzu University	18	295	16.39	116
2	Yang, Xinwang	Kunming Medical University	16	251	15.69	121
3	Tang, Jing	Kunming Medical University	15	436	29.07	94
4	Gallo, Richard L	University of California, San Diego	14	2001	142.93	2
5	Gourdie, Robert G	Virginia Polytechnic Institute & State University	14	678	48.43	12
6	Nishida, Teruo	Kindai university	14	365	26.07	23
7	Niyonsaba, Francois	Juntendo University	14	834	59.57	41
8	Ogawa, Hideoki	Juntendo University	14	834	59.57	41
9	Mangoni, Maria Luisa	Sapienza University of Rome	13	662	50.92	16
10	Nusrat, Asma	University of Michigan	13	1265	97.31	27

collaboration with each other researchers. It is also worth noting that Gallo, Richard L had the most total citations (2001 times) and average citations per paper (143 times). Figure 6 shows a visualisation network of the author involved in the study of peptide and wound healing using VOSview, including the authors with at least five publications.

Different from the visualisation map of the institutions, the network's clustering was introduced to the analysis of the connections of authors. In Figure 6, different colours denote different clusters, and there were 13 clusters, 124 nodes and 490 links. The modularity Q value and Silhouette value, as the basic indicators, were

employed to gauge the network's clustering effect and homogeneity, respectively. A Q value higher than 0.3 implies that the community structure is consequential; an S value higher than 0.5 indicates that clustering is credible, and an S value higher than 0.7 means that clustering is persuasive.²⁸ The modular Q value was 0.9564, and the mean silhouette S value peaked at 0.9773 (Figure S1), indicating outstanding network homogeneity and clustering impact.

Co-cited authors referring to more than two authors are cited simultaneously in one or even more works. Table 4 shows the top 10 cited writers, and the visualisation network of the co-cited author is shown in

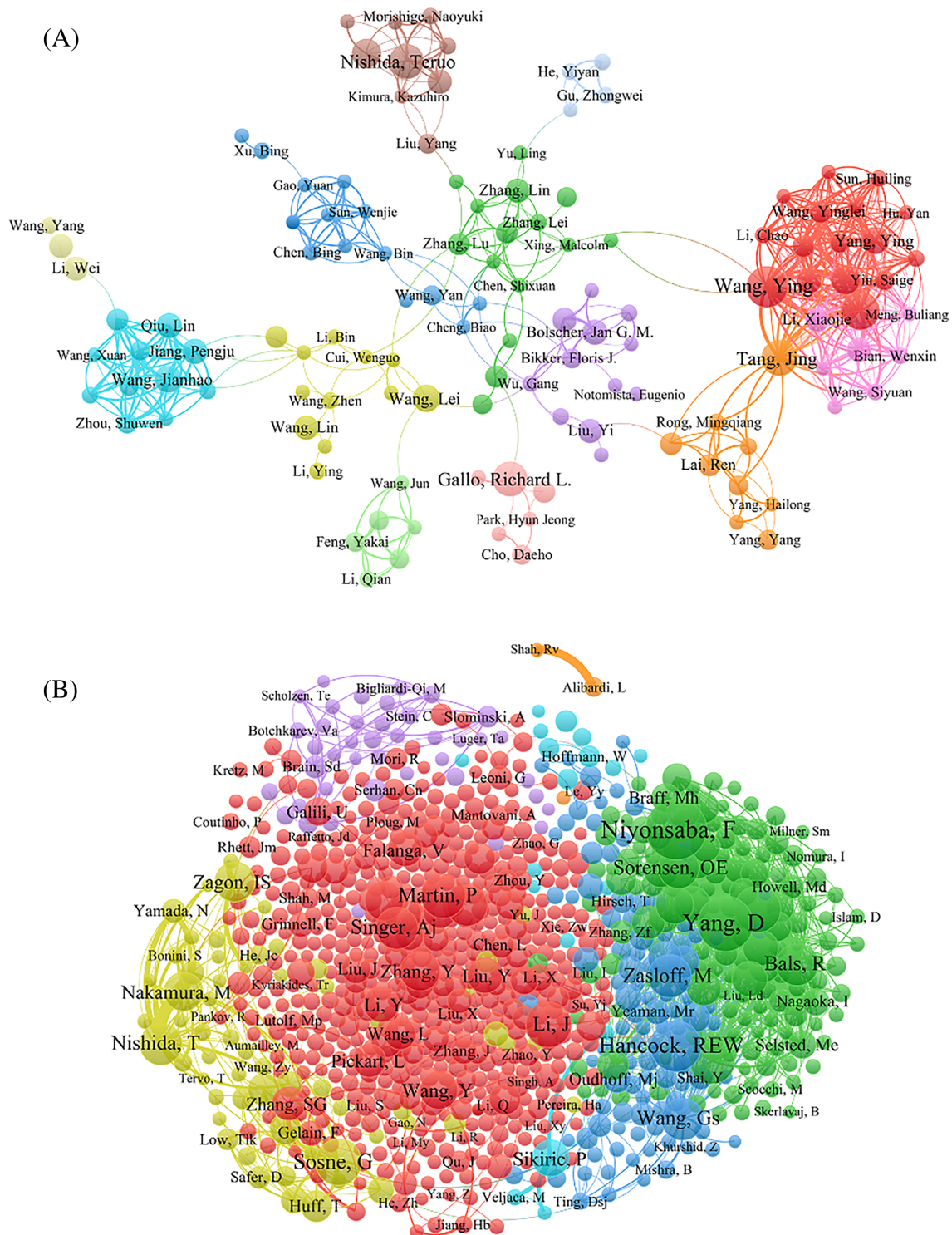


FIGURE 6 The visualisation map of co-authorship (A) and co-citation (B) analysis of authors.

Figure 6B. The most notable nodes were associated with Niyonsaba, F (367 times), Yang, D (308 times), and Hancock, REW (264 times), who received the most co-citations. Regarding the clustering impact of the co-cited author, the modular Q value was 0.9108, and the mean silhouette S value peaked at 0.9439.

3.5 | Distribution of source journals and the top 10 high-cited articles

A total of 3263 articles related to peptide and wound healing published in 1064 journals. Table 5 lists the top 10 journals with the most articles published, accounting for

Rank	Author	Total citations	Total link strength (TLS)
1	Niyonsaba, F	367	15 848
2	Yang, D	308	14 381
3	Hancock, REW	264	9111
4	Harder, J	228	11 094
5	Sosne, G	225	5300
6	Li, J	209	4969
7	Martin, P	203	3321
8	Ganz, T	199	9492
9	Zasloff, M	196	7038
10	Nishida, T	185	6064

TABLE 4 The top 10 highly co-citations authors in peptides research on wound healing.

TABLE 5 The Top10 most productive journals related to peptides and wound healing.

Rank	Journal	Publications	Total citations	Average citation per paper	Total link strength (TLS)	IF	JCR
1	Plos One	79	2557	32.3671	277	3.7	Q2
2	Wound Repair and Regeneration	55	2040	37.0909	224	2.9	Q3
3	Acta Biomaterialia	54	2781	51.5	242	9.7	Q1
4	Scientific Reports	52	1103	21.2115	144	4.6	Q2
5	International Journal of Molecular Sciences	49	957	19.5306	154	5.6	Q1
6	Biomaterials	43	3177	73.8837	138	14	Q1
7	International Journal of Biological Macromolecules	36	771	21.4167	95	8.2	Q1
8	Journal of Biological Chemistry	34	2540	74.7059	72	8.2	Q1
9	Peptides	34	1219	35.8529	188	3	Q3
10	Journal of Investigative Dermatology	32	2658	83.0625	298	6.5	Q1

14.25%. Plos One was the most productive journal, with 79 articles published, followed by Wound Repair and Regeneration (55 articles), Acta Biomaterialia (54 articles), Scientific Reports (55 articles), International Journal of Molecular Sciences (49 articles), and Biomaterials (43 articles). Ranking based on the citation count, Biomaterials (3177 times), Acta Biomaterialia (2781 times), and Journal of Investigative Dermatology (2658 times) were the top three journals. Although they did not have the most publications, they both have higher JCR quartile rankings (Q1) and impact factor (IF). The top 10 co-cited journals are presented in Table 6. The most co-cited journal was Journal of Biological Chemistry (6151 times), followed by Proceedings of the National Academy of Sciences of the United States of America (4006 times), Biomaterials (3664 times), and Journal of Investigative Dermatology (3423 times).

The visualisation networks of the journals and co-cited journals related to the study of peptides and wound

healing are presented in Figure 7 and Figure 8, respectively. The size of the nodes denotes the citation frequency, and the thickness of the link represents close cooperation. The red circles indicate journals that have suddenly exploded in co-citation in recent years. The analysis of publications' journals and co-cited journals involved in peptide and wound healing indicated that articles on this topic mainly focused on journals in biology, materials, dermatology and immunology, and the cross reference between journals in different disciplines is gradually increasing.

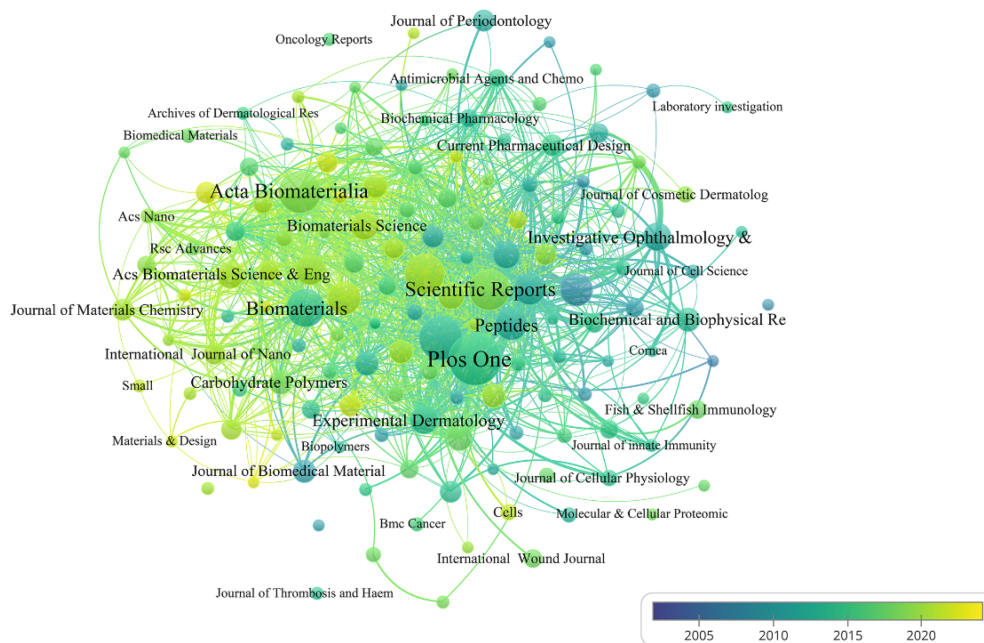
3.6 | Keywords analysis of research hotspots

The research areas of interest, hotspots, and future research directions in this discipline can be identified

TABLE 6 Top10 journals with most co-citation related to peptides and wound healing.

Rank	Journal	Total citations	Total link strength (TLS)	IF	JCR
1	Journal Of Biological Chemistry	6151	571 143	8.2	Q1
2	Proceedings of the National Academy of Sciences of the United States of America	4006	391 730	11.1	Q1
3	Biomaterials	3664	337 448	14	Q1
4	Journal of Investigative Dermatology	3423	353 482	6.5	Q1
5	Journal of Immunology	3129	371 831	4.4	Q2
6	Nature	2703	281 191	64.8	Q1
7	Plos One	2589	245 751	3.7	Q2
8	Science	2239	220 458	56.9	Q1
9	Wound Repair and Regeneration	2049	155 390	2.9	Q3
10	Journal of Clinical Investigation	1916	186 135	15.9	Q1

FIGURE 7 The visualisation map of published journal analysis.



through keyword bibliometric analysis. It is important to define the important research trends and summarize the perspective for studies on peptides in the wound treatment field by analysing the associated keywords. There were 13 823 keywords extracted from 3263 selected articles, and 1235 keywords appeared over five times. Figure 9A, B displays the density visualisation and network visualisation map using VOSviewer and CiteSpace, respectively. The top 10 keywords with the most occurrences were “wound healing” (702 items), “expression” (597 items), “in vitro” (366 items), “antimicrobial peptides” (331 items), “angiogenesis” (294 items), “inflammation” (267 items), “peptide” (266 items), skin (263 items), “cells” (250 items), and “peptides” (233 items). Obviously, the antimicrobial peptides were studied with the highest frequency among various

peptides, and skin wound healing was one of the main research directions. In addition, in vitro experiments were the most conducted and the most research therapeutic targets were focused on the regulation of antimicrobial, angiogenesis and inflammation.

Figure 9C exhibited the keywords clusters, with each cluster displaying a different colour and demonstrating how the keywords were grouped into different clusters. The first 15 cluster labels (#0–#14) were selected for further analysis. The top three clusters were “human beta defensin”, “delivery”, and “cell migration”, 15 clusters mainly focused on 3 directions¹: exploration of numerous peptides, including clusters #0, #8, and #11²; mechanism of peptide in wound healing, including clusters #2, #3, #4, #5, #6, #7, #9, #10, #12, #13 and #14³; delivery of peptides, including clusters #1. Figure 9D presented the clustering time map,

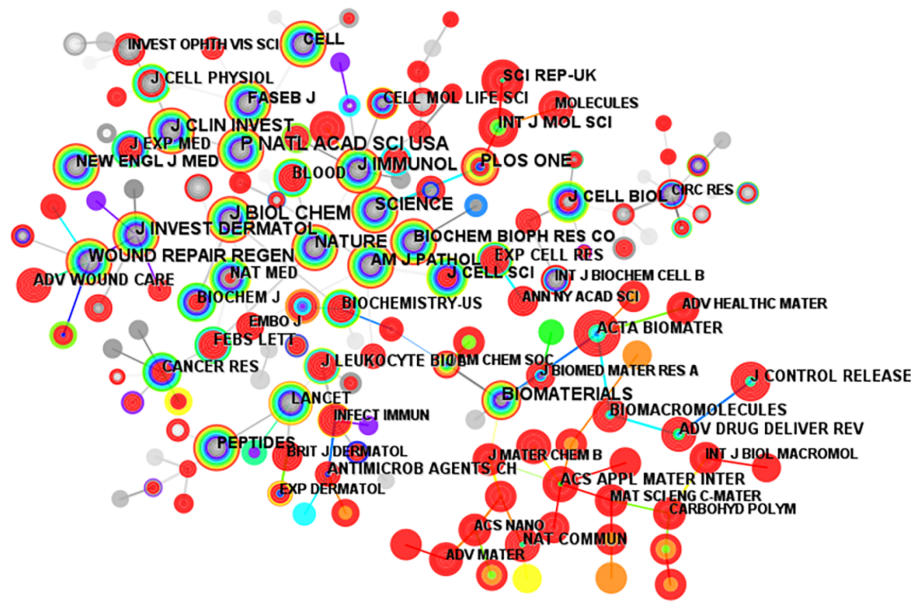
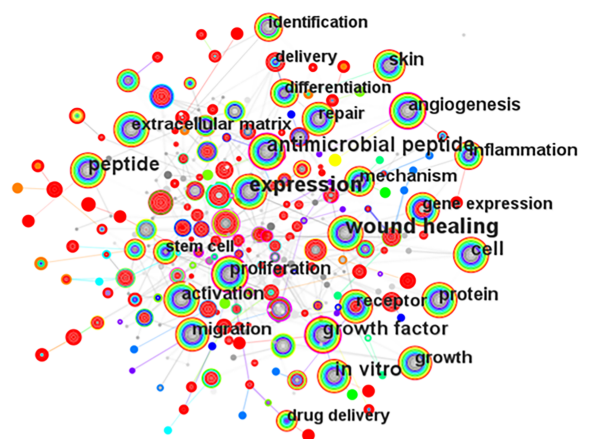


FIGURE 8 The visualisation map of journal co-citation analysis.

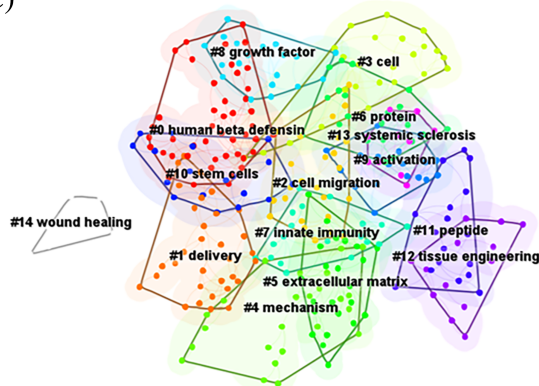
(A)



(B)



(C)



(D)

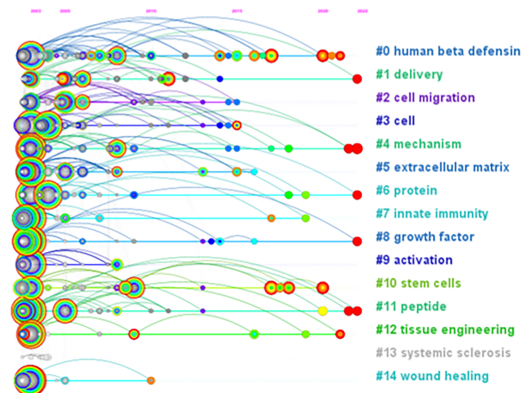
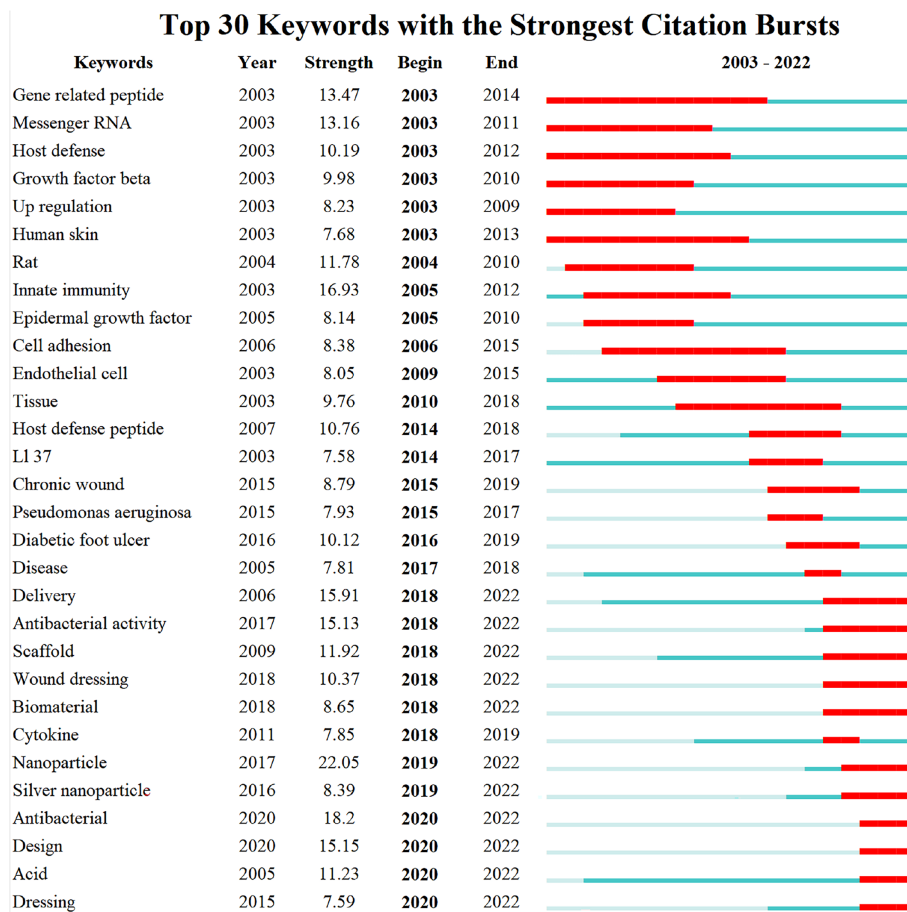


FIGURE 9 Visualisation analysis of keywords, including the density (A) and network visualisation map of keyword (B); Map of keyword clusters (C); Timeline view of keyword co-occurrence (D).

FIGURE 10 Top 30 keywords with the strongest citation bursts.



which helps to show the occurrences and bursts of each cluster specifically, and the appearance, end and time trends can reflect the importance, degree, and distribution period of a cluster. From 2003 to 2022, the keywords in cluster “#0 human beta defensin” were always a hot spot for peptides and wound healing research. Furthermore, the study related to the mechanism of peptide in wound healing also attracted a lot of attention. The strength of the keywords' bursts is another crucial sign of the study frontiers, hotspots, and rising trends throughout time. Top 30 Keywords with the Strongest Citation Bursts are shown in Figure 10. The citation burst time of terms such as “delivery” (2018–2022), “scaffold” (2018–2022), biomaterial” (2018–2022), “nanoparticle” (2019–2022), and “dressing” (2019–2021) has persisted into 2022 and the related researches are still continued, demonstrating that the development of the peptide-based on delivery system and wound dressing were the recently hot research trends.

3.7 | Analysis of citation and co-cited reference

The citation frequency of publications indicates its value to a certain extent and important impact.⁴¹ A total of

1186 references were cited in our investigation, and the top 10 globally cited articles are shown in Table 7. The article titled “APD3: the antimicrobial peptide database as a tool for research and education” published in *Nucleic Acids Research* in 2016 had the largest number of citations (1182 times). Followed by the article titled “Antimicrobial Peptides: An Emerging Category of Therapeutic Agents” (1007 times), and the total citation of other publications was no more than 1000. Co-cited references can be used to measure the degree of mutual influence among publications, and highly co-cited studies are the basis of the discipline in this field. The top 10 co-cited references are listed in Table 8. Among them, the most co-cited reference was “Cutaneous wound healing”, published in *The New England Journal of Medicine* by Singer Aj et al. in 1999.

Figure 11A shows a graphic representation of the reference co-citation network map. All references were clustered into 21 major clusters, including “#0 diabetic foot ulcer”, “#1 EGF”, “#2 diabetic wound healing”, and “#3 silver nanoparticle”. According to the analysis using CiteSpace, the modularity Q was 0.8813, and the mean silhouette S reached a high of 0.9168, demonstrating both a strong clustering effect and a homogeneous network. The co-citation references are also displayed in a timeline

TABLE 7 The information about top 10 global cited articles of peptides in wound healing.

Rank	Title	Journal	Year	First authors	Total citations	Average citation per year
1	APD3: the antimicrobial peptide database as a tool for research and education ⁴²	Nucleic Acids Research	2016	Wang, GS	1182	147.75
2	Antimicrobial Peptides: An Emerging Category of Therapeutic Agents ⁴³	Frontiers In Cellular and Infection Microbiology	2016	Mahlapuu, M	1007	125.88
3	Alginate-Based Biomaterials for Regenerative Medicine Applications ⁴⁴	Materials	2013	Sun, JC	768	69.82
4	Stimulus-responsive hydrogels: Theory, modern advances, and applications ⁴⁵	Materials Science & Engineering R-Reports	2015	Koetting, MC	653	72.56
5	Calcitonin Gene-Related Peptide: Physiology and Pathophysiology ⁴⁶	Physiological Reviews	2014	Russell, FA	633	63.30
6	TGF-beta and the TGF-beta Family: Context-Dependent Roles in Cell and Tissue Physiology ⁴⁷	Cold Spring Harbour Perspectives in Biology	2016	Morikawa, M	626	78.25
7	Biochemical and Biological Attributes of Matrix Metalloproteinases ⁴⁸	Matrix Metalloproteinases And Tissue Remodelling in Health and Disease: Cardiovascular Remodelling	2017	Cui, N	577	82.43
8	The immunology of host defence peptides: beyond antimicrobial activity ⁴⁹	Nature Reviews Immunology	2016	Hancock, REW	566	70.75
9	Collagen-Based Biomaterials for Wound Healing ⁵⁰	Biopolymers	2014	Chattopadhyay, S	556	55.60
10	Antimicrobial host defence peptides: functions and clinical potential ⁵¹	Nature Reviews Drug Discovery	2020	Mookherjee, N	518	129.50

perspective in Figure 11B, which depicts how research hotspots have changed over time. According to the clustering results, the top three research hotspots were “ocular surface” (#0), “formyl peptide receptor” (#1), and “skin regeneration” (#2), indicating that an increasing number of scientists are focusing on peptides in skin wound healing. Additionally, “ocular surface” (#0) was the largest cluster, and “human defensin” (#5) was the subject of the initial studies in this field. Figure S3 presents the top 30 references with the strongest citation bursts. The increase in citations related to this area began in 2005, and the reference of “Mangoni ML, 2016, EXP DERMATOL, V25, P167, DOI 10.1111/exd.12929 DOI” had the longest burst period from 2017 to 2022. Meanwhile, other references were still widely cited in recent years. In general, the analysis of citations and cocited

references in our study indicated that peptides in wound healing remained a research hotspot, especially in skin wound healing.

4 | DISCUSSION

4.1 | General information

Numerous peptides and peptide-based molecules, drugs or materials have been developed for the treatment of wound healing in the past few years and have been confirmed to be effective strategies for chronic wound healing treatment, such as diabetic ulcer foot.^{1,7} It is critical to clarify future research directions in the field of peptide and wound healing.⁶² In this study, we comprehensively

TABLE 8 The information about top 10 co-cited references of peptides in wound healing.

Rank	Title	Journal	Year	First authors	Total citations	Total link strength (TLS)
1	Cutaneous wound healing ⁵²	The New England Journal of Medicine	1999	Singer Aj	158	690
2	Wound repair and regeneration ⁵³	Nature	2008	Gurtner GC	143	650
3	An angiogenic role for the human peptide antibiotic LL-37/hCAP-18 ⁵⁴	Journal of Clinical Investigation	2003	Koczulla R	133	2642
4	Antimicrobial peptides of multicellular organisms ⁵⁵	Nature	2002	Zasloff M	131	1759
5	Wound healing-aiming for perfect skin regeneration ⁵⁶	Science	1997	Martin P	121	630
6	The Cathelicidin Anti-Microbial Peptide LL-37 is Involved in Re-Epithelialization of Human Skin Wounds and is Lacking in Chronic Ulcer Epithelium ⁵⁷	Journal of Investigative Dermatology	2003	Heilborn JD	115	2217
7	Regulation of wound healing by growth factors and cytokines ⁵⁸	Physiological Reviews	2003	Werner S	105	537
8	LL-37, the Neutrophil Granule-And Epithelial Cell-Derived Cathelicidin, Utilizes Formyl Peptide Receptor-Like 1 (Fpr1) as a Receptor to Chemoattract Human Peripheral Blood Neutrophils, Monocytes, and T Cells ⁵⁹	Journal of Experimental Medicine	2003	Yang D	103	2299
9	Antimicrobial Peptides Human β -Defensins Stimulate Epidermal Keratinocyte Migration, Proliferation and Production of Proinflammatory Cytokines and Chemokines ⁶⁰	Journal of Investigative Dermatology	2007	Niyonsaba F	99	1364
10	Growth factors and cytokines in wound healing ⁶¹	Wound Repair and Regeneration	2008	Barrientos S	94	455

analyse the research progress and identify the hotspots in this field via bibliometric methods. Briefly, we extracted 3263 publications containing 2679 articles and 584 reviews from the WOS between 2003 and 2022. The number of publications and citations reflect the research activities and scientific impact in this field, respectively. In this work, the number of published global articles showed a rapid increasing trend with an annual growth rate of 26.67%. As shown in Figure 2, the count of citations was impressive, with a total of 134 740 citations; meanwhile, the average annual citation frequency was 6737 times, and the average citations per document was 41.28 times during the last 20 years. Obviously, studies related to peptides and wound healing have gained growing traction and promising prospects. There were 17 302 writers from 1674 institutions in 81 countries or regions who contributed 3263 articles. United States is

the most productive country, with 1008 articles in terms of total publications, followed by China (762 records) and Germany (213 records), indicating that United States, China and Germany were the core countries for international research on this topic. Meanwhile, the United States, China and Germany, as the top three countries with the most citations and high h-index, play an important role in international cooperation. Table 2 and Figure 5 show the institutions with high productivity. The United States and China had the large bulk of the institutions engaged in scientific research related to this topic, and most articles were produced by the Chinese Academy of Sciences (62 items), Harvard University (41 items), and Shang Hai Jiao Tong University (36 items). In addition, the Chinese Academy of Sciences cooperated closely with numerous internal and international academic institutions. Considering

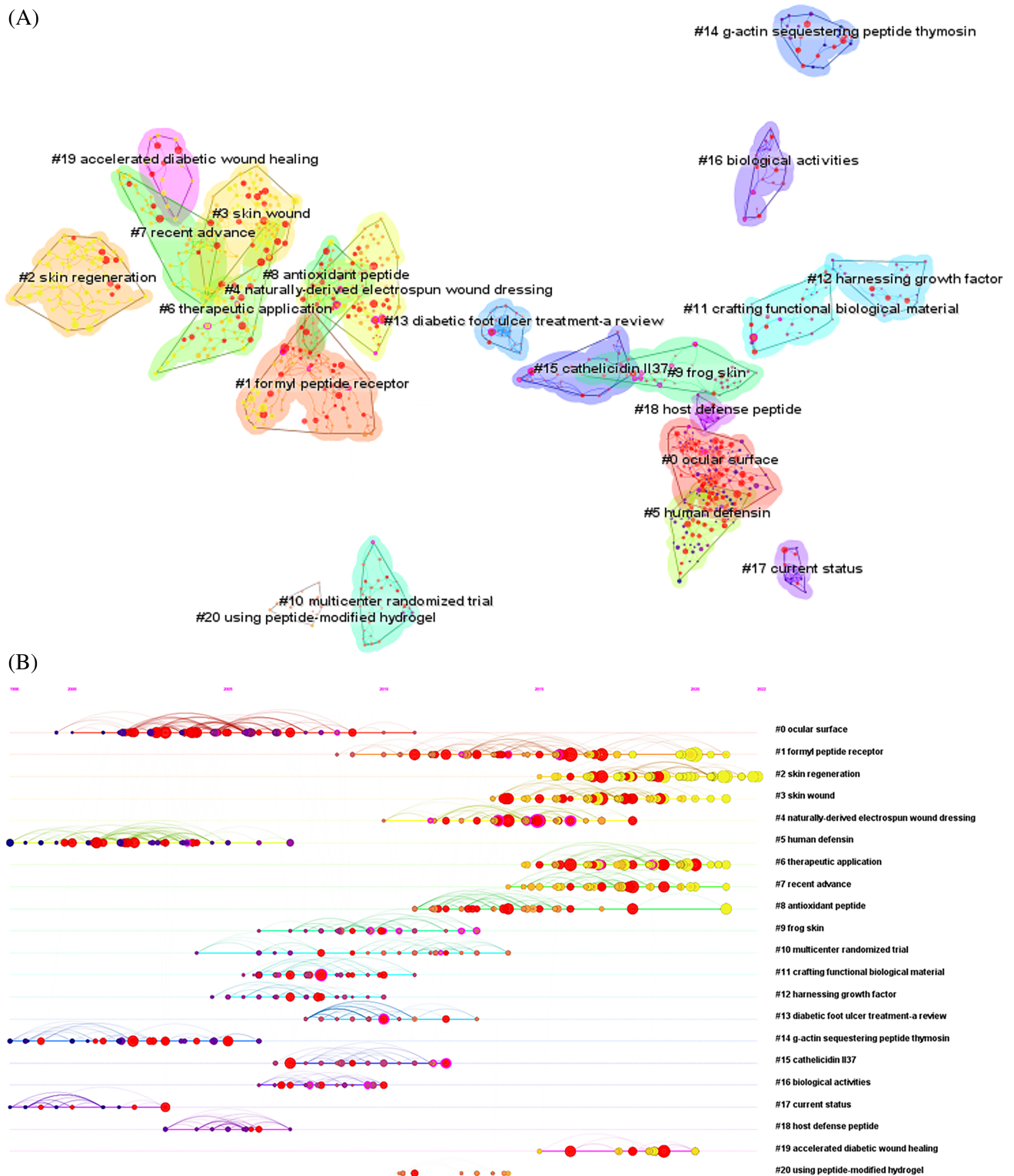


FIGURE 11 The visualisation map of references analysis. Map of cited references clusters (A); Timeline view of cited references co-occurrence (B).

authors, the top 10 most productive authors related to peptide and wound healing published 147 articles with a total of 7621 citations, which are listed in Table 3. The top three authors with the most papers were Wang, Ying

(18 items), Yang, Xinwang (16 items), and Tang, Jing (15 items), who contributed considerably to this field. Interestingly, the top three authors were both from Yunnan province of China. This phenomenon might be

explained by geographical factors since Yunnan is a province in terms of species diversity, and various peptides were originally discovered by researchers from Yunnan's institutions.^{63,64} The articles related to peptide and wound healing were published in 1064 journals. Table 4 lists the top 10 journals, and Figure 7 and Figure 8 present the visualisation network of the journal and co-cited journal, respectively. Plos One was the most productive journal, with 79 articles published, followed by Wound Repair and Regeneration (55 articles) and Acta Biomaterialia (54 articles). Similarly, the most co-cited journals were Journal of Biological Chemistry (6151 times), Proceedings of the National Academy of Sciences of the United States of America (4006 times), and Biomaterials (3664 times). The information of the journal and co-cited journal in this field indicated that articles related to the studies in peptide and wound healing mainly focused on journals in biology, materials, dermatology and immunology, and the citations between journals in different disciplines are increasing.

4.2 | Research trends and hotspots

The evolution of keywords and cited references maps the dynamic changes in research trends and hotspots.^{33,65} Therefore, multiple visualisation maps, including network, cluster analysis, timeline view, and citation bursts of the references and keywords, were conducted with different bibliometric tools in this study. Analysis of keywords and co-cited references showed that the study

related to the mechanisms of peptides in wound healing was an encouraging trend. Trend topics were presented in Figure 12, in recent years, “nanoparticle”, “antibacterial”, “design”, “delivery”, “hydrogel”, and “scaffold” are the research hotspots. And Figure 10 showed the Top 30 keywords with the strongest citation bursts. The keywords with a high frequency of occurrence included “wound healing” (702 records), “expression” (597 records), “in vitro” (366 records), “antimicrobial peptides” (331 records), “angiogenesis” (294 records), “inflammation” (267 records), “peptide” (266 records), skin (263 records), “cells” (250 records), and “peptides” (233 records). There were a total of 1186 references cited in this investigation, indicating the value of published articles to the important impact. “APD3: the antimicrobial peptide database as a tool for research and education” published in Nucleic Acids Research in 2016 had the largest number of citations (1182 times), and the most co-cited reference was “Cutaneous wound healing” published in The New England Journal of Medicine by Singer Aj et al. in 1999. It is worth noting that antimicrobial peptides attract more attention than other peptides,²⁰ and skin wound healing is still the main future research direction. What's more, most research on therapeutic targets and mechanisms has focused on the regulation of antimicrobial activity, angiogenesis and inflammation. Figure 13 presented the delivery and mechanisms related to the research hotspots. There are numerous types peptide applied in the field of wound healing. For example, human α -defensin 3 and human α -defensin 6 are natural antimicrobial peptides that contribute broadly to innate

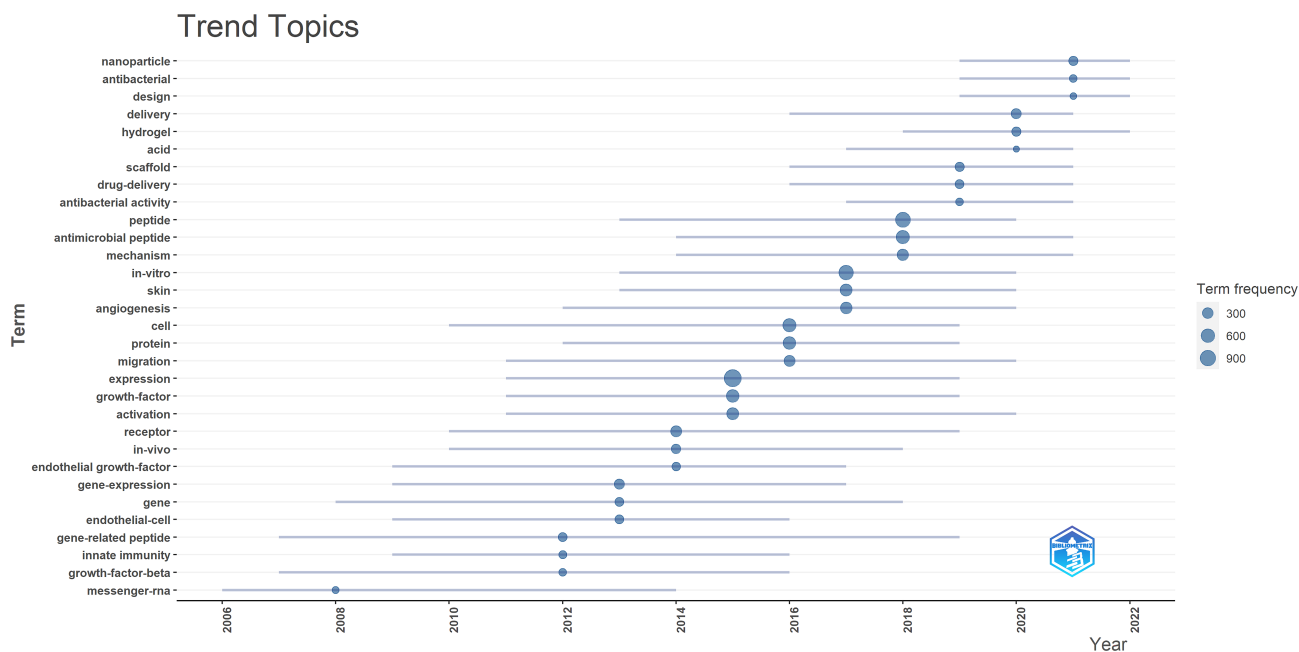


FIGURE 12 The trend topics of peptides in wound healing.

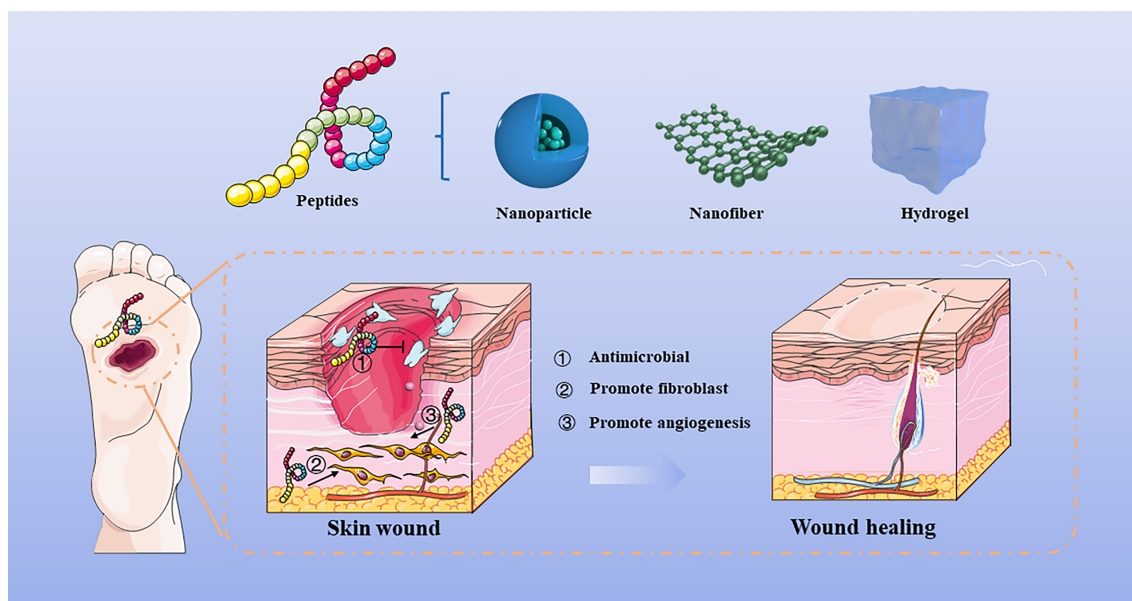


FIGURE 13 The diagram of the application of peptide-based drug delivery systems in wound healing.

immunity.⁶⁶ And dextrorotary (D)-peptides are considered to have great potential as and therapeutic agents due to the good enzymatic stability and prolonged plasma half-life.^{67,68} Meanwhile, the composition of peptides is critical to the shape and biological function. For instance, self-assembling peptide hydrogel, bionic hydrogel, gel coating and self-healing materials are widely used in wound healing.^{30,69–72} Another novel chiral therapeutic and homo-PROTAC to peptide-derived chiral supramolecular nanomedicine also presented secure and efficient therapeutic effect targeting MDM2 with the potential of clinical translation.⁷³

Recently, the study of peptide-based drug delivery systems has been one of the hot research trends attributed to the multifunctionality, good biocompatibility, various forms, and ease of design and synthesis. There are three main types peptides in the drug delivery system, including functional, self-assembled and smart responsive peptides.⁷⁴ Usually, researchers interested in developing peptide-based biomaterials modified with targeting peptide,⁷⁵ cell-penetrating peptide,⁷⁶ and treatment peptide.⁷⁷ Besides, self-assembled peptide-based drug delivery system led to various forms benefit to improving the delivery efficiency under different physical conditions.^{78–80} And there were couple of novel proof of concept studies using bionic peptide-based delivery system³² and “mirror-image peptide grafting” method.⁸¹

In addition, the approaches to overcome the limitations of peptide applications are essential research trends. Natural peptides with low yield, poor stability, and hemolytic toxicity limit the clinical application in wound healing. Researchers tried to overcome the difficulties with

lots of strategies. There are several novel studies improve the biological activities of peptide. For instance, endowing antimicrobial peptides with antioxidative function through combining with antioxidative moieties⁸² and chiral and cationic sites⁸³; improving the affinity of peptides utilized with adding homodimerize structure⁸⁴ and proteolysis-targeting chimeras (PROTAC) technology⁸⁵; using bionic skeletons constituted by the oligomeric Au(I)-peptide complex to depress macrophage uptakes, increase colloidal stability, and prolong blood circulation.⁸⁶ What's more, delivery systems are promising approaches to improve the parameters of peptides. More and more “smart” biomaterials have been developed to stimuli-control peptide release or morphological change which is responsive to wound microenvironments such as high-level ROS, glucose, slight acid pH, and specific enzymes.^{87–89} Latest research focus on the development of more intelligent peptide-based materials. For example, in situ enzyme-induced self-assembly of peptides were established to promote wound healing,⁸² and 3D high-precision and injectable formulation were applied in peptide biomaterials.^{90,91} In a word, peptides in wound healing remain a research hotspot and deserve further exploration by researchers.

5 | CONCLUSION

The present study is the first to perform a bibliometric and visualisation analysis of peptides in wound healing. We conducted a comprehensive analysis of countries, institutions, authors, journals, co-occurrence of

keywords, and co-citation references in this field from 2003 to 2022. Simultaneously, multiple visualisation results revealed the bibliometric characteristics of the field, including network visualisation maps, cluster analysis, timeline view, and citation bursts of the references and keywords, which were presented utilizing various scientific bibliometric tools. In general, studies involved in the mechanism of peptides for wound healing and peptide-based drug delivery or biomaterials such as scaffold are current research topics. Additionally, the top countries, institutions and researchers with the most production should enhance international cooperation, which will greatly benefit the development of this field. As a promising perspective of peptide and wound healing, there remain a couple of challenges and difficulties. For instance, peptides with low yield, poor stability, and toxic effects such as hemolysis limit the clinical application. Nevertheless, the therapeutic efficacy of peptides in clinical wound treatment could be further promoted by combining developments in physiology, materials science and chemistry. Currently, several researchers are focusing on delivery systems based on peptides. Novel carriers and optimized chemical structure modifications may improve the likelihood of successful translation of peptide, peptide-based molecular or drug delivery into practical applications.

ACKNOWLEDGEMENTS

All authors acknowledge the funding support by Chongqing Key Specialty of Clinical Pharmacy and Chongqing University.

FUNDING INFORMATION

This research was funded by Chongqing Key Specialty of Clinical Pharmacy. And this work was supported by the Fundamental Research Funds for the Central Universities (project No. 2022CDJYGRH-017), and supported by the Chongqing Jiangjin District Science and Technology Project (No. Y2022072).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests in this article.

DATA AVAILABILITY STATEMENT

The origin data that support the findings of this study are available from the corresponding author, Ying Fan, upon reasonable request.

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How to cite this article: He X, Wu W, Hu Y, et al. Visualizing the global trends of peptides in wound healing through an in-depth bibliometric analysis. *Int Wound J.* 2024;1-22. doi:[10.1111/iwj.14575](https://doi.org/10.1111/iwj.14575)