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Application of tissue engineering in wound healing

A 20-year bibliometric and visualized study

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Abstract

Background: Tissue engineering has recently been shown to have a considerable advantage in promoting wound healing in clinical studies and animal models, with an increasing number of documents in designing and mechanism investigations. The lack of bibliometric analysis and knowledge mapping in this field would hinder comprehensive understanding of this field and the development of future research.

Methods: Our investigation into the application of tissue engineering in wound healing involved a search of the Web of Science Core Collection (WoSCC). To identify research hotspots and promising future trends in this field of study, we employed several software tools such as VOSviewer, CiteSpace, and R packages to evaluate the contribution and co-occurrence relationships across countries/regions, institutions, journals, authors, keywords, and references.

Results: Ultimately, a total of 9820 documents were reviewed and analyzed. China emerged as the leading country in terms of productivity and influence in this particular field. Shanghai Jiao Tong University emerged as the top publisher, spearheading a group of prominent research institutions. Among journals, Biomaterials garnered the highest number of citations and co-citations, boasting impressive H-index, G-index, and M-index scores. Notably, Reis emerged as the most cited author, while Liu topped the list in terms of co-citations. Keyword and reference analyses unveiled 3 major research directions: natural endogenous technology involving multiple cells and functional factors, mechanism research on the practical application of tissue engineering technology in wound healing, and artificially synthesized and reprocessed exogenous technology. Among these, the latter represented the current focal point in the field.

Conclusion: This research offered a comprehensive outlook on the present status and prospective direction of tissue engineering in wound healing applications worldwide. A thorough evaluation was conducted on diverse tissue engineering techniques, furnishing profound perspectives for scholars and serving as a credible resource that propelled advancements in the field while piquing the curiosity of researchers.

Abbreviations: GC = global citations, LC = local citations, MCP = multiple country publications, NGC = normalized global citations, NLC = normalized local citations, SCI-Expanded = science citation index expanded, SCP = single countries publications, WoSCC = Web of Science Core Collection.

Keywords: bibliometric analysis, CiteSpace, tissue engineering, VOSviewer, wound healing

1. Introduction

The process of wound healing is intricate, consisting of overlapping stages like hemostasis, inflammation, proliferation and remodeling, which are affected and controlled by a variety of factors.[1] Furthermore, the incidence of nonhealing wounds in developed nations ranges from 1% to 2%, with a notable escalation in less developed regions, leading to elevated rates of treatment and expenses, impacting the broader populace and presenting a public health challenge.[2] Common treatments for

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The manuscript does not report or involve the use of any animal or human data or tissues.

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chronic wounds encompass techniques such as skin grafting, flap transplantation, negative-pressure wound therapy, and the use of gauze dressings. However, these approaches may potentially result in tissue harm or restrictions in activities, hard to achieve satisfactory results of the balance between costs and health recovery. Additionally, plastic surgeons and nurses play a significant role in optimizing the healing of various wounds, which include large wounds, wounds in sensitive areas, wounds with exposed blood vessels, nerves, and bones, and first failure treatment, and even the choice of next treatment approaches.[3] Therefore, comprehension of the related measures for skin regeneration or wound repairing along with an understanding of wound healing mechanisms, can empower healthcare professionals to provide enhanced care for patients experiencing wounds.[4]

Tissue engineering or regeneration involves the integration of biomaterials, biological cues, and cells, taking into account their compatibility, activity, strength, manufacturability, and functional appropriateness[5] and widely used in the significant advances of skin, bone, muscles, liver, spinal cord, blood vessels, etc.[6] This nascent technology has experienced rapid advancement in recent years, marked by a plethora of publications emerging globally. However, the application principles, mechanisms, progress, and shortcomings of tissue engineering technologies in the various aforementioned domains have not been thoroughly discussed and critiqued. Specifically, despite of uncertain challenges posed (e.g., scarce real-word use, including scalability, durability under physiological conditions, etc), tissue engineering technologies still have been proven to hold great promise in the field of wound healing.[7] Therefore, it is very important to comprehensively understand the advanced knowledge base and future application of tissue engineering in wound healing.

Over the last 2 decades, a multitude of research papers had explored the use of tissue engineering in wound healing. Nevertheless, these inquiries had yet to be systematically organized and analyzed. For better identifying the best applications and gaining insightful information about potential future technical developments by systematically analyzing current research, we commonly utilized software tools for bibliometric analysis including VOSviewer,[8,9] CiteSpace,[10] HistCite™,[11] and R-bibliometrix[12] for bibliometrics analysis and knowledge visualization. These tools served as efficient means for assessing the thematic progression of organized content and can aid in fostering reader comprehension in a straightforward manner[13] by exploring diverse publications using the following indicators: publication year, document type, language, country of origin, institution, authorship, journal, keywords, and citation counts.[14–16] Briefly, the aim of this report was to explore the current research status, focal points, and cutting-edge aspects of literature pertaining to the utilization of tissue engineering in wound healing, further to construct knowledge maps to offer guidance for prospective research in this area.

2. Materials and methods

2.1. Source database and data collection

The targeted data were derived from the web of science core collection (WoSCC), followed by the organized search strategy in Figure 1 with publications from January 1, 2004 to December 31, 2023. A total of 9820 documents were finally confirmed, based on the search terms in Appendix 1, Supplemental Digital Content, https://links.lww.com/MD/P249, like “tissue engineer*,” “wound*,” “healing*,” etc. The database, documents language, publications type and fixed data retrieval and processing time were also stated in it. Two reviewers (YX and ZH) autonomously extracted all pertinent data and research articles, excluding duplicates and irrelevant studies, to ensure the precision and dependability of the included data. Any discrepancies between the 2 investigators (YX and ZH) will be deliberated and assessed by a third party (LC).

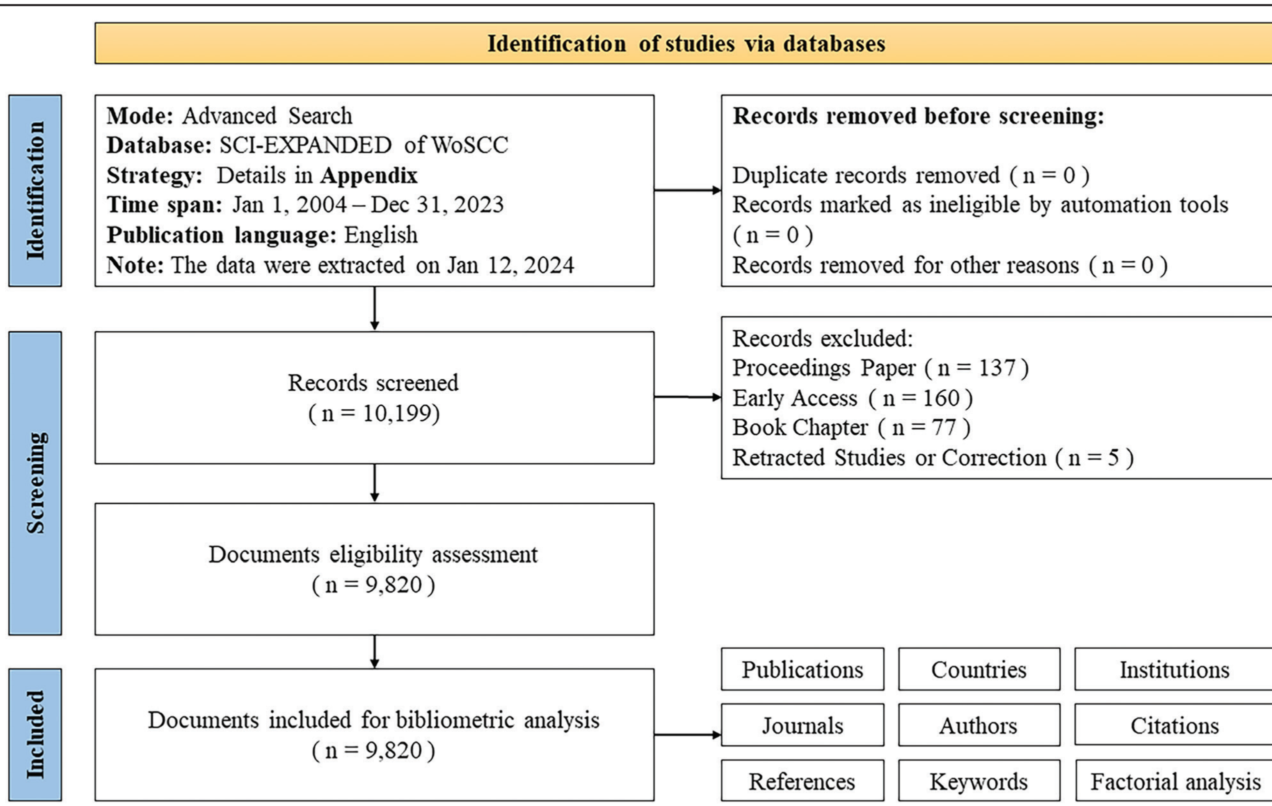

Figure 1. The flow chart.

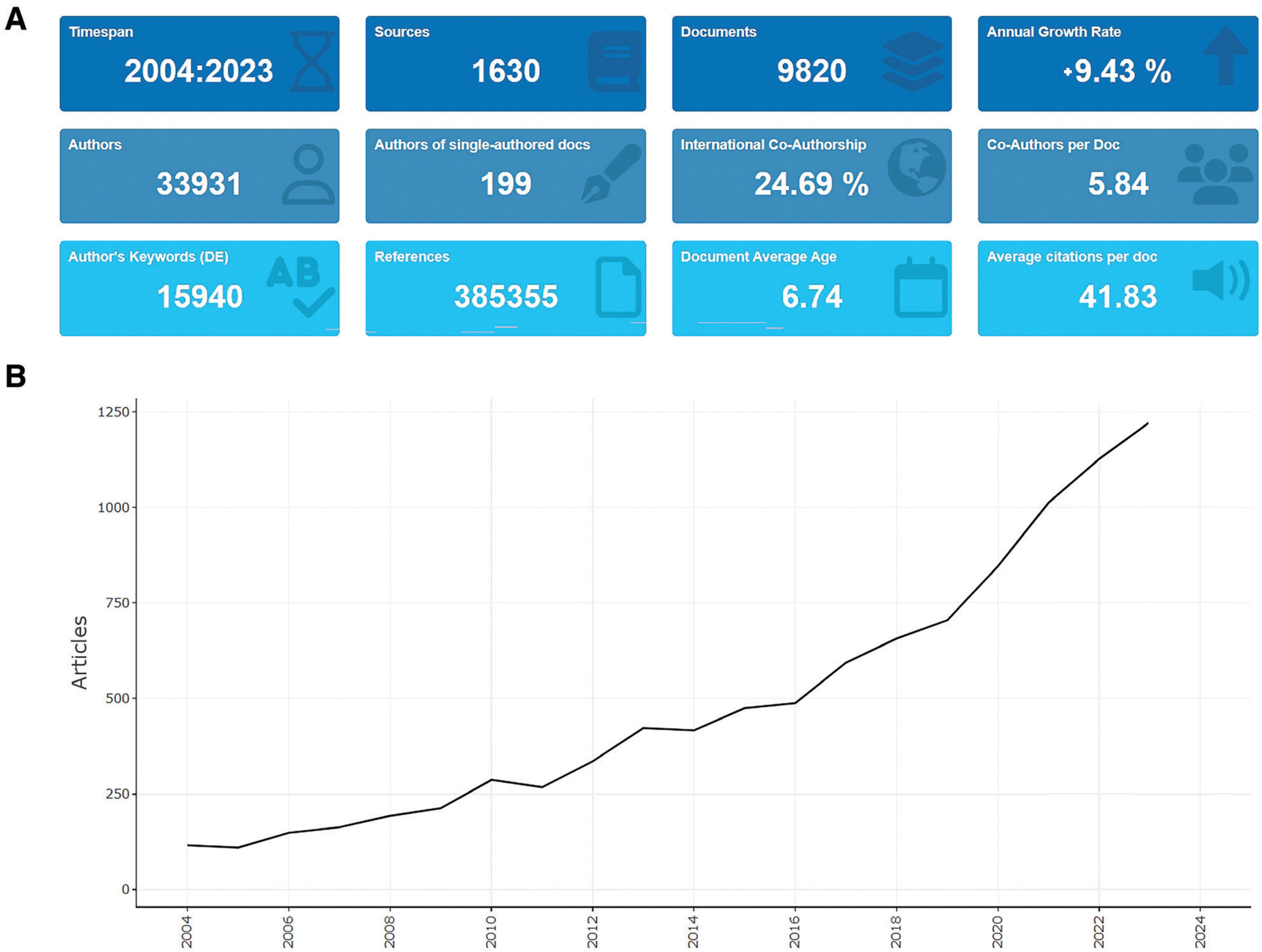

Figure 2. (A) The basic characteristics of included literature from 2004 to 2023. (B) The trend analysis of annual publications and growth trend engaged in the application of tissue engineering in wound healing from 2004 to 2023.

2.2. Data extraction and analysis

Microsoft Office Excel 2023 was used to collect and process the data about the publications of countries, institutions, authors and journals. Visual representations illustrating the nationwide distribution of publications were generated using Python (v.3.11.4, https://www.python.org/downloads/) for enhanced visual comprehension. Simultaneously, we employed the sophisticated and widely acclaimed VOSviewer software (v.1.6.20, Leiden University) to construct bibliometric maps showcasing co-authorship, co-citation, and co-occurrence relationships among them visually. Each distinctive term, including keywords, countries, affiliations, references, journals, and authors, was depicted as a node, with the size and proximity of nodes indicating the significance, recurrence, and collaborative strength of these terms. Moreover, the thickness of the lines was meticulously adjusted to symbolize the intensity of their collaboration, and the utilization of colored circles to signify distinct term clusters was particularly insightful. Conducting bibliometric analyses with CiteSpace (v.6.2.R6) was a prevalent method used to explore research trends in specific study areas. The CiteSpace parameters included were as follows: link retaining factor (LRF = 3), the value for top N (e = 1), time span (2004–2023), years per slice (2), look back years (LBY = 5), links (strength: cosine, scope: within slices), selection criteria (g-index: k = 15), and minimum duration (MD = 1).[17] In addition, we leveraged R software (v.4.3.1, https://www.r-project.org) to generate the illustrations demonstrating the basic characteristics of the included literature, word clouds of keywords, topic dendrograms from factor analysis, and thematic maps to meticulously scrutinize keyword usage and comprehensively investigate trends within intricate academic collaboration networks for predictive analysis.

3. Results

3.1. Annual publication output and growth trend

From 2004 to 2023, a comprehensive compilation of 9820 scholarly publications focusing on the application of tissue engineering in wound healing was identified based on the aforementioned search strategy in Figure 2A. Subsequent investigation utilizing the WoSCC database verified the inclusion of 1630 esteemed academic journals in this endeavor. During the specified timeframe, there was an average annual increase in publication volume at a rate of 9.43%. This growth trend culminated in its peak in 2023, while notably, the publication rate experienced a discernible acceleration in the past 2 years in Figure 2B.

3.2. Countries/regions and institutions analysis

A total of 111 countries and 7891 scientific organizations making significant contributions to this field were confirmed in Table 1 and Figure 3. The most frequent contributor is China, with 2051 publications, followed by the United States (N = 1911), India (N = 513), Iran (N = 492), and Italy (N = 477) in Table 1, which was consistent with the results in Figure 3C,

Table 1

The top 10 prolific countries and affiliations involved in tissue engineering and wound healing.

Rank	Country	Publications	SCP	MCP	Affiliations	Publications
1	China	2051	1708	343	Shanghai Jiao Tong University	169
2	USA	1911	1531	380	Harvard University	153
3	India	513	378	135	Sichuan University	134
4	Iran	492	345	147	Chinese Academy of Sciences	134
5	Italy	477	340	137	Zhejiang University	127
6	Germany	421	272	149	Tehran University of Medical Sciences	110
7	South Korea	394	307	87	National University of Singapore	106
8	United Kingdom	344	257	87	University of Michigan	97
9	Japan	322	281	41	Islamic Azad University	96
10	Canada	241	190	51	University of Minho	90

MCP = Multiple country publications, SCP = Single country publications.

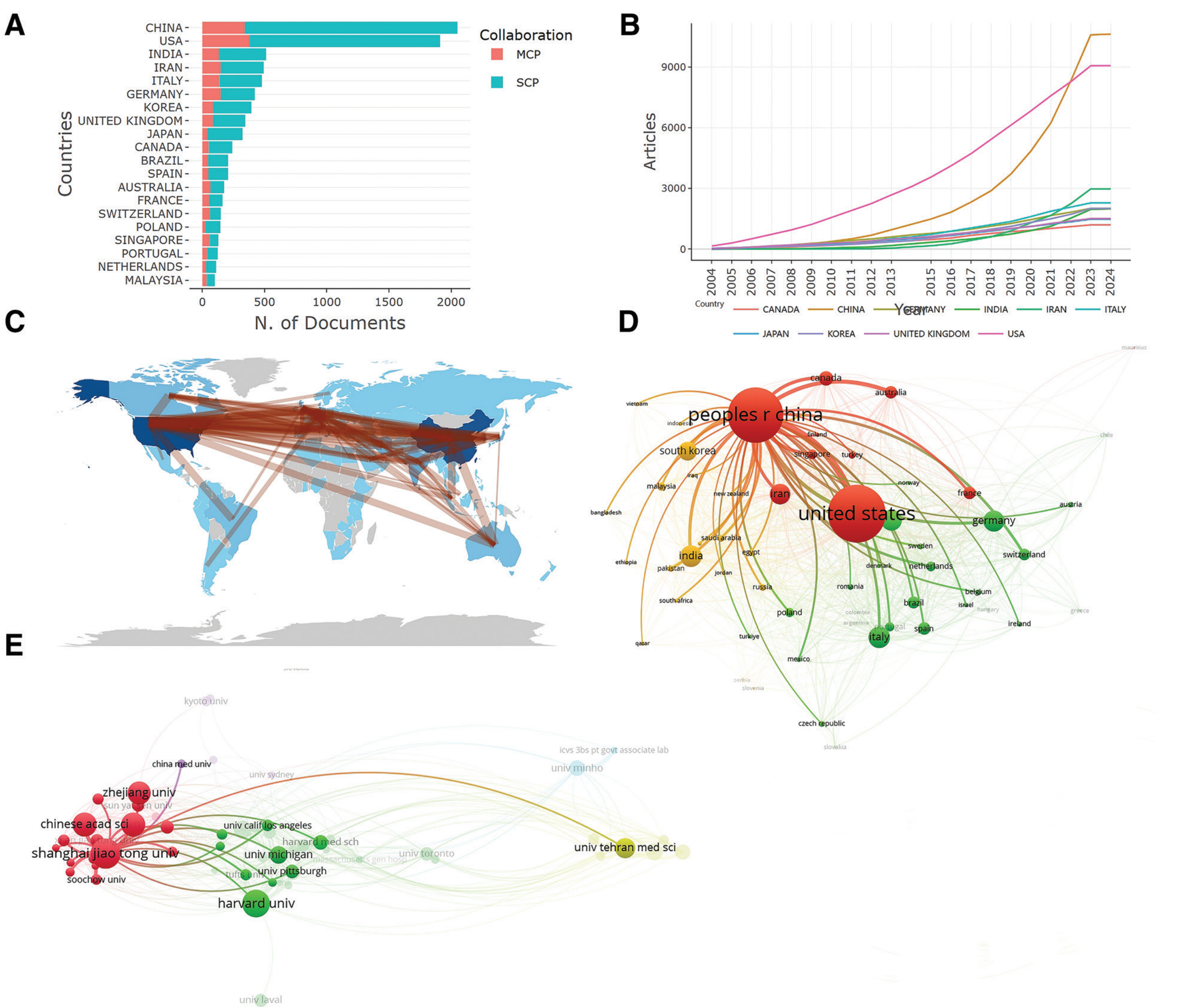

Figure 3. Analysis of countries and affiliations involved in tissue engineering and wound healing. (A) The top 20 most productive SCP and MCP countries. (B) The dynamic publications analysis of the top 10 most prolific countries. (C) The distribution and cooperative relationship of countries in terms of publications. (D) A network map showing countries centered on China. (E) A network map showing institutions centered on Shanghai Jiao Tong University. MCP = multiple country publications, SCP = single country publications.

where darker shades of blue sites represent countries with a greater number of related publications. In addition, we conducted an analysis of the characteristics of single Country publications (SCP) and multiple Country publications (MCP) related to each country. SCP pertains to autonomous research or publications concentrated on individual nations, furnishing valuable resources for exploring and examining diverse facets within those countries by delving into their unique attributes.[18] Conversely, MCP, referring to Multiple Country Publications, encompasses cross-national studies that provide comprehensive perspectives aiding in the comprehension of interactions between nations and the influential factors affecting global development.[17] In Figure 3A, the countries with most collaborations of MCP and SCP are China and the United States, more than 1500 documents, and far surpassing other countries. Furthermore, the extent to which the 2 countries had surpassed other countries in recent years had become increasingly evident, and China surpassed the United States in terms of overall collaborations outputs in 2022, becoming the country with the highest number in Figure 3B. Meanwhile, the width and density of the network of collaborative linking with China and the United States were significantly greater than those with other countries in Figure 3C, which may be attributed to the large volume of publications and active collaborations between nations, highly consistent with the results in Figure 3A and B, demonstrating the rigor and reliability of the analysis. More specifically, taking the node "China" as an example and analyzing the countries closely cooperating with China, closer node distances and wider node connections represent closer cooperation, as shown in the visualization in Figure 3D. We conducted a vivid analysis of research institutions relevant to this study field, including publication lists and visualized collaboration networks. As shown in Table 1, China occupied 4 seats in the top 5 institutions, with Shanghai Jiao Tong University (N = 169) leading the group of research institutions, followed closely by Sichuan University (N = 134), Chinese Academy of Sciences (N = 134), and Zhejiang University (N = 127), with Harvard University (N = 153) from the United States, ranking second. More specifically, taking the node "Shanghai Jiao Tong University" as an example and analyzing the countries closely cooperating with it, closer node distances and wider node connections represented closer cooperation, as shown in the visualization in Figure 3E.

3.3. Authors and co-cited authors analysis

A total of 45,465 authors and 202,856 co-cited authors making significant contributions to this field were confirmed in Table 2 and Figure 4. The 2 most frequently published authors in this field were Reis (N = 43) and Ramakrishna (N = 42). Furthermore, Liu Y (N = 648), Li Y (N = 591), and Wang Y (N = 574) were the 3 co-cited authors who had received the most co-citations in Table 2. Moreover, we utilized VOSviewer and R software to showcase visualizations of the network relationship diagram among authors and co-cited authors, as well as the distribution curve of authors' publications and proportions. Figure 4A and B presented authorship networks centered on author Reis as the most publications author and Liu Y as the most co-citations author, respectively, with closer node distances and wider node connections representing closer cooperation. Meanwhile, in the curve we plotted, we observed that authors with more than 10 publications accounted for only 0.2% of all the authors.

Table 2

The top 10 academic authors and co-cited authors involved in tissue engineering and wound healing.

Rank	Authors	Counts	Citations	Co-cited authors	Co-citations
1	Rui L.Reis	43	2043	Liu Y	648
2	Ramakrishna S	42	2377	Li Y	591
3	Fu X	30	889	Wang Y	574
4	Germain L	29	954	Zhang Y	555
5	Kaplan DL	28	4367	Li J	517
6	Cui W	24	1662	Zhao X	507
7	Wu J	22	669	Yannas IV	503
8	Machens HG	22	591	Wang J	499
9	Atala A	22	1991	Boyce ST	487
10	Zhang W	22	556	Falanga V	480

3.4. Journals and co-cited academic journals analysis

A total of 1630 journals and 31,050 co-cited journals making significant contributions to the field of application of tissue engineering in wound healing were confirmed in Table 3 and Figure 5. According to Table 3, *Biomaterials* (N = 264) had the highest publication volume among the top 10 most potential journals, followed by *Acta Biomaterialia* (N = 237), *International Journal of Biological Macromolecules* (N = 199), and *International Journal of Molecular Sciences* (N = 181). It was noteworthy that *Biomaterials* had the highest H-index, G-index and M-index. The H-index[19] is a widely employed measure for evaluating the productivity and influence of academic researchers, defined as the "highest value H, where an individual has published H papers that have received at least H citations each." And the G-index was proposed as a refinement to Hirsch h-index, designed to assess the overall citation impact of a group of articles.[20] The M-index was a relatively new supplement to the H-index, which calculated H-index per year since the initial publication.[21] By comparing the above 3 indexes, the characteristics and influence of journals can be compared in many aspects. In terms of co-citation, *Biomaterials* (N = 33,148) was the most co-cited journal, followed by *Acta Biomaterialia* (N = 11,861) and *Carbohydrate Polymers* (N = 10,060), all of which exceeded 10,000 citations. *Biomaterials* and *Acta Biomaterialia* were listed as the top 2 most co-cited journals, indicating their high significance in this field and extensive links with other journals. In addition, all 10 of the most co-cited journals had citation counts above 5000, which highlighted the active mutual cooperation between journals in this field. The variations in annual publication output of the top 5 journals, as shown in Figure 5A, revealed that *Biomaterials* consistently maintained a large publication volume and held the first position. Since 2018, there had been a rapid increase in the publication output of *Acta Biomaterialia*, *International Journal of Biological Macromolecules*, and *International Journal of Molecular Sciences*, placing them at the second to fourth positions. Bradford suggested that the first zone's citations would originate from a tiny core group of journals when all references on a given topic were evenly divided into 3 zones. The second and third zone needed more journals than the previous zone does in order to receive the same number of citations. There was a diminishing productivity phenomenon from the first zone to the third zone, which was known as Bradford scattering law. It was possible to utilize it to locate the journals with the highest citations in a certain field or topic.[22] Figure 5B demonstrated the application of Bradford law to evaluate nearly 10 journals as the source clustering, which was in agreement with the findings presented in Table 3. As mentioned above, in the VOSviewer network diagrams, various nodes represented elements like countries/regions, institutions, and journals. The node size corresponded to the volume of studies or co-occurrence frequencies. Connections between nodes symbolize co-occurrence associations, with link sizes indicating the frequency of co-occurrence between 2 nodes.[23,24] In Figure 5C and D, *Biomaterials*, as the most prolific journal in terms of publications and co-cited journals owing to larger nodes, served as an example to analyze the visualized journal network associated with it, suggested to be closely associated with *Acta Biomaterialia*, *International Journal of Biological Macromolecules*, *International Journal of Molecular Sciences*, *Carbohydrate Polymers*, *Journal of Biomedical Materials Research Part A*, etc.

Figure 6 utilized a dual-map overlay to present the subject distribution of journals. The left-hand side portrayed citing journals, and the right-hand side depicted cited journals. Links between the 2 sides represented citation routes, with purple, green, and yellow trails indicating different citation linkages from left to right. Various clusters denoted distinct regions. Among them, 2 significant citation pathways were yellow, while 1 was purple. The primary citation clusters were made up of articles from the

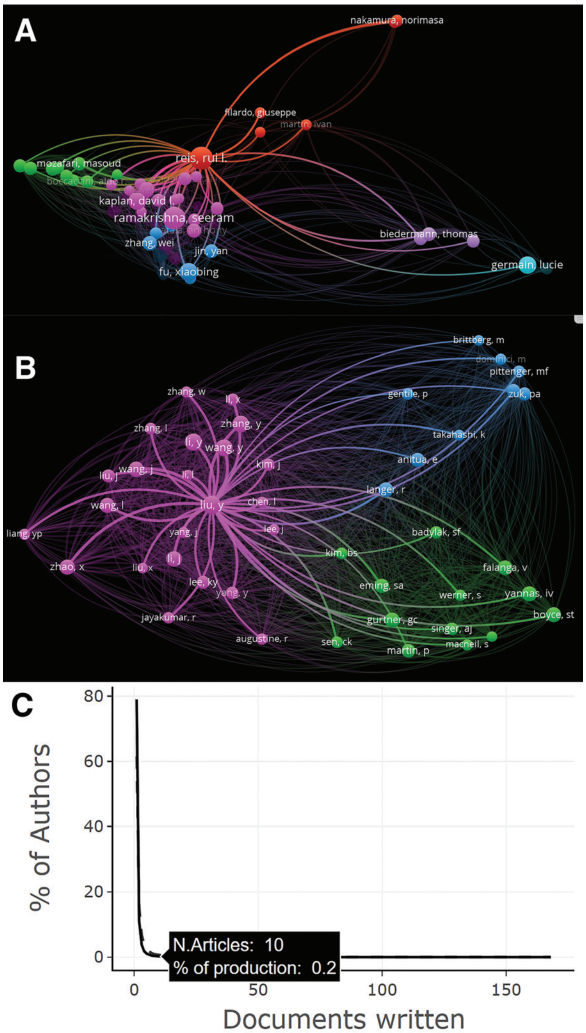

Figure 4. A network map showing authors centered on author Reis Rui L (A) and co-cited authors centered on author Liu Y (B) publishing researches involved in tissue engineering and wound healing. (C) The fitted curve graph depicting the relationship between authors and publication volume.

Molecular/Biology/Immunology journals, Medicine/Medical/Clinical journals, Physics/Materials/Chemistry journals, while the primary co-cited clusters were located in the journals from Molecular/Biology/Genetics, Health/Nursing/Medicine and Chemistry/Materials/Physics.

3.5. Analysis of keywords and thematic map

There were 27,528 keywords depriving from the documents contributing to this subject of tissue engineering and wound healing discerned. The research tree map depicting 50 keywords were demonstrated in Figure 7A, among which tissue (7%) ranked first, followed by cells (6%), wound (6%), healing (4%). etc. Figure 7B was the thematic map analysis of the 4 identified clusters. It was suggested that regeneration, stem-cells and differentiation with motor themes were more significant and promising keywords. While, in vitro, scaffolds and delivery with emerging or declining themes were marginal keywords due to their low density and centrality. Distinct colors signify diverse research directions, with akin research directions categorized under the same color. Node sizes denote the frequency of co-occurrence, while interconnecting lines between nodes represent associations among different keywords.[18,25] The significant 3 clusters in Figure 7C

Table 3

The top 10 academic journals and co-cited journals involved in tissue engineering and wound healing.

Rank	Journals	Counts	H-index	G-index	M-index	Co-cited Journals	Co-citations	H-index	G-index	M-index
1	Biomaterials	264	90	156	4.286	Biomaterials	33,148	90	156	4.286
2	Acta Biomaterialia	237	61	110	3.389	Acta Biomaterialia	11,861	61	110	3.389
3	International Journal of Biological Macromolecules	199	54	96	3.176	Carbohydrate Polymers	10,060	40	83	2
4	International Journal of Molecular Sciences	181	34	64	2.429	International Journal of Biological Macromolecules	9130	54	96	3.176
5	Journal of Biomedical Materials Research Part A	145	43	65	2.048	PNAS	7895	31	40	1.476
6	Journal of Tissue Engineering and Regenerative Medicine	140	32	54	1.778	Materials Science and Engineering: C-Materials for Biological Applications	7604	38	61	2.714
7	Polymers	130	34	59	2.267	Journal of Biomedical Materials Research Part A	7021	43	65	2.048
8	Tissue Engineering Part A	126	36	55	2.118	ACS Applied Materials & Interfaces	6511	36	54	2.769
9	Frontiers in Bioengineering and Biotechnology	120	26	43	2.6	Nature	6491	27	40	2.077
10	Journal of Biomedical Optics	98	25	50	1.19	Plos One	6487	28	51	1.647

PNAS = Proceedings of the National Academy of Sciences of the United States of America.

were classified based on the primary keywords: Cluster 1, natural endogenous technology with multiple cells and functional factors; Cluster 2, artificially synthesized and reprocessed exogenous technology; Cluster 3, mechanism researches of tissue engineering technology practice in wound healing. In Figure 7D, the results of keyword co-occurrence analysis were presented using an overlay visualization map. The color scale transitioned from purple to blue, green, and yellow, representing the time frame from 2016 to 2019. Among them, Cluster 2 included many more yellow nodes, representing the most advanced and hot research direction at present, covering the researches like hydrogel, drug-delivery, chitosan, gelatin, fabrication, nanofibers, nanoparticles, antibacterial, hyaluronic-acid, etc.

The variation trend between the occurrence frequency of keywords and corresponding years, which were related to tissue engineering and wound healing studies were shown in Figure 8A. Over the past 20 years, the following keywords had exhibited a significant level of consistency and frequency due to their larger nodes: scaffolds, nanoparticles, drug-delivery, in vitro, stem-cells, differentiation, regeneration, repair, hydrogels and antibacterial activity with a concentration between 2017 and 2021. The findings indicated that these areas of research related to tissue engineering and wound healing had been consistently studied and received sustained attention. And the following 5 emerging aspects including hemostasis, co-delivery, hydrogel, antibacterial and exosomes had been hot topics ever since, suggesting currently potential and promising research directions. The term "keywords with the strongest citation bursts" refers to research papers with related keywords in a specific field that have received a substantial number of citations within a short period of time.[26] By detecting significant fluctuations in the frequency of keywords, keyword burst detection analysis facilitated the identification of research trends and popular areas of interest. There were top 30 keywords with the strongest citation bursts confirmed in Figure 8B. Among them, the strength of the 4 keywords were more than 30, including tissue engineering (strength = 38.61), marrow stromal cells (strength = 35.36), antibacterial (strength = 33.81) and artificial skin (strength = 32.64). Meanwhile, there were 7 keywords, like antibacterial, wound dressing, 3d bioprinting, exosome, injectable hydrogels, wound and extracellular vesicles, all of which highlighted the period lasted until the time of analysis. In general, the strengths of the top 30 keywords ranged from 18.1 to 38.61 with a long duration from 5 to 14 years.

3.6. Analysis of references and co-cited references

The number of times a publication is cited by other publications within a particular region or country is known as its local citation count, while the number of times a publication is cited by other publications worldwide is referred to as its global citation count.[17,27] The impact and significance of a publication within its local sphere can be assessed by comparing the number of local citations to global citations (LC/GC). The top 10 papers that received a significant number of local citations were presented in Table 4 within this context. For instance, MacNeil review titled 'Progress and opportunities for tissue-engineered skin' published in Nature received the highest number of local citations (N = 249).[28] The remaining 9 references, with local citation counts ranging from 114 to 173, all below 200, would be thoroughly analyzed in the discussion section. Additionally, Lee review titled 'properties and biomedical applications' published in Progress in Polymer Science had the highest global

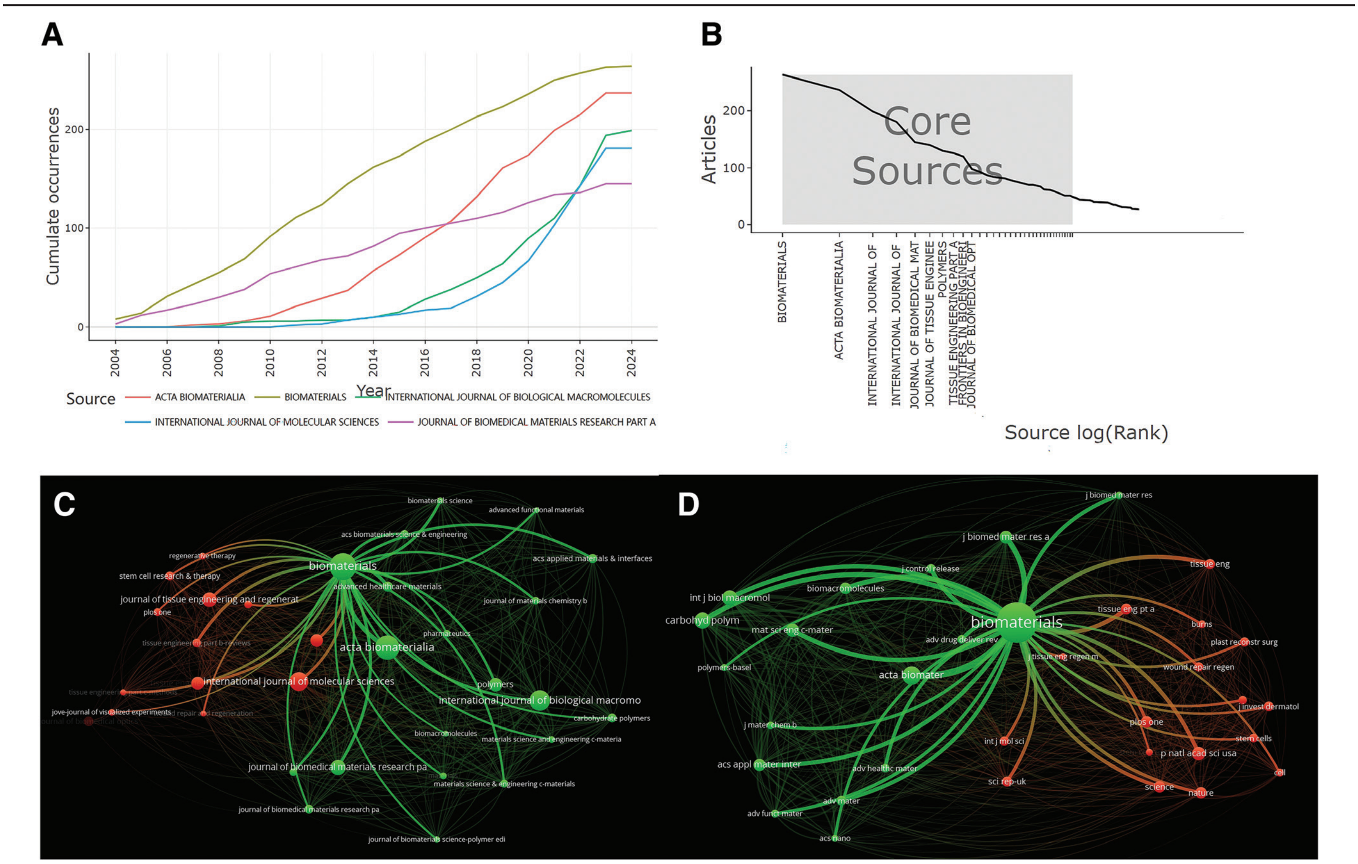

Figure 5. Analysis of journals and co-cited journals involved in tissue engineering and wound healing. (A) The dynamic analysis of the top 5 most prolific journals. (B) Core source clustering through Bradford law. (C and D) A network map showing journals centered on *Biomaterials* (N = 33) and co-cited journals centered on *Biomaterials* (N = 34) publishing researches involved in tissue engineering and wound healing.

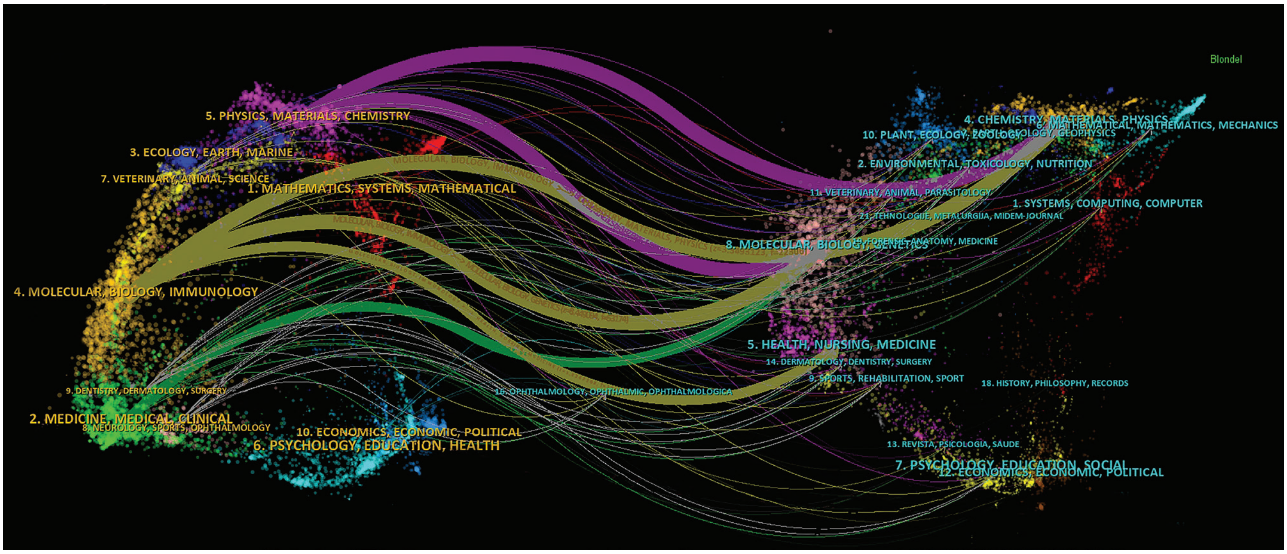

Figure 6. The dual-map overlay of journals related to tissue engineering and wound healing.

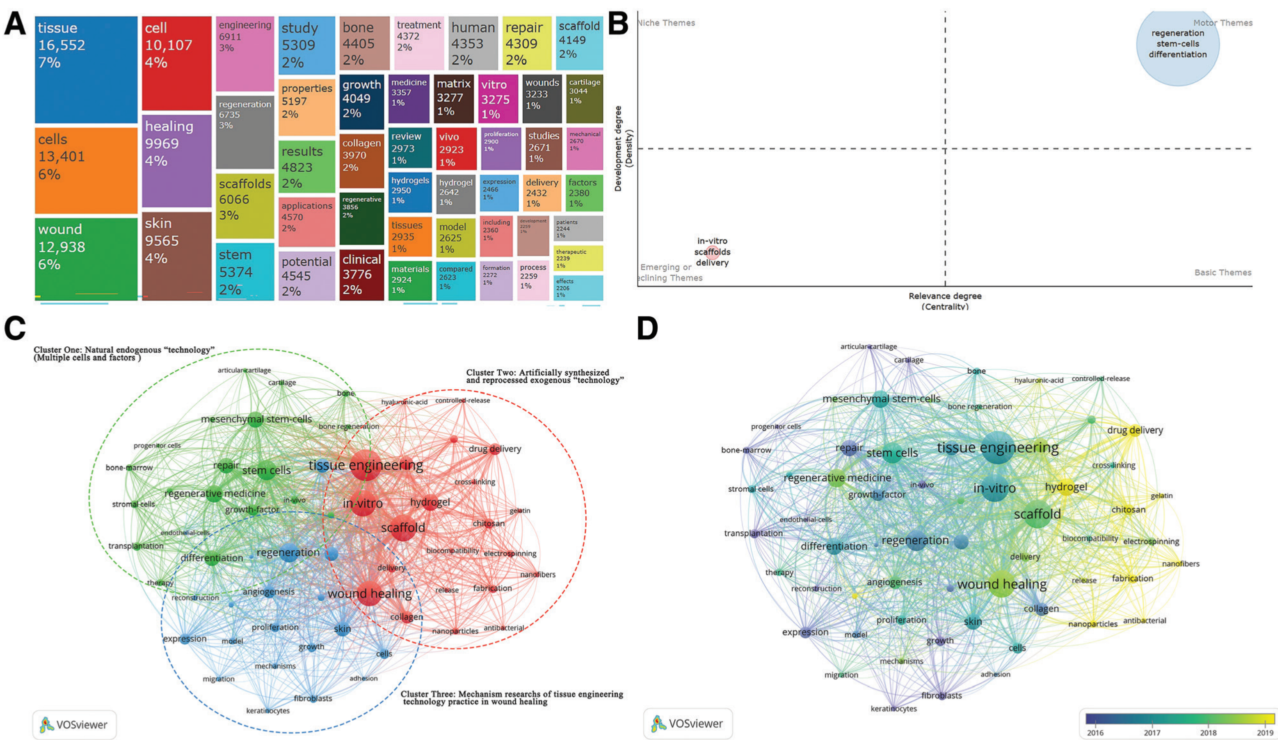

Figure 7. Analysis of keywords and thematic map involved in tissue engineering and wound healing. (A) The proportional tree map of different keywords (N = 50). (B) Thematic map analysis of the 4 identified clusters. (C) Network map and different clusters showing keywords analysis by VOSviewer. (D) Overlay visualization map of keywords and corresponding year analysis in this field.

citation count (N = 4826).[29] Furthermore, Vig review titled "Advances in Skin Regeneration Using Tissue Engineering," published in International Journal of Molecular Sciences had the highest LC/GC Ratio (37.08%),[30] indicating a significant impact within its local domain.

Figure 9A displayed the network diagram of all 50 references pertaining to tissue engineering and wound healing. The 3 distinct nodes in different colors indicated clusters of references on various subjects. 'Wound repair and regeneration' by Gurtner et al[31] in 2008 was the more important reference due to its larger node. "Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement." by Dominici et al[32] in 2006 and "Multilineage potential of adult human mesenchymal stem cells" by Pittenger et al[33] in 1999 were notable references in red clustering. While "Tissue engineering" by Langer and Vacanti[34] in 1993 and "Progress and opportunities for tissue-engineered skin" by MacNeil[28] in 2007 were critical references in green clustering. These selected references also demonstrated a strong co-occurrence relationship among themselves as well as with other references. Also, we created a historiography to understand the developing history in this field, based on higher local citation score, containing 14 most cited works in this field (2004-present) with a whole chained

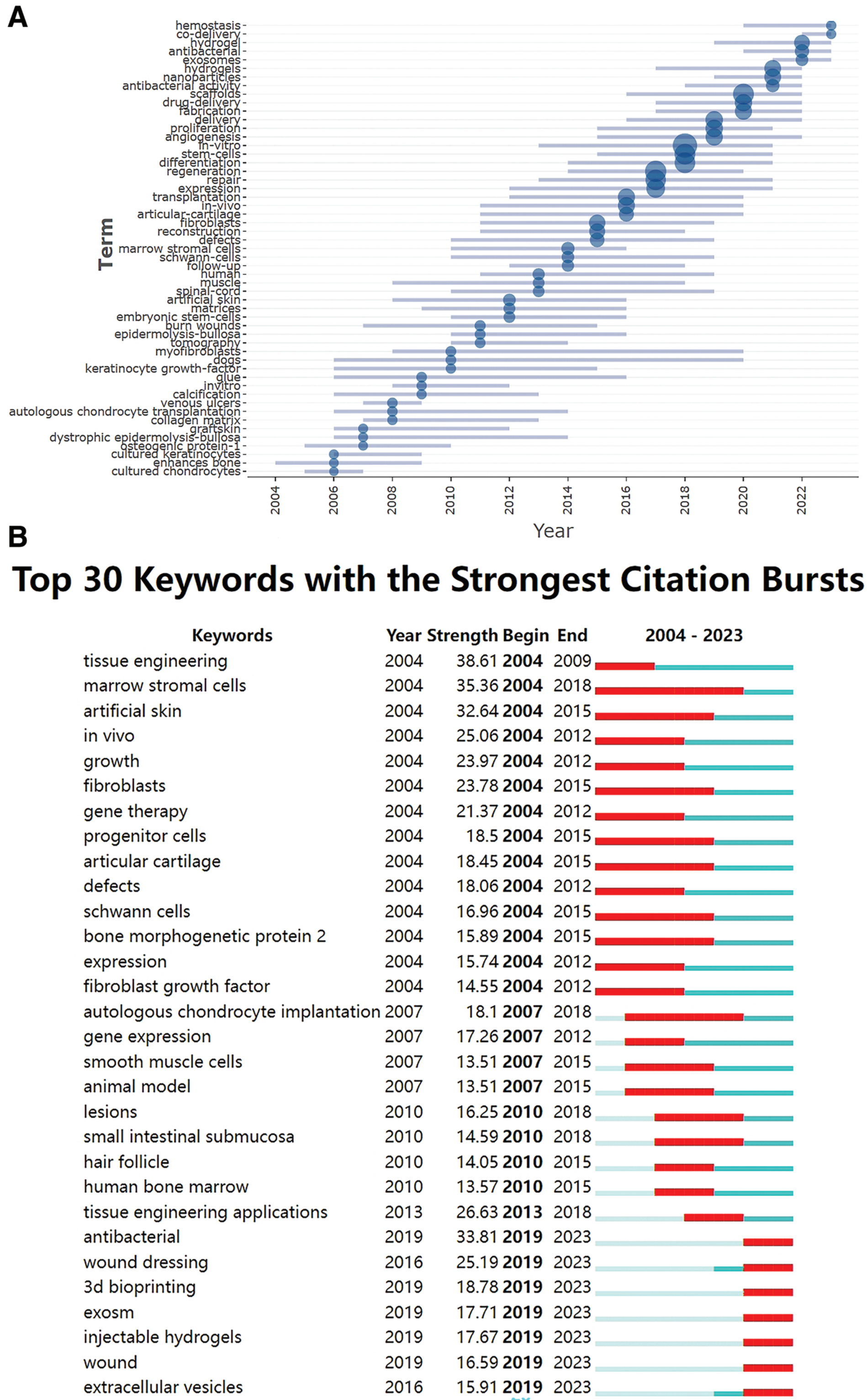

Figure 8. (A) Temporal evolution of key research themes: keyword frequency and burst analysis (B) Top 30 keywords with the strongest citation burstiness. The red bars mean some references cited frequently; the blue bars were references cited infrequently.

connection depicted in Figure 9B. The earliest highly cited publications are "O'Brien et al, 2005,"[35] "Rho et al, 2006"[36] and "Supp and Boyce, 2005,"[37] which focused on collagen-GAG scaffolds for skin regeneration, cross-linked collagen nanofibers for biomedical applications and engineered skin substitutes. Meanwhile, the latest highly cited publications are "Tottoli et al, 2020,"[38] "Rodrigues et al, 2019"[39] and "Vig et al, 2017,"[30] which concentrated on the clinical complications and advanced treatment for chronic wounds, the association between cellular alterations and wound healing, and the development, availability and application of tissue-engineered skin substitutes.

Citation bursts, in the context of references, denote researches within a specific field that have received a significant number of citations within a certain period of time. This phenomenon aids in the exploration process and can forecast future areas of study.[23,40,41] The top 30 references with the strongest citation bursts, were presented in Figure 9C, using lines to indicate the timeframe, with red lines denoting the year of the citation bursts. Out of the references, 4 out of 30 exhibited a strength value of over 25. And the strongest burst (strength = 29.18) was the study"3D bioprinting of tissues and organs" by Murphy and Atala,[42] bursting from 2016 to 2019. The following 3 references were the researches "Wound repair and regeneration" by Gurtner et al,[31] bursting from 2008 to 2015, "Progress and opportunities for tissue-engineered skin" by MacNeil,[28] bursting from 2008 to 2015 and "Wound repair and regeneration: mechanisms, signaling, and translation" by Eming et al[43] from 2016 to 2019. Overall, the top 30 references had a strength between 13.35 and 29.18 and a citation bursts period between 3 and 7 years. It was important to note that among them, the time span of 7 references extended until the analysis period. Firstly, the article "Antibacterial antioxidant electroactive injectable hydrogel as self-healing wound dressing with hemostasis and adhesiveness for cutaneous wound healing" by Zhao et al[44] in 2017 reported a new designed injectable self-healing hydrogel dressing. Secondly, the review "Advances in Skin Regeneration Using Tissue Engineering" by Vig et al[30] in 2017 summarized the development, availability and application of tissue-engineered skin substitutes. Thirdly, the review "Future Prospects for Scaffolding Methods and

Table 4

The top 10 references in terms of local citation about tissue engineering and wound healing.

Rank	Type	Document	LC	GC	LC/GC Ratio (%)	NLC	NGC
1	Review	Macneil, 2007, Nature, DOI 10.1038/nature05664	249	791	31.48	30.24	7.22
2	Review	Shevchenko, 2010, J R Soc Interface, DOI 10.1098/rsif.2009.0403	173	481	35.97	46.36	6.15
3	Review	Lee, 2012, Prog Polym Sci, DOI 10.1016/j.progpolymsci.2011.06.003	152	4826	3.15	54.27	69.01
4	Review	Metcalfe, 2007, J R Soc Interface, DOI 10.1098/rsif.2006.0179	149	550	27.09	18.10	5.02
5	Review	Vig K, 2017, Int J Mol Sci, DOI 10.3390/ijms18040789	145	391	37.08	56.93	8.45
6	Review	Anderson, 2008, Semin Immunol, DOI 10.1016/j.smim.2007.11.004	143	3382	4.23	22.38	25.40
7	Review	O'Brien, 2011, Mater Today, DOI 10.1016/S1369-7021(11)70058-X	136	1859	7.32	40.54	21.72
8	Review	Rodrigues, 2019, Physiol Rev, DOI 10.1152/physrev.00067.2017	132	1021	12.93	53.24	23.75
9	Article	Chong, 2007, Acta Biomater, DOI 10.1016/j.actbio.2007.01.002	119	722	16.48	14.45	6.59
10	Review	Supp, 2005, Clin Dermatol, DOI 10.1016/j.clindermatol.2004.07.023	114	312	36.54	25.28	3.01

GC = global citations, LC = local citations, NGC = normalized global citations, NLC = normalized local citations.

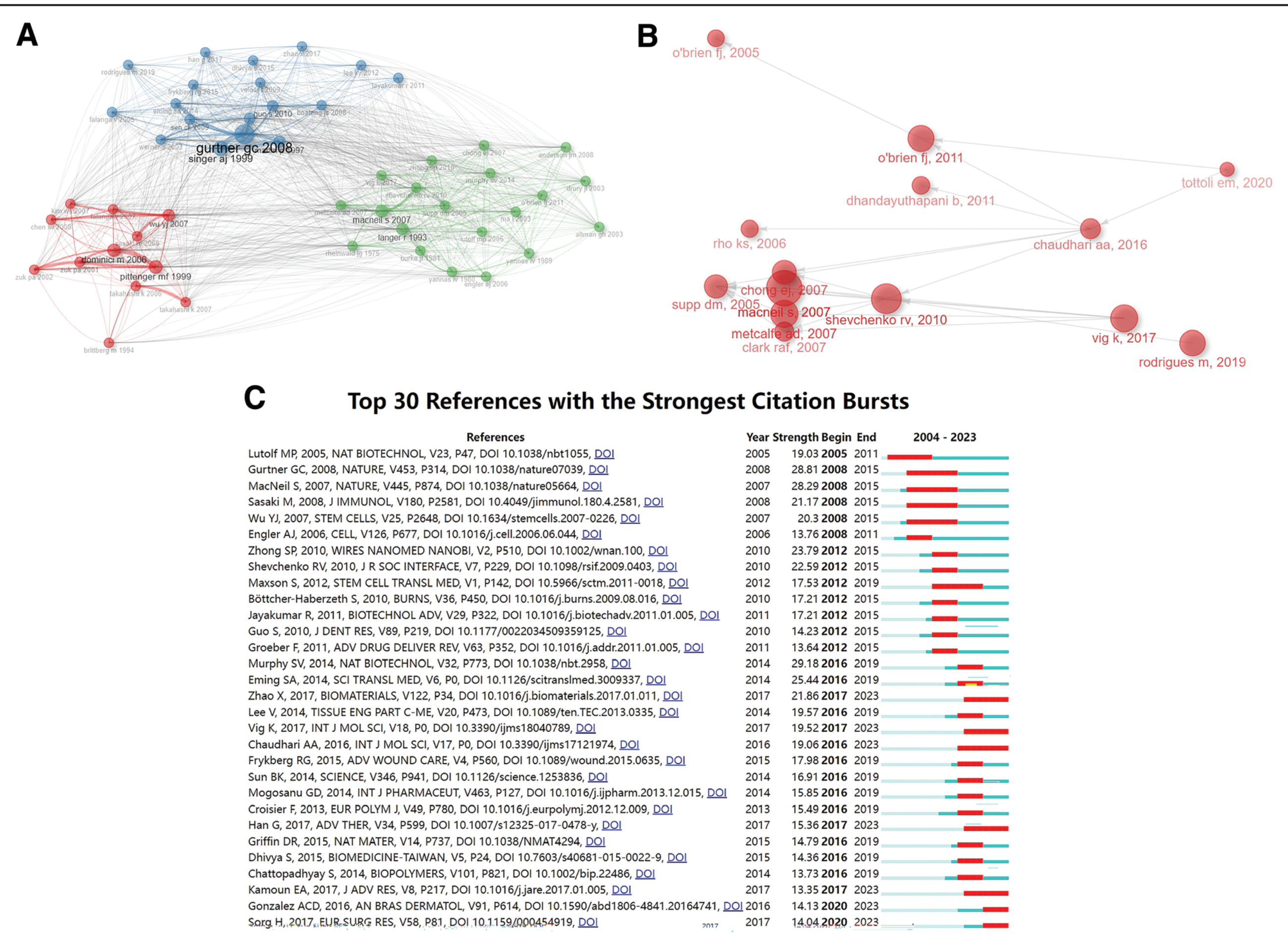

Figure 9. Analysis of references with the visualization, historiograph and strongest citation bursts. (A) The network map of all references (N = 50) involved in tissue engineering and wound healing. (B) Historiograph of the 14 most cited works in this field from 2004 to 2023. (C) Top 30 references with the strongest citation burstiness. The red bars mean some references cited frequently; the blue bars were references cited infrequently.

Biomaterials in Skin Tissue Engineering: A Review" by Chaudhari et al[45] in 2016 summarized various types of scaffolding approaches and biomaterials used in skin tissue engineering or regeneration, and their future prospects. Fourthly, the review "Chronic Wound Healing: A Review of Current Management and Treatments" by Han and Ceilley[46] in 2017 discussed wound healing physiology and treatment approaches. Meanwhile, the review "A review on polymeric hydrogel membranes for wound dressing applications: PVA-based hydrogel dressings" by Kamoun et al[47] in 2017 presented the featured properties and applications of hydrogel membranes in wound dressing. Furthermore, the review "Wound healing – A literature review" by Gonzalez et al[48] in 2016 described the various cellular and molecular aspects involved in the skin healing process. Finally, the review "Skin Wound Healing: An Update on the Current Knowledge and Concepts" by Sorg et al[49] in 2017 analyzed the existing literature specifically targets the key stages of skin wound healing for therapeutic purposes and presented the high interest aspects.

3.7. Factorial analysis

By applying multiple correspondence analysis (MCA), we conducted a detailed analysis of the keywords. MCA simplifies multidimensional data into low-dimensional forms and measures keyword similarity by computing plane distance, which allowed us to create 2-dimensional diagrams. The proximity of a keyword to the center depicts the level of attention that the keyword is receiving. Conversely, if a keyword is farther away from the center, it indicates less interest in the subject.[18] Figure 10A demonstrated the optimal dimension reduction for both the first and second dimensions of MCA. Stem-cells, tissue, growth factors, in vitro, delivery, collagen, endothelial cells, mesenchymal stem-cells and angiogenesis were terms with closer distance from central points, which were all associated with the factors and mechanisms of wound healing. Additionally, the hierarchical clustering dendrogram of the top 50 entries displaying a high degree of correlation was constructed in Figure 10B. The hierarchical clustering dendrogram showed that the terms with the highest correlation were significantly closer. A maximum of 12 levels could be calculated. The complex hierarchical relationships indicated the merging of disciplines and the intensity of research in the field of expertise. At the lowest level of keywords, there were overlaps between different items and the classes were not mutually exclusive. By clustering the top 50 entries into about 3 categories based on term frequency and relevance, readers could gain a quick and comprehensive understanding of the distribution of popular research topics in this field.

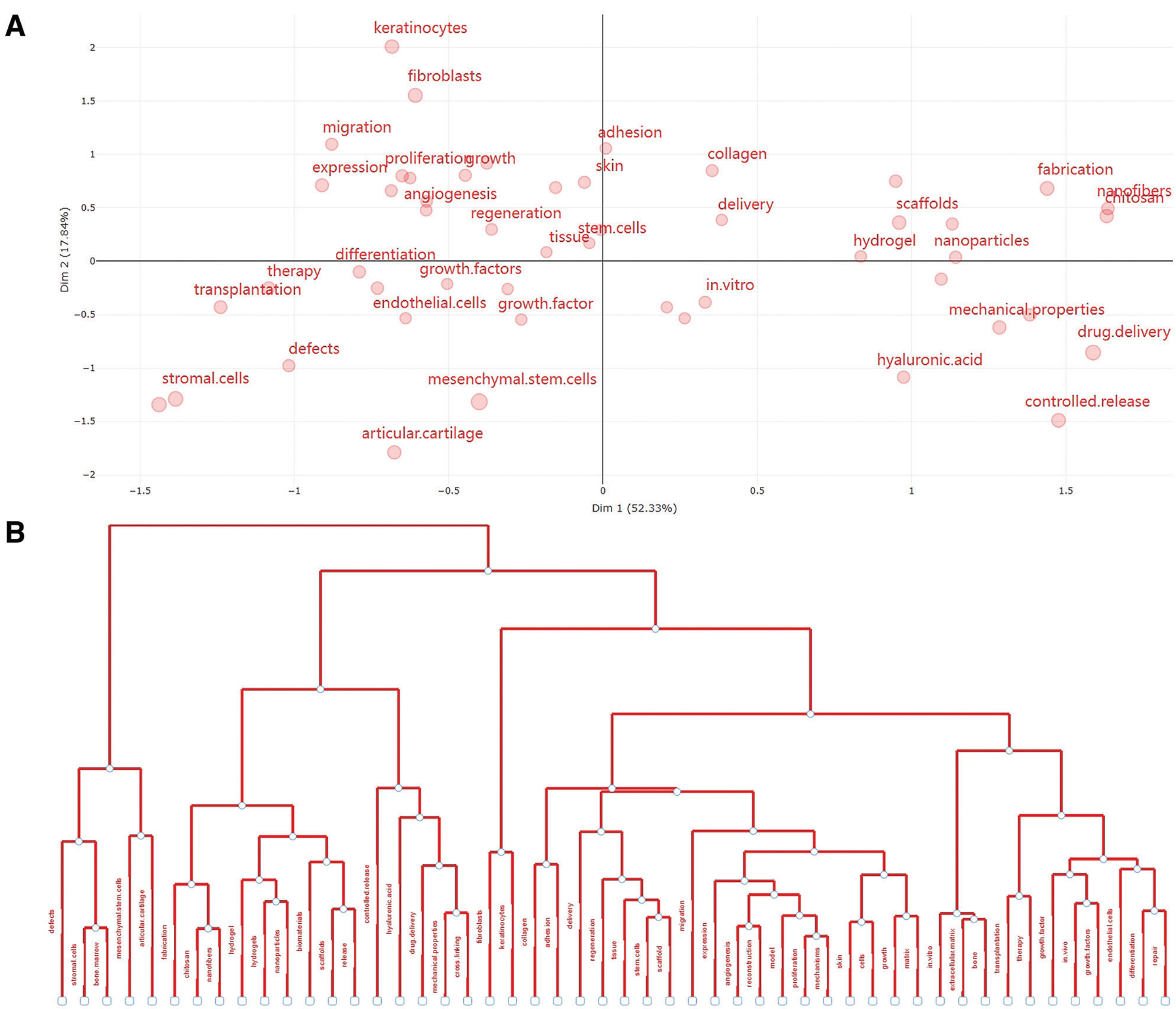

Figure 10. (A) Factorial map of different components of tissue engineering and wound healing. (B) Hierarchical clustering dendrogram of the top 50 entries with correlation.

4. Discussion

4.1. General information

Based on the scientometrics analysis of research data sourced from the WoSCC within the SCI-Expanded database spanning from 2004 to 2023, a total of 9820 targeted documents from 111 countries/regions and 7891 scientific organizations were confirmed across 1630 scholarly journals. These publications collectively referenced 31,050 sources and delved into the current state, emerging patterns, and prospective focal points within the field.

Between 2004 and 2023, the volume of research reports concerning "tissue engineering in wound healing" exhibited an annual uptrend, indicating notable advancements and impact in recent years. Notably, China, the United States, and India emerged as the top 3 contributors, with comparable publication numbers from the top 2 contributors. Among prolific research entities, Shanghai Jiao Tong University in China claimed the leading position, followed by Harvard University and Sichuan University. Moreover, China dominated 4 out of the top 5 spots, highlighting its leadership role and substantial contributions to academic discourse, cultural exchange, and global progress. Collaboration between institutions was robust, notably with Chinese establishments actively engaging with others. For instance, Shanghai Jiao Tong University fostered close ties with Harvard University in the USA and Sichuan University in China, indicating ample collaboration opportunities with Chinese institutions. The journal *Biomaterials* stood out among the top 10 journals in terms of publication volume, citations, H-index, G-index, M-index, and Total link strength, demonstrating its pivotal role and significant research contributions in this domain, with considerable academic influence. Dual-map overlays of journals facilitated the identification of interdisciplinary research avenues and focal points. Within the authorship landscape, Reis and Ramakrishna S made noteworthy publication contributions, while Liu ranked highest in co-citations, underscoring their scholarly impact and substantial academic footprint in the field. Visualization maps generated by VOSviewer depicted stable and fruitful collaborations among these active authors and coauthors.

The observations highlighted in Figure 8A, regarding the co-occurrence and frequency of keywords, suggest that these topics have been continuously investigated and have garnered sustained interest within this field. Additionally, Figure 7C delineated 3 primary clusters based on all keywords: the exploration of natural endogenous technology involving multiple cells and functional factors; the development of artificially synthesized and reprocessed exogenous technology; and investigations into the mechanisms underlying the practical application of tissue engineering technology in wound healing.

4.2. Knowledge base

Local citation analysis involves aggregating references that cite a particular source to determine its citation frequency within a specific research area.[50] These citing sources provide insights into how frequently the relevant research has been referenced in scholarly literature. The compilation of highly cited local citation literature represents core literature and significant research achievements within the field. Therefore, local citation analysis serves as an indicator of the knowledge foundation of a particular field. By examining the research domain and identifying the top 10 commonly cited local references, we established a knowledge base for the study of "tissue engineering and wound healing" in this investigation.

In 2007, MacNeil[28] published the most highly cited paper, summarizing the progress and opportunities for tissue-engineered skin. In 2010, Shevchenko et al[51] outlined materials currently accessible for clinical application and provide a brief overview of those in the developmental phase. Its objective was to furnish skin scientists and tissue engineers with the necessary information not only to construct in vitro skin models but also to progress towards the ultimate objective of creating readily available, fully functional full-thickness skin substitutes. In 2012, Lee and Mooney[29] offered an extensive examination of the fundamental characteristics of alginate and its hydrogels, their various biomedical uses, and propose novel avenues for prospective research involving these polymers, applying for wound healing, drug-delivery, and tissue engineering applications. In 2007, Metcalfe and Ferguson[52] proposed insights from mammalian tissue regeneration offer potential strategies for minimizing scar formation. Advances in DNA microarray and proteomic technology, along with nonviral gene delivery and stem cell research, may lead to smarter skin replacements designed to mimic natural regeneration processes. In 2017, Vig et al[30] centered on presenting a comprehensive outline of progress in the domain of developing tissue-engineered skin substitutes, highlighting the diverse range of types available and their practical utilization. In 2008, Anderson et al[53] suggested a profound comprehension of the interplay between the immune system and these cells, as well as the impact of biomaterials or tissue-engineered constructs on these interactions, could be crucial for ensuring the safety, biocompatibility, and functionality of the device or system being evaluated. In 2011, O'Brien outlined the functional prerequisites and varieties of materials utilized in creating cutting-edge scaffolds for tissue engineering applications. Additionally, it delineated the obstacles and identifies areas where future research and direction are necessary in this swiftly progressing domain. In 2019, Rodrigues et al[39] revealed that deciphering the functions of each of these cellular varieties and their interplay with 1 another is crucial for comprehending the mechanisms involved in typical wound healing and pointed the potential applications of single cell technologies. In 2007, Chong et al[54] suggested an economical composite comprising a nanofibrous scaffold electrospun onto a polyurethane dressing, presenting an appropriate 3-dimensional scaffold for autogenous fibroblast populations. This approach holds significant promise for dermal wound treatment through layered application. In 2005, Supp and Boyce[37] reviewed that artificial skin replacements had been created to meet the medical demand for wound coverage and tissue regeneration, encompassing acellular biomaterials and composite cultured skin analogs incorporating allogeneic or autologous cultured skin cells.

In general, within the top 10 locally cited references, the subjects primarily focused on various cellular engineering technologies, functional factors, impacted mechanisms, and artificially synthesized and reprocessed exogenous technologies, consistent with the findings of keyword co-occurrence analysis.

4.3. Research hotspots

Figure 7 illustrated 3 primary research clusters in tissue engineering research for wound healing from 2004 to 2023, identified through co-occurrence cluster analysis of prominent keywords. Through an examination of keyword frequencies, reference analysis, and term bursts related to various topics, we had outlined both present and future research avenues, as depicted succinctly in Figure 11. Among them, the artificially synthesized and reprocessed exogenous technology had become a hot topic in this field, mainly including nanoparticles, drug-delivery systems, nanofibers, exosomes, 3D bioprinting, hyaluronic-acid, chitosan, hydrogel, etc.

Progress in tissue engineering had led to the emergence of innovative and promising strategies to expedite the healing of wounds. The employment of diverse biomaterials that could facilitate the regeneration of injured tissue was vital within the field of tissue engineering. Nanoparticles or nanofibers of

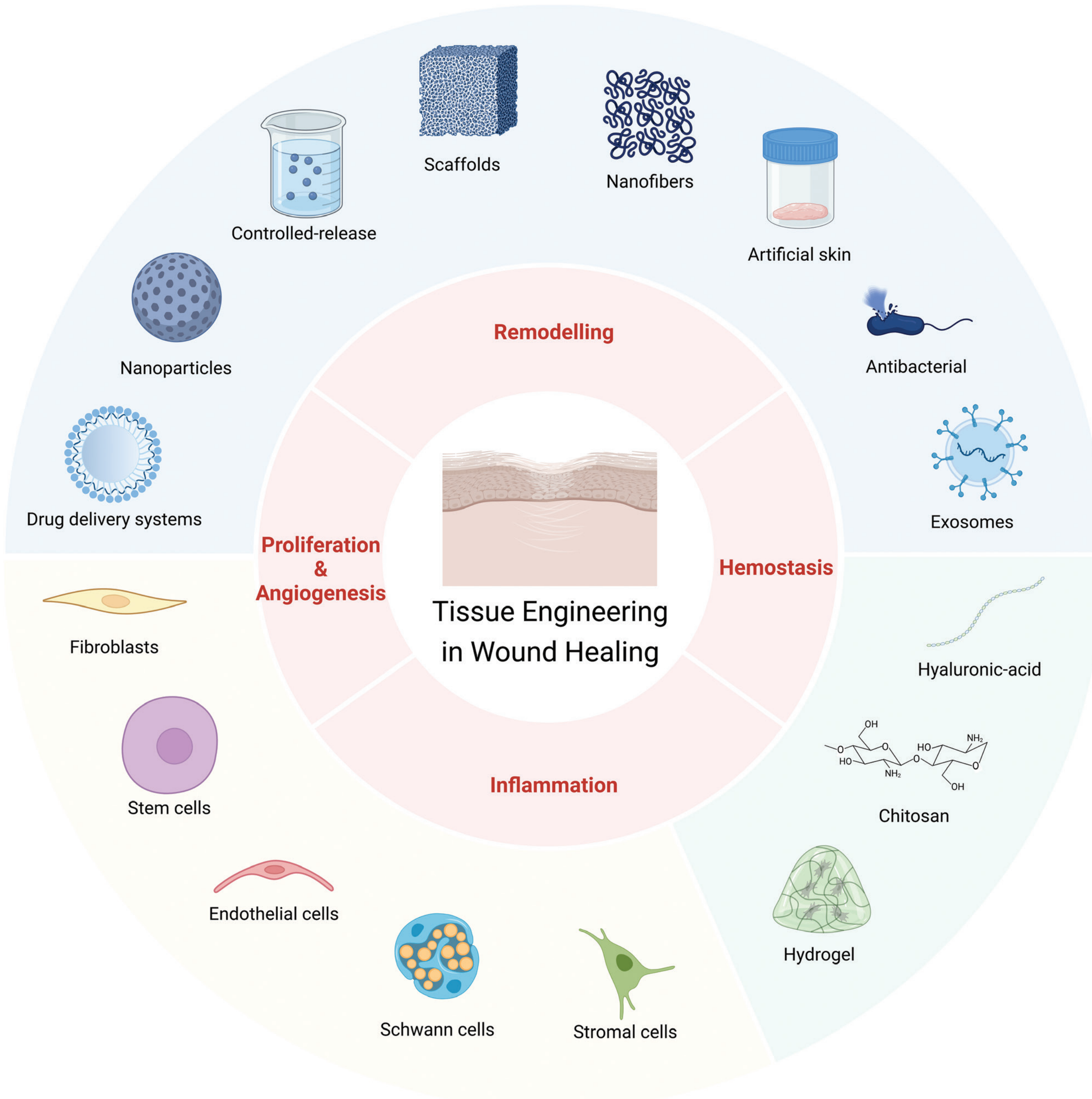

Figure 11. The schematic diagram of the application of tissue engineering in wound healing based on keywords and references visualization analysis.

different biological components with excellent biological properties, including antibacterial, anti-inflammatory, antioxidant, and angiogenic characteristics had aroused huge interest of scholars.[55] Nanoparticles, nanofibers, scaffolds, drug-delivery systems and 3D bioprinting structures were often utilized as carriers in wound repair. And chitosan, chitin, cellulose acetate, hyaluronic-acid, pullulan, bacterial cellulose, fibrin, alginate, and other wound dressings fabricated from natural resources with prominent biological properties, had been extensively incorporated into synthetic wound dressings to achieve excellent biocompatibility and biodegradability.[56] For example, Li et al[57] pointed the successful practice of bioactive antibacterial silica-based nanocomposites hydrogel scaffolds for diabetic wound healing. Similarly, engineered exosomes formulated as exosome@biomaterial-based miRNA delivery systems had shown efficacy in loading miR146a and binding to silk fibroin protein patches (SFP), with demonstrated anti-inflammatory and regenerative benefits in fostering the healing of diabetic wounds.[58] Wang et al[59] implemented an in situ microfluidic-assisted 3D bioprinting strategy to generate a novel category of living photosynthetic scaffolds engineered to conform to irregularly shaped wounds and expedite their recuperation. Meanwhile, hyaluronic-acid,[60] chitosan,[61] hydrogel[62] or their modified substances[63,64] had been proven to have unique advantages in mitigating local hypoxia, enhancing angiogenesis, and stimulating the synthesis of extracellular matrix, etc. However, the application methods, compositions, and application scenarios of these different biomaterials varied depending on the type and severity of the wound, which presented challenges in developing future wound healing treatment strategies.[65] Furthermore, the application of tissue engineering in wound healing still faced challenges and uncertainties despite of the surge in literature and the development of novel materials. This was mainly due to the lack of multicenter clinical trial data, the feasibility and cost of future clinical application, the insufficiency of biosafety and biocompatibility, and the standardization and monitoring of outcomes.[66–69] Herein, deliberately addressing the above-mentioned issues and handling them properly would render the application research worthy of more attention and further in-depth studies in the future.

4.4. Strengths and limitations

This study employed bibliometrics and visual analysis to explore the focal points and emerging patterns within the realm research of tissue engineering and wound healing. Nonetheless, several constraints remained apparent. Initially, integrating data from multiple databases posed a challenge, potentially leading to oversight of relevant findings housed in alternate repositories beyond our exclusive reliance on the WOS database and its English-language publications. However, after we tried to search them in different databases like Scopus and PubMed, etc, the core author collaboration patterns and dominant research themes remained mostly consistent, suggesting the most principal conclusions were robust despite partial data exclusion. Additionally, the inadequate citation of noteworthy papers may result in the oversight of valuable contributions that surpassed those garnering extensive citations. Lastly, predicting future research trajectories may involve subjective interpretations due to the intricate and uncertain nature of forthcoming events. Despite these limitations, this research established a theoretical framework for prospective investigations while reflecting the ongoing advancements within the domains of tissue engineering research and wound healing.

5. Conclusion

A multidimensional and comprehensive analysis was performed to examine the utilization of tissue engineering in wound healing, encompassing annual trends, countries or regions, institutions, journals, authors and their relationships, focal topics, potential directions, and an extensive literature review, which offered scholars the opportunity to broaden and delve into the interconnections. Keyword and reference analyses unveiled 3 major research directions: natural endogenous technology involving multiple cells and functional factors, mechanism research on the practical application of tissue engineering technology in wound healing, and artificially synthesized and reprocessed exogenous technology. Among these, the latter represented the current focal point in the field, worthy of more attention and further in-depth studies in the future.

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The partial figure was created with https://biorender.com/ with an academic license.

Author contributions

Conceptualization: Yixuan Xing, Liping Cao.
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Funding acquisition: Liping Cao.
Supervision: Liping Cao.
Visualization: Yixuan Xing.
Writing – original draft: Yixuan Xing, Liping Cao.
Writing – review & editing: Yixuan Xing, Zhen Huang, Liping Cao.

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