

World Journal of *Stem Cells*

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ABOUT COVER

Editorial Board of *World Journal of Stem Cells*, Rui-Li Yang, DDS, PhD, Associate Professor, Department of Orthodontics, Peking University School and Hospital of Stomatology, National Clinical Research Center for Oral Diseases & National Engineering Laboratory for Digital and Material Technology of Stomatology, Beijing 100081, China. rui.liyangabc@163.com

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Research progress and challenges in stem cell therapy for diabetic foot: Bibliometric analysis and perspectives

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Abstract

BACKGROUND

Stem cell therapy has shown great potential for treating diabetic foot (DF).

AIM

To conduct a bibliometric analysis of studies on the use of stem cell therapy for DF over the past two decades, with the aim of depicting the current global research landscape, identifying the most influential research hotspots, and providing insights for future research directions.

METHODS

We searched the Web of Science Core Collection database for all relevant studies on the use of stem cell therapy in DF. Bibliometric analysis was carried out using CiteSpace, VOSviewer, and R (4.3.1) to identify the most notable studies.

RESULTS

A search was conducted to identify publications related to the use of stem cells for DF treatment. A total of 542 articles published from 2000 to 2023 were identified. The United States had published the most papers on this subject. In this field, Iran's Shahid Beheshti University Medical Sciences demonstrated the highest productivity. Furthermore, Dr. Bayat from the same university has been an outstanding researcher in this field. *Stem Cell Research & Therapy* is the journal with the highest number of publications in this field. The main keywords were "diabetic foot ulcers," "wound healing," and "angiogenesis."

CONCLUSION

This study systematically illustrated the advances in the use of stem cell therapy to treat DF over the past 23 years. Current research findings suggested that the hotspots in this field include stem cell dressings, exosomes, wound healing, and adipose-derived stem cells. Future research should also focus on the clinical translation of stem cell therapies for DF.

Key Words: Stem cells; Diabetic foot; Bibliometric; CiteSpace; VOSviewer; R-bibliometrix

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Core Tip: Through the utilization of bibliometric analysis, this study systematically presented the body of research concerning stem cell therapy in diabetic foot cases, while also identifying focal points and burgeoning trends within this domain.

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INTRODUCTION

Diabetic foot (DF) is one of the most common complications of diabetes. Once infections and recurrences occur in DF patients, wounds are prone to deteriorate, leading to sepsis and an increased risk of amputation[1]. DF constitutes a significant contributor to disability and mortality among individuals with diabetes[2], with as many as 20% of diabetic patients requiring hospitalization due to this condition[3]. Evidence indicates that approximately 4%-10% of individuals with type 2 diabetes may experience DF ulcers (DFUs). Furthermore, the risk of mortality within a 5-year period for those affected by DF is notably elevated, as it is 2.5 times higher than the risk among diabetes patients without DF[4]. It is estimated that a diabetes-related amputation is performed every 20 s globally. The annual mortality rate for DFU patients is as high as 11%, and for amputees, it is as high as 22%[5]. Unfortunately, over the past few decades, there has been no improvement in the incidence and disability rates of DF. Traditional DF therapies have also been unsatisfactory. Moreover, standalone interventions or vascular bypass surgeries are inadequate to address the fundamental pathological mechanisms of widespread blood vessel constriction and blockage in DF as well as nerve and tissue impairments[6].

Currently, most treatment methods for DF mainly target a single factor related to wound healing. Due to advances in regenerative medicine in the clinical setting, there has been widespread interest in the potential impact of stem cells on DF[7]. As a highly promising approach for treating DF[8], the main advantage of stem cell therapy lies in its ability to comprehensively regulate tissue regeneration by improving the microenvironment[9-11]. The mechanisms that contribute to the effectiveness of stem cell therapy involve promoting the deposition of collagen, instigating the formation of new blood vessels, enhancing lower limb blood flow, and mitigating inflammation[12].

Bibliometric analysis, which focuses on the systematic and characteristic features of literature, has been widely used to qualitatively and quantitatively analyze scientific literature[13,14]. It has been extensively applied in gynecology[15], orthopedics[16], complementary and alternative medicine[17], and other medical fields. Bibliometrics serves not only as a tool for comprehensively understanding research trends and hotspots within a particular domain but also as a means to assess the distribution of authors, countries/regions, and journals associated with a specific research field. Therefore, bibliometric analysis lays the foundation for future research directions and development[18]. In this study, a scientific knowledge map of stem cell research within the realm of DF was constructed using CiteSpace, VOSviewer, and R (4.3.1). This approach was employed to examine the hotspots and development trends within this field.

MATERIALS AND METHODS

Publication sources and search methods

For this study, the Web of Science Core Collection (WoSCC) database was selected as the publication source. This database is widely used within the academic community and encompasses a range of internationally renowned scientific journals of significant impact and exceptional quality. It provides a comprehensive and standardized dataset for bibliometric analysis[19]. Due to the dynamic nature of the database, the literature search was performed on 1 d (August 1, 2023) to mitigate potential biases arising from rapid updates. The search strategy for this study is presented in Table 1. The publication types included articles and reviews, and the language limitation was set to English.

Publication screening and access

Two researchers (SHS and YX) independently screened the publications for inclusion in this study. The collected literature was exported in two formats: Complete records and references. They were saved as plain text files under the label "download_txt." The file content included the title, abstract, author information, affiliations, keywords, publication date, and cited references.

Table 1 Literature screening

Set	Publications	Screen
1	597	Topic: (TS=("Stem Cells" OR "Cell, Stem" OR "Cells, Stem" OR "Stem Cell" OR "Progenitor Cells" OR "Cell, Progenitor" OR "Cells, Progenitor" OR "Progenitor Cell" OR "Mother Cells" OR "Cell, Mother" OR "Cells, Mother" OR "Mother Cell" OR "Colony-Forming Unit" OR "Colony Forming Unit" OR "Colony-Forming Units" OR "Colony Forming Units")) AND TS=("Foot, Diabetic" OR "Diabetic Feet" OR "Feet, Diabetic" OR "Foot Ulcer, Diabetic" OR "Diabetic Foot")
2	547	Types of publications: (ARTICLES OR REVIEWS)
3	543	Languages of publications: (ENGLISH)

Data analysis

All pertinent documents retrieved from the WoSCC database were imported into bibliometrix (based on R 4.3.1.), VOSviewer, and CiteSpace for visualization analysis. Two essential metrics commonly employed to evaluate research performance are the number of publications (Np), which serves as a gauge of productivity, and the number of citations (Nc), which serves as an indicator of impact.

R-bibliometrix is used to conduct bibliometric analysis on leading research nations, institutions, and journals[20]. The primary application of the h-index is to assess researchers' academic contributions and anticipate their forthcoming scientific accomplishments. The g-index, which is derived from the h-index, can further measure the impact and scholarly achievements of researchers[21]. Moreover, these indices can be obtained to characterize the publication output of a country or region as well as the output of an institution or journal[19,22].

VOSviewer is a network analysis software for scientometric research that was developed by the Centre for Science and Technology Studies at Leiden University in the Netherlands. It provides visual analysis and allows the creation of maps based on network data. The software enables connections between items through cocitation links, co-occurrence, citations, and bibliographic coupling. VOSviewer offers three types of visual maps: Network; overlay; and density visualization[23,24].

The CiteSpace software is a citation visualization and analysis tool rooted in scientometrics and data visualization. It was created by Professor Chaomei Chen at Drexel University using the Java programming language[25]. By leveraging data mining, information analysis, and map visualization techniques, it effectively illustrates the architecture, patterns, and dissemination of scientific knowledge[26].

RESULTS

An overview of stem cells in DF publications

After retrieving and filtering publications from the WoSCC database, a total of 543 publications were included. Among them, 350 articles and 193 reviews were ultimately included in this analysis. The studies were published between 2000 and 2023, and the h-index was 71.

Figure 1 illustrates the geographic distribution of the overall research paper count across all countries and regions. Among the 543 articles, the top two countries accounted for more than half of the total. The United States had the highest number of published papers, followed by China, Iran, England, and Italy.

Between 2000 and 2022, the annual Np increased rapidly and exhibited a polynomial fit, $y = 0.1484x^2 - 593.9x + 594231$, $R^2 = 0.9714$. The annual cumulative publication volume followed an exponential curve, $y = 2E-247e^{0.2843x}$, $R^2 = 0.9601$ (Figure 2).

Country/region contributions to global publications

The top 10 countries/regions in terms of output are shown in Table 2. The country with the highest number of published papers was the United States (183/543, 33.70%), followed by China (152/543, 27.99%), Iran (35/543, 6.45%), England (33/543, 6.08%), and Italy (28/543, 5.16%). Papers from the United States were cited 9663 times, accounting for 44.84% of the total citations, followed by China (3828; 17.76%) and England (2449; 11.36%). In addition, the United States (46) had the highest h-index, followed by China (32) and England (20). The network (Figure 3A) and density (Figure 3B) maps constructed using VOSviewer also indicated the research influence of the United States and China. As shown in Figure 3C, the largest connected component in the co-occurrence network of countries/regions consisted of 60 nodes and 185 connections (density = 0.01). The purple hue corresponds to the betweenness centrality coefficients of countries/regions, encompassing the United States (0.83), England (0.23), Italy (0.17), and China (0.15). This indicates that these countries/regions assume a "bridging" role within this domain, and this finding was also confirmed by the multiple-country publication value in Figure 3D.

Analysis of author institution publications

We compiled a list of the 10 institutions with the highest Np (Table 3). These institutions were located in the United States (5/10), China (4/10), and Iran (1/10). The top six institutions in terms of publication ranking included Shahid Beheshti University Medical Sciences (Iran, 13/2.39%), University of Louisville (the United States, 12/2.21%), Army Medical University (China, 12/2.21%), Tongji University (China, 11/2.03%), Chinese Academy of Medical Sciences-Peking Union

Table 2 Top 10 countries/regions with the highest research productivity

No.	Country	Np	Np, %	h-index	Nc	Nc, %	Centrality
1	United States	183	33.70	46	9663	44.84	0.83
2	China	152	27.99	32	3828	17.76	0.15
3	Iran	35	6.45	16	901	4.18	0.03
4	England	33	6.08	20	2449	11.36	0.23
5	Italy	28	5.16	14	721	3.35	0.17
6	India	25	4.60	11	1249	5.80	0.02
7	Germany	24	4.42	13	766	3.55	0.05
8	South Korea	16	2.95	11	953	4.42	0.06
9	Spain	16	2.95	8	362	1.68	0.02
10	Ireland	13	2.39	8	981	4.55	0.09

Np: Number of publications; Nc: Number of citations.

Table 3 Top 10 most productive affiliations

No.	Institutions	Country	Np	Np/N1, %	h-index	Nc	Nc, %	Centrality
1	Shahid Beheshti University Medical Sciences	Iran	13	2.39	8	241	0.01	0
2	University of Louisville	United States	12	2.21	7	160	0.01	0
3	Army Medical University	China	12	2.21	11	331	0.02	0
4	Tongji University	China	11	2.03	10	499	0.02	0.02
5	Chinese Academy of Medical Sciences-Peking Union Medical College	China	11	2.03	6	272	0.01	0.04
6	Boston University	United States	11	2.03	9	813	0.04	0.13
7	University of California System	United States	10	1.84	10	386	0.02	0.13
8	Harvard University	United States	10	1.84	12	909	0.04	0.06
9	University of Miami	United States	9	1.66	8	859	0.04	0
10	Shanghai Jiao Tong University	China	7	1.29	4	191	0.01	0.06

Np: Number of publications; Nc: Number of citations.

Table 4 Top 5 authors and cocited authors with the most publications

No.	Ref.	Np	h-index	Institution	Country	Cocited author	Centrality	Cocitation
1	Bayat <i>et al</i> [28]	12	7	Shahid Beheshti University of Medical Sciences	Iran	FALANGA V	0.36	151
2	Amini <i>et al</i> [29]	12	7	Shahid Beheshti University of Medical Sciences	Iran	BREM H	0.12	87
3	Tomic-Canic <i>et al</i> [30]	12	3	University of Miami	United States	ARMSTRONG DG	0.21	86
4	Veves <i>et al</i> [31]	6	7	Harvard Medical School	United States	BOULTON AJM	0.06	70
5	Pastar <i>et al</i> [32]	4	6	University of Miami	United States	MARSTON WA	0.10	59

Np: Number of publications.

Medical College (China, 11/2.03%), and Boston University (density = 0.01). Boston University (0.13) and the University of California System (0.13) had the highest centrality, and their nodes were identified by purple circles (Figure 4).

Author analysis and cocitation author analysis.

In 1997, economists Katz and Martin provided a definition for “scientific collaboration,” wherein scholars unite to collab-

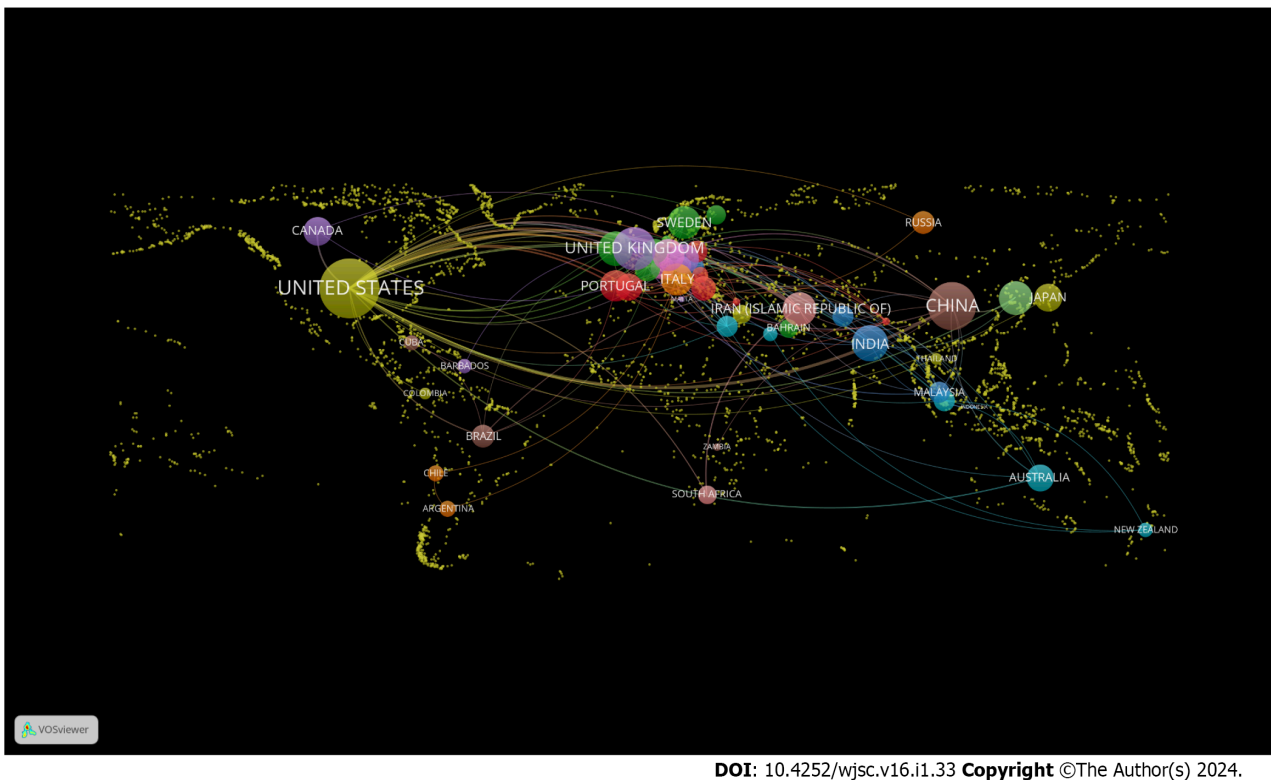


Figure 1 Geographical distribution of publications on stem cells in diabetic foot research.

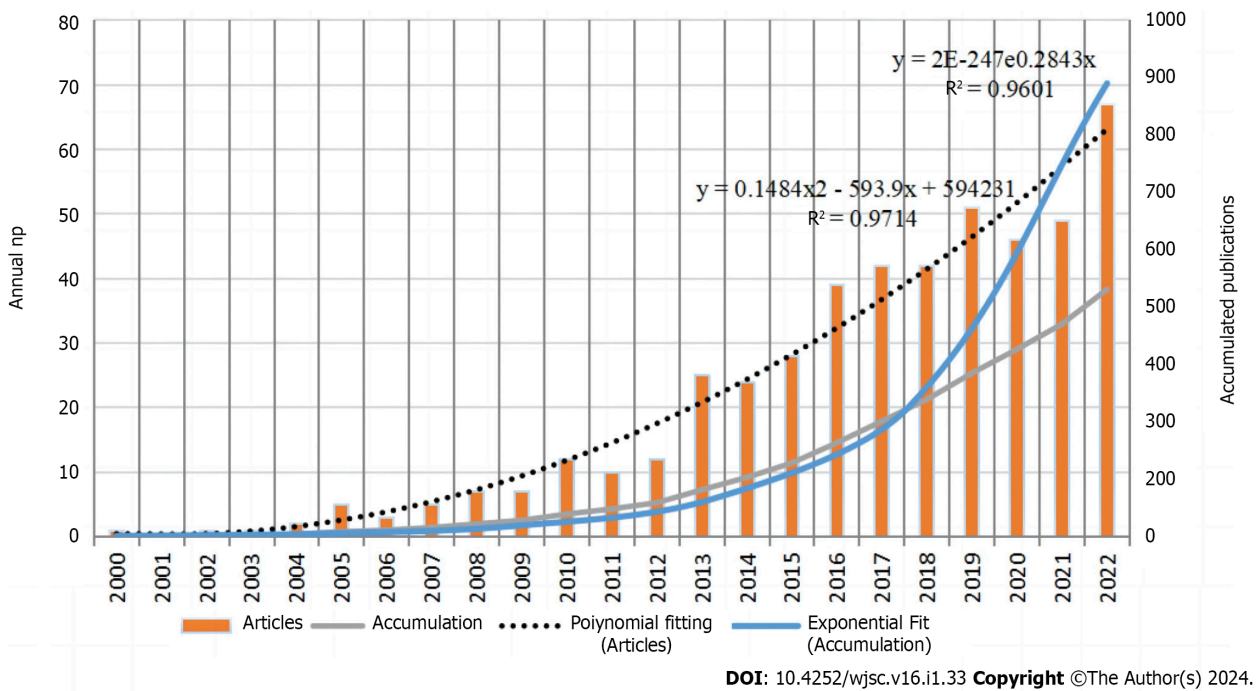
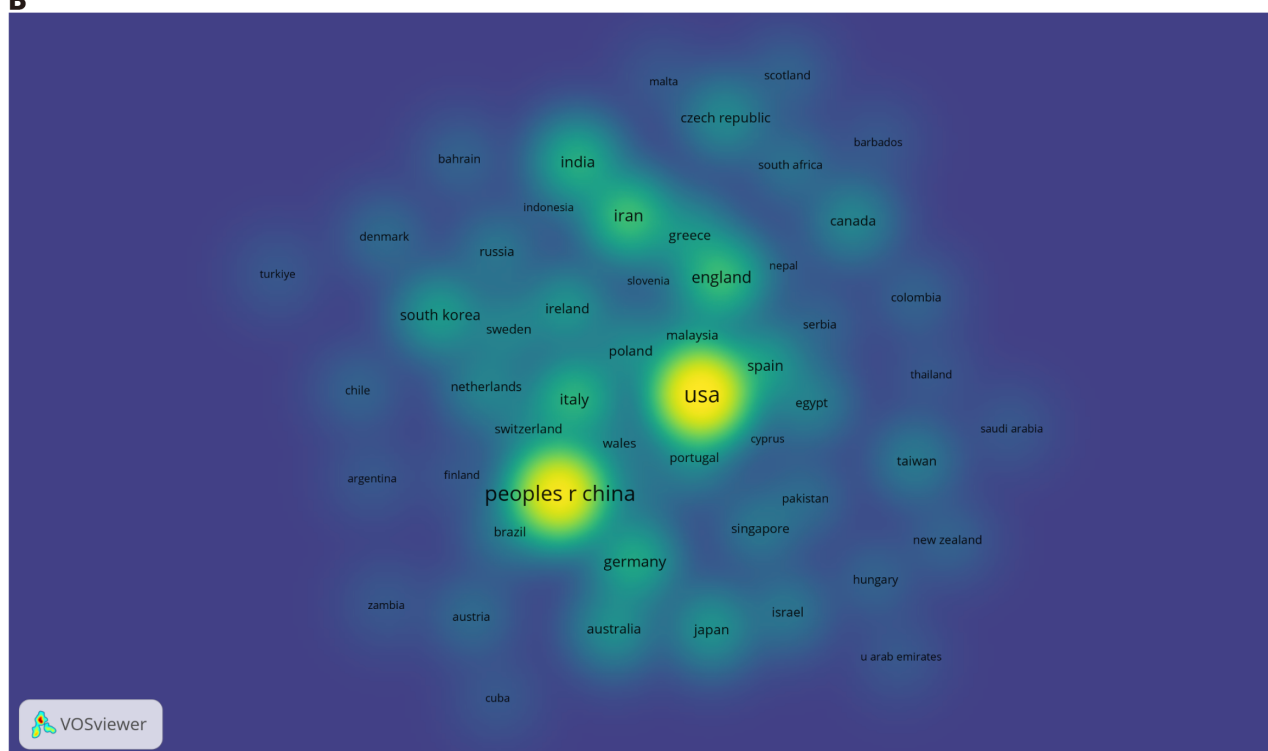


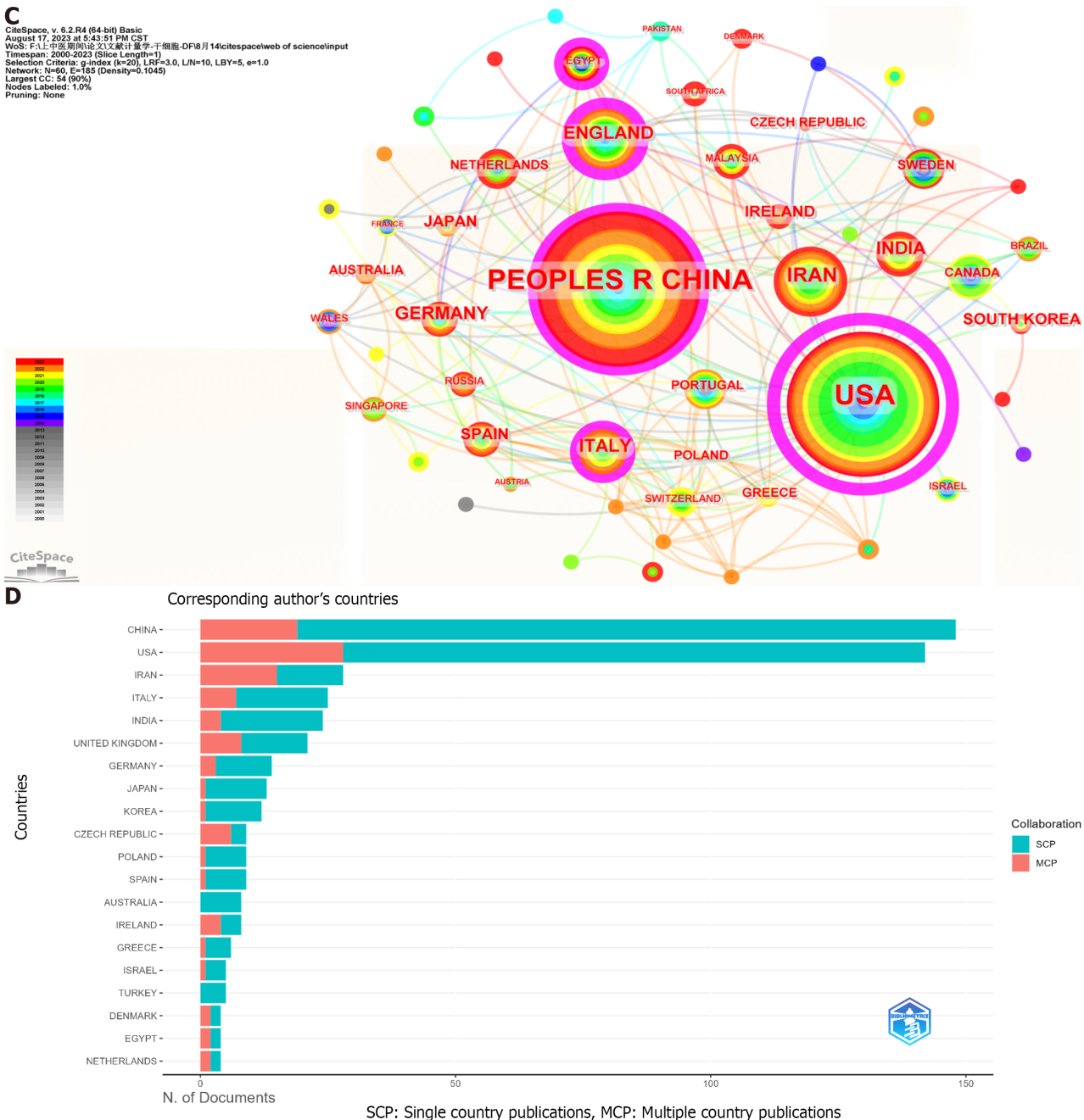
Figure 2 Publication count divided by year over the past 23 years. Np: Number of publications.

oratively pursue shared scientific objectives[27]. We identified 2798 authors who have published articles on the topic of stem cells in DF research. Figure 5A displays the 10 authors with the highest average annual publication count. Among them, Bayat[28], Amini[29], and Tomic-Canic[30] published the highest number of studies ($n = 12$), followed by Veves ($n = 6$)[31] and Pastar C ($n = 4$)[32] (Table 4). Cocitation authors refer to the authors who are cited together in the same article. Figure 5B and C show the network and density maps of cocited authors, respectively. Among the 28753 cocited authors, 173 have been cited together more than 20 times. The top five cocited authors were FALANGA V ($n = 151$), BREM H ($n = 87$), ARMSTRONG DG ($n = 86$), BOULTON AJM ($n = 70$), and MARSTON WA ($n = 59$) (Table 4). As shown



C

CiteSpace, v. 6.2.R4 (64-bit) Basic
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WoS: 上中医学期间论文文献计量学-细胞组-DF18月14
citespace\web of science\input
Timespan: 2000-2023 (Slice Length=1)
Selection Method: g-index (k=20), LRF=3.0, L/N=10, LB=5, e=1.0
Network: N=60, E=185 (Density=0.1045)
Largest CC: 54 (90%)
Nodes Labeled: 1.0%
Pruning: None



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Figure 3 Contributions of different countries to research on stem cells in the diabetic foot field. A: Network visualization of country collaboration; B: Density map of cooperation between countries; C: A network diagram showing international collaborations, with purple circles representing intermediation centrality; D: Top 20 countries for corresponding authors. MCP: Multiple-country publications; SCP: Single-country publications.

in **Figure 5D**, the author with the highest betweenness centrality in terms of citations was FALANGA V (0.36), followed by ARMSTRONG DG (0.21) and BOULTON AJM (0.12).

Journals and cocited journals

Studies related to the use of stem cell therapy in DF patients were published in a total of 280 different journals. The journal *Stem Cell Research & Therapy* [22/7.86%, impact factor (IF): 7.5, Journal Citation Reports (JCR): Q1] had the highest output quantity; this journal emphasizes basic, clinical, and translational research on stem cell therapy and regenerative medicine. The next most productive journal was *International Wound Journal* (17/6.07%, IF: 3.1, JCR: Q2). Among the top 10 journals, 8 belonged to the JCR Q1 category, with 9 having an IF exceeding 3 (Table 5). Additionally, *Stem Cell Research & Therapy* had the highest h-index (Figure 6A) and g-index (Figure 6B).

Among the 4667 cocited journals, 82 journals have been cited more than 100 times. Table 2 shows that *Wound Repair and Regeneration* (1297/27.79%, IF: 2.9, JCR: Q1) had the highest number of citations, followed by *Diabetes Care* (951/20.38%, IF: 16.2, JCR: Q1) and *Biomaterials* (681/14.59%, IF: 14, JCR: Q1). Among the top 10 cocited journals, 8 were in JCR Q1, and they all had an IF exceeding 3 (Table 5 and Figure 6C).

Table 5 Top 10 journals and cocited journals with the most publications								
No.	Journal	Np	IF in 2020	JCR	Cocited journal	Cocitation, %	IF in 2020	JCR
1	Stem Cell Research & Therapy	22	7.5	Q1	Wound Repair and Regeneration	1297 (27.79)	2.9	Q1
2	International Wound Journal	17	3.1	Q2	Diabetes Care	951 (20.38)	16.2	Q1
3	Wound Repair and Regeneration	14	2.9	Q1	Biomaterials	681 (14.59)	14.0	Q1
4	Advances in Wound Care	11	4.9	Q1	Journal of Investigative Dermatology	668 (14.31)	6.5	Q1
5	Diabetes-Metabolism Research and Reviews	9	8.0	Q2	PLOS One	626 (13.41)	3.7	Q2
6	International Journal of Molecular Sciences	9	5.6	Q1	Plastic and Reconstructive Surgery	576 (12.34)	3.6	Q1
7	Frontiers in Endocrinology	8	5.2	Q1	International Wound Journal	575 (12.32)	3.1	Q2
8	Biomedicines	8	4.7	Q1	Stem Cell Research & Therapy	488 (10.46)	7.5	Q1
9	Plastic and Reconstructive Surgery	8	3.6	Q1	Stem Cells	462 (9.90)	5.2	Q1
10	Diabetes	7	7.7	Q1	Advances in Wound Care	457 (9.79)	4.9	Q1

IF: Impact factor; JCR: Journal Citation Reports; Np: Number of publications.

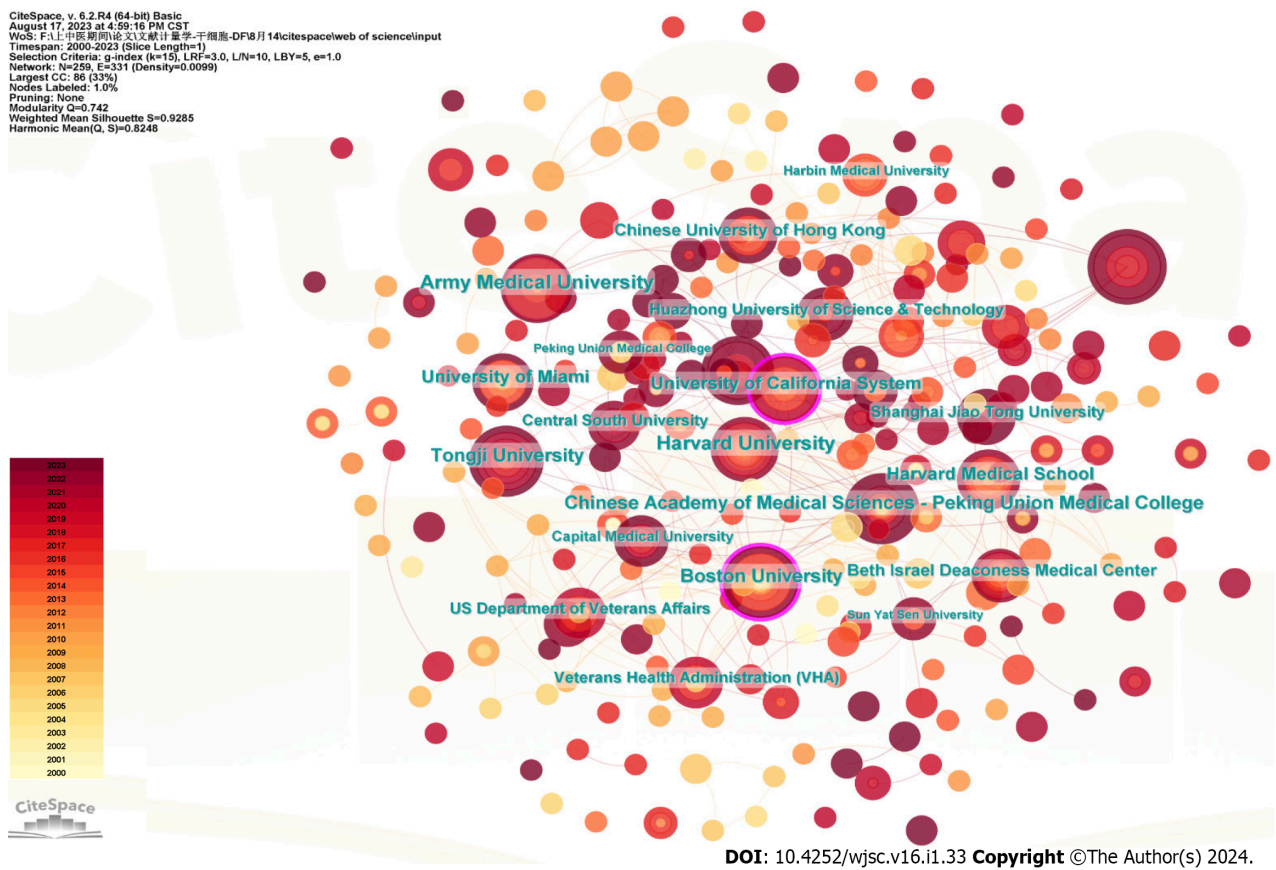


Figure 4 Institutional collaboration network diagram, with purple circles representing intermediation centrality.

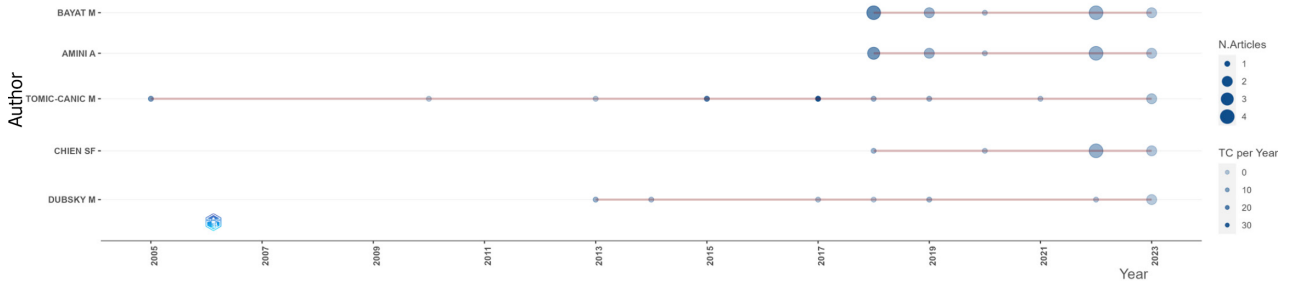
The dual plot of the journals displays the distribution of relationships between them. As shown in Figure 6D, there are primarily four citation pathways, consisting of two orange paths and two green paths. The relevant pathways are listed in Table 6.

Cocited reference analysis

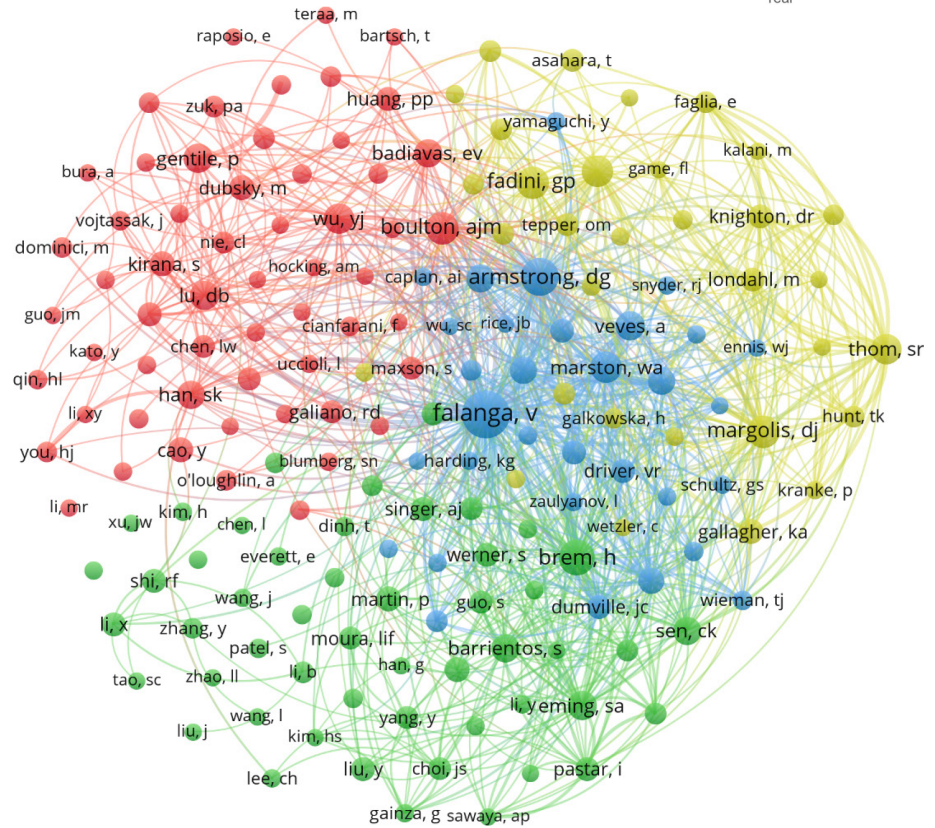
Cocitation describes how often two documents are referenced jointly[33]. Table 7 lists the top 10 referenced articles that were most commonly cocited. Among the 28717 cited articles, 27 articles have been cited more than 30 times. The top six referenced articles have all been cited more than 50 times. The article by Armstrong *et al*[34] that was published in the *New England Journal of Medicine* in 2017 had the highest number of cocitations, followed by the article published by Lopes *et al*[35] in 2018 (Figure 7A). Based on cluster analysis, a total of eight clusters were identified (Figure 7B), indicating the

A

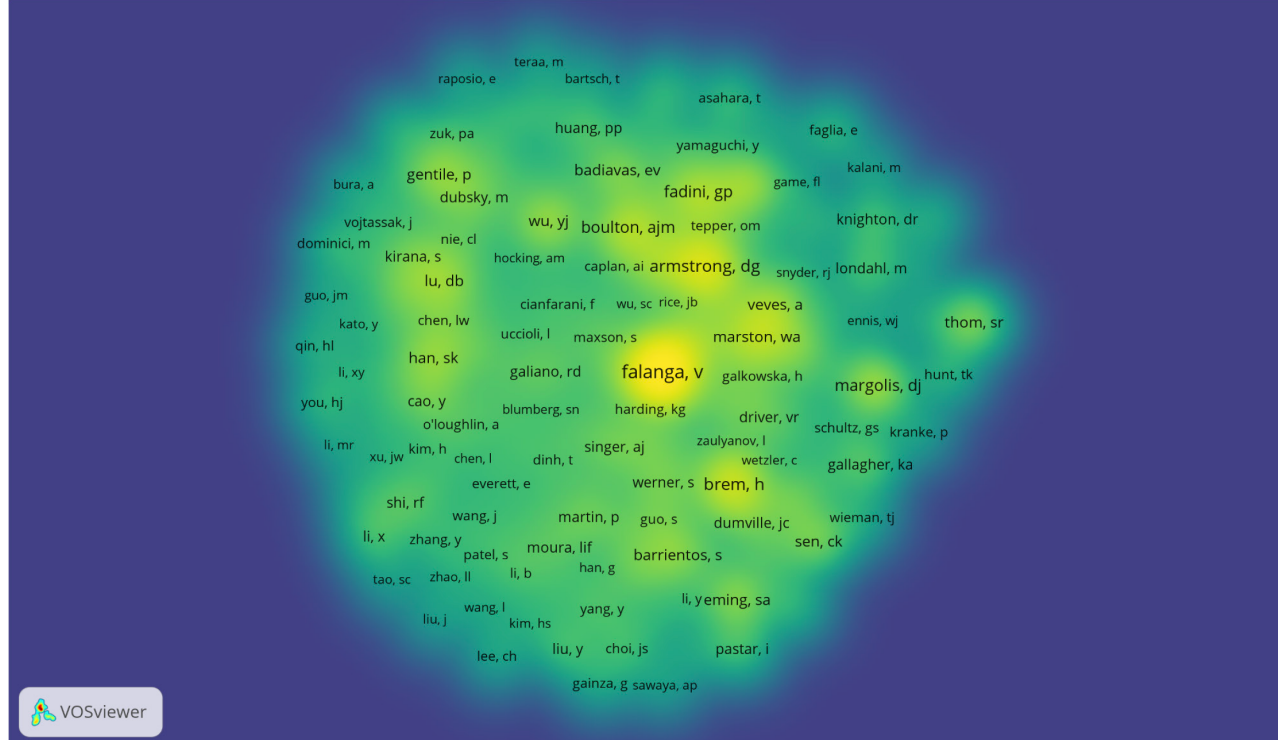
Authors production over time

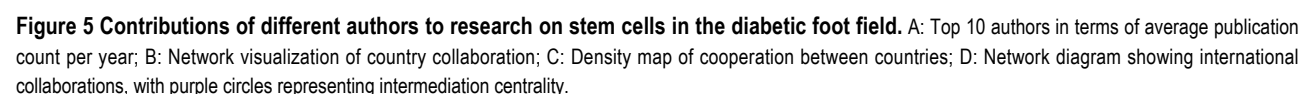


B



C





Analysis of co-occurrence keywords

DISCUSSION

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Table 6 Paths between citing journals and cited journals

No.	Journal	Cited journal	Path color
1	Molecular/Biology/Immunology	Molecular/Biology/Genetics	Orange
2	Molecular/Biology/Immunology	Health/Nursing/Medicine	Orange
3	Medicine/Medical/Clinical	Molecular/Biology/Genetics	Green
4	Medicine/Medical/Clinical	Health/Nursing/Medicine	Green

Table 7 Top 10 cocited references referring to cocitations

Ref.	Year	Journal	DOI	Cocitations	Centrality
Armstrong <i>et al</i> [34]	2017	New England Journal of Medicine	10.1056/NEJMra1615439	32	0.42
Lopes <i>et al</i> [35]	2018	Stem Cell Research & Therapy	10.1186/s13287-018-0938-6	26	0.09
Li <i>et al</i> [61]	2018	Experimental & Molecular Medicine	10.1038/s12276-018-0058-5	25	0.02
Everett and Mathioudakis[62]	2018	Annals of the New York Academy of Sciences	10.1111/nyas.13569	25	0.09
Cao <i>et al</i> [63]	2017	Journal of Diabetes Research	10.1155/2017/9328347	23	0.10
Patel <i>et al</i> [64]	2019	Biomedicine & Pharmacotherapy	10.1016/j.biopha.2019.108615	22	0.04
Moon <i>et al</i> [65]	2019	Diabetes	10.2337/db18-0699	20	0.06
Maxson <i>et al</i> [38]	2012	Stem Cells Translational Medicine	10.5966/sctm.2011-0018	19	0.10
Zhang <i>et al</i> [39]	2017	Annals of Medicine	10.1080/07853890.2016.1231932	18	0.06
Li <i>et al</i> [66]	2020	About Molecular Therapy – Nucleic Acids	10.1016/j.omtn.2019.11.034	16	0.02

Table 8 Top 20 keywords based on their frequency

No.	Occurrence frequency	Centrality	Year	Keywords	No.	Occurrence frequency	Centrality	Year	Keywords
1	253	0.51	2004	Diabetic foot ulcers	11	47	0.04	2007	Expression
2	119	0.04	2011	Wound healing	12	44	0.12	2005	Chronic wounds
3	98	0.05	2013	Mesenchymal stem cells	13	40	0.02	2013	Stem cells
4	78	0.04	2011	Stem cells	14	38	0.08	2004	Diabetes mellitus
5	75	0.13	2006	Angiogenesis	15	37	0.03	2005	Skin
6	71	0.06	2005	Diabetic foot	16	34	0.04	2012	Critical limb ischemia
7	57	0.06	2011	Therapy	17	33	0.03	2011	In vitro
8	55	0.09	2004	Management	18	32	0.02	2011	Stromal cells
9	51	0.12	2006	Endothelial progenitor cells	19	31	0.03	2014	Proliferation
10	48	0.05	2004	Differentiation	20	30	0.02	2011	Foot ulcers

trends in this field[40,41].

General information

Based on the information retrieved from the WoSCC database as of August 1, 2023, there have been a total of 982 studies related to stem cell therapy and DF published across 280 academic journals. These studies involve a total of 2798 authors affiliated with 543 institutions across 60 countries/regions. The yearly fluctuations in Np serve as a significant gauge for discerning development trends within this domain[42,43]. The publication trends from 2000 to 2003 indicate a lack of research during this period, suggesting a limited depth of study on stem cell therapy in DF. The year 2004 was a turning point for this topic[44], as an increasing number of researchers started focusing on the role of stem cell therapy in the treatment of DF. At that time, the number of relevant publications began to show a rapid upward trend.



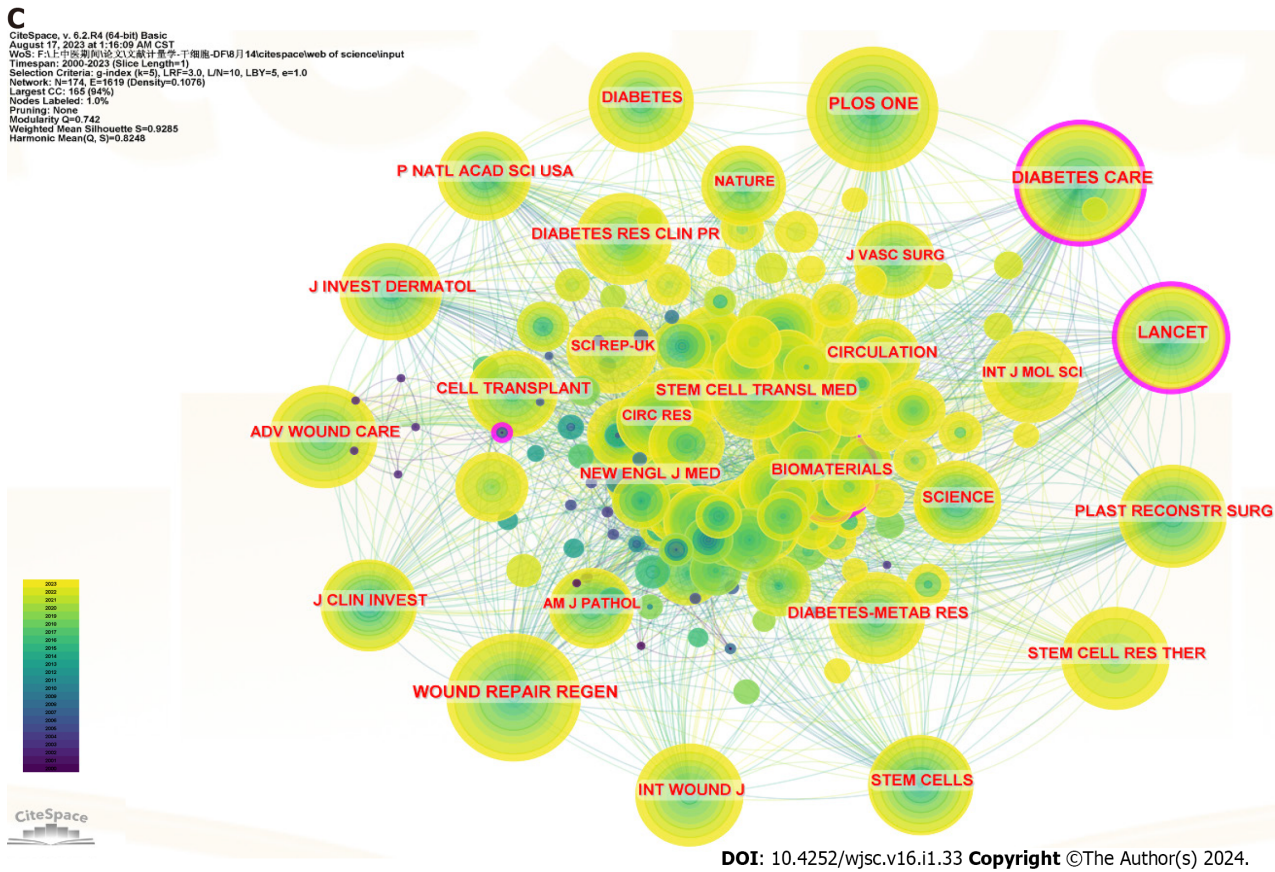


Figure 6 Contributions of different authors to research on stem cells in the diabetic foot field. A: Top 10 journals in terms of h-index; B: Top 10 journals in terms of g-index; C: CiteSpace visualization of cocited journals; D: Biplot overlay of journals on stem cells in the diabetic foot field (left side represents areas covered by citing journals, and the right side represents areas covered by cited journals).

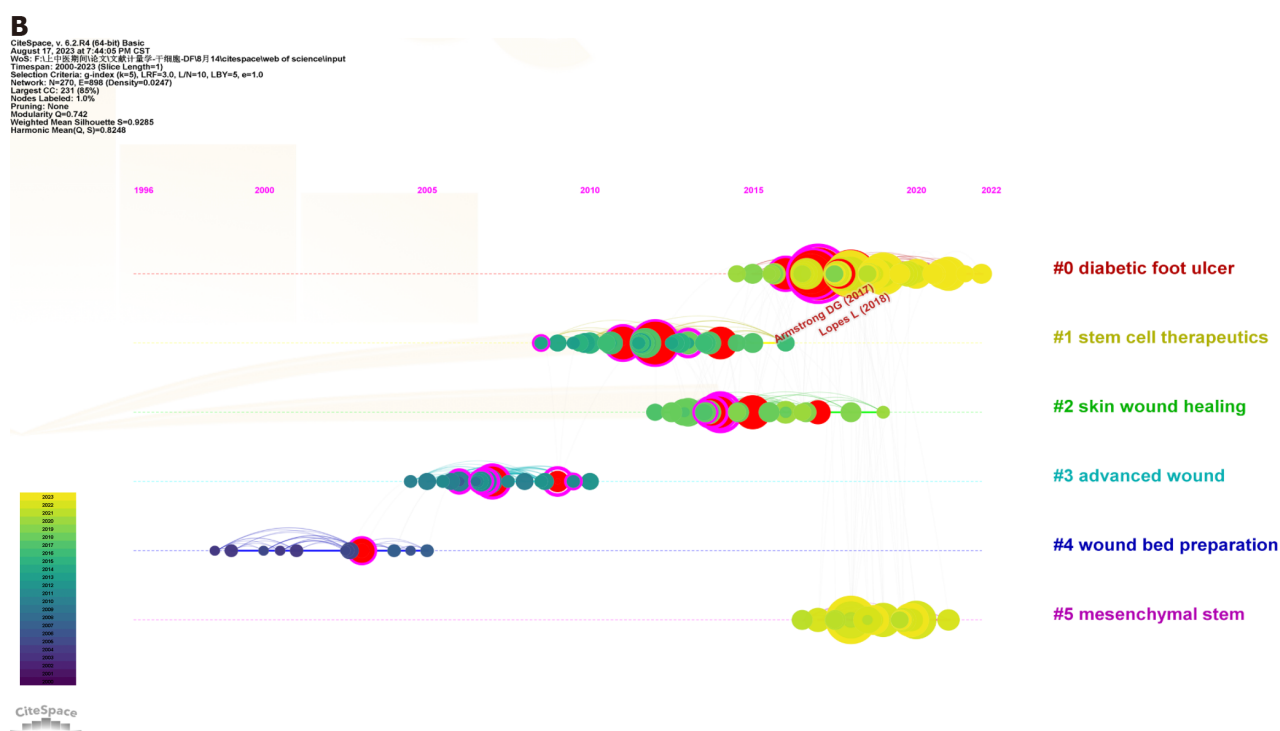
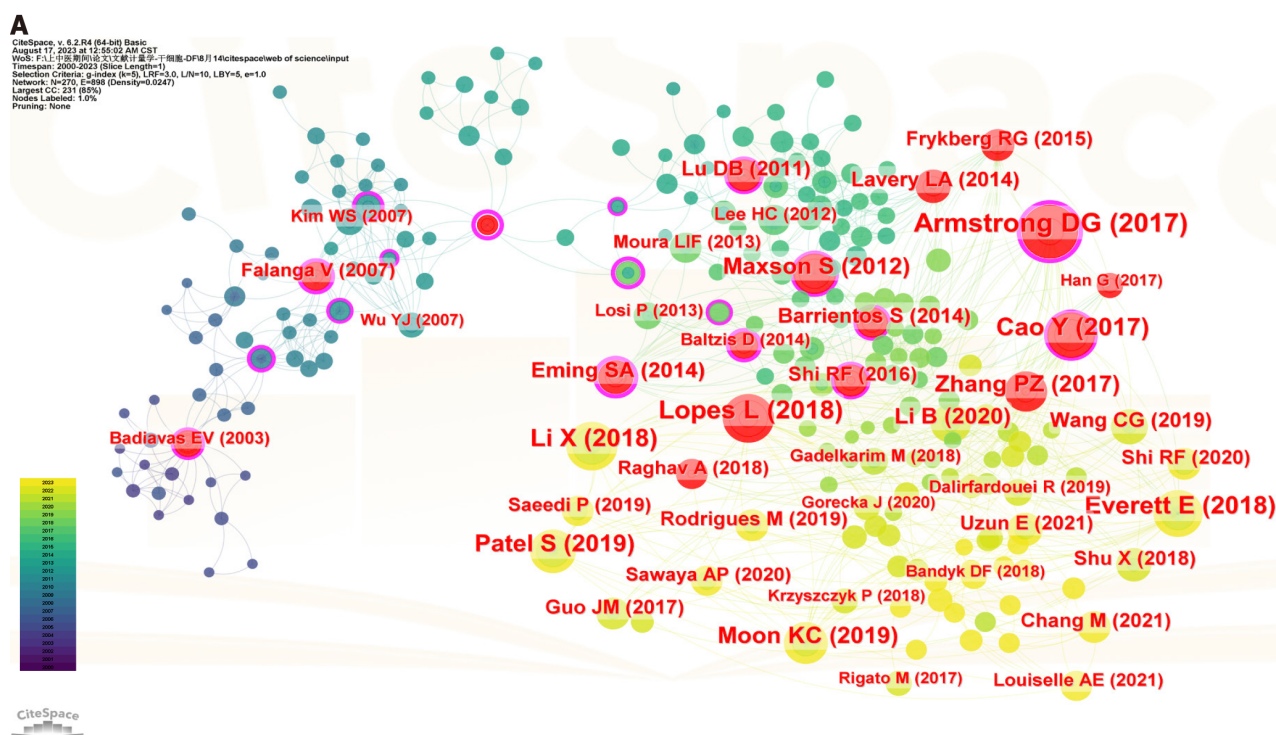
Through visual analysis of national and institutional distribution, we can see that the United States and China are the leading countries in the research and development of stem cell therapy for DF. Among the top 10 institutions researching this topic, the majority (90%) are located in the United States and China, including the University of Louisville, Army Medical University, and Tongji University. Within the 10 highest-ranked nations, the United States (0.83) demonstrated the strongest centrality and maintained the highest multiple-country publication value, signifying its substantial impact within this area. Other countries, such as China (0.15), England (0.23), and Italy (0.17), also had centrality values exceeding 0.1, suggesting their involvement in international exchanges and collaborations to a certain extent.

Identifying the core authors in this field can help researchers find potential collaborators[45]. Professor Bayat, from Shahid Beheshti University of Medical Sciences in Iran, was the author with the highest number of published papers. He has conducted a series of studies on the mechanisms and therapeutic effects of photobiomodulation in stem cell therapy for DF[46,47]. His research has shown that subjecting diabetic adipose-derived stem cells to photobiomodulation prior to treatment markedly expedites the process of wound healing[48]. Among the cited authors, Vincent Falanga from Boston University School of Medicine has been referenced 151 times and had the largest node in this field. He has conducted several high-quality reviews on the use of stem cells for the treatment of chronic wounds[49,50].

The analysis of the distribution of academic journals helps to identify the core journals in specific research fields[51]. Multiple studies on the use of stem cells in DF have been published in influential journals such as *Stem Cell Research & Therapy* and the *International Wound Journal*. Among the top 10 journals, 8 are classified as JCR Q1, which indicates that the research quality of articles in the field is high. From the perspective of commonly cited academic journals, we can see that most of the research comes from highly influential journals in the field of stem cells or wound repair. The journal dual overlay represents the thematic distribution of academic journals, with four citation paths. This implies that current research related to stem cells and DF is focused not only on basic research but also on translational medical research.

Intellectual base

Analysis of cocited references can provide in-depth insights into the core themes and major discoveries of current research[52]. The primary emphasis of the top 10 most cocited references revolves around the pathological and physiological mechanisms, treatment approaches, and everyday handling of stem cells in the context of DF. The results of citation analysis revealed that the article written by Armstrong *et al*[34] published in the *New England Journal of Medicine* in 2017 had the highest frequency of cocitations. This article described the epidemiology and health management of recurrent DFUs and emphasized that the focus of work should be on prevention. Another study published by Lopes *et al* [35] in 2018, which has a citation count of 32, proposed that stem cell therapy was an effective method for treating DFUs.



C

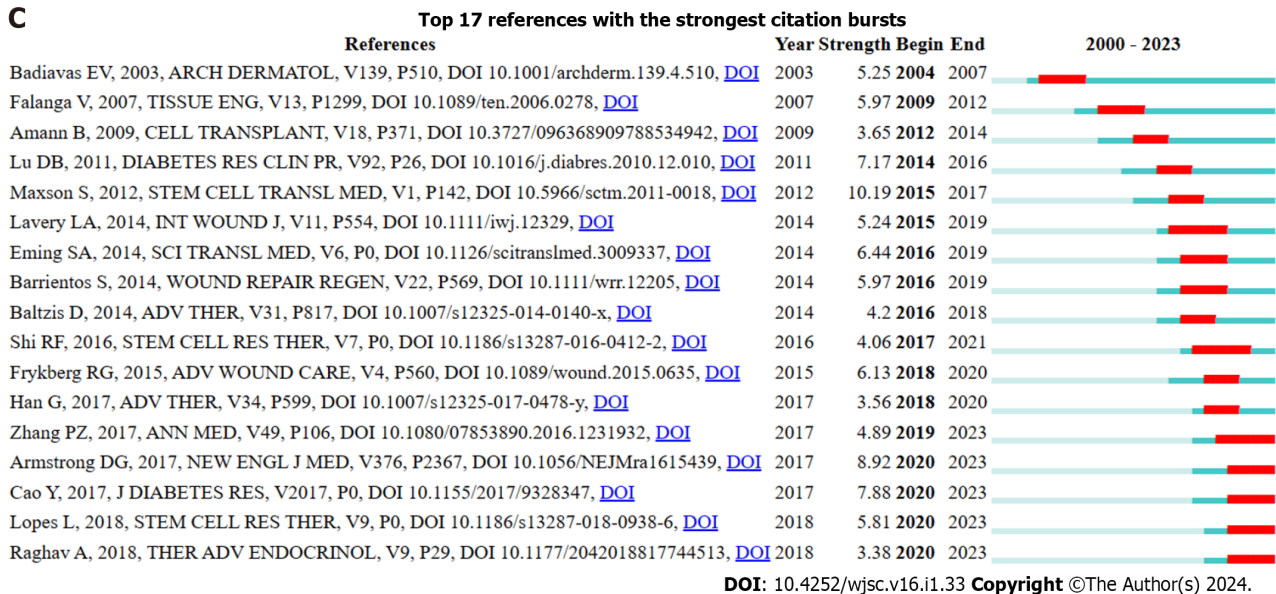


Figure 7 Analysis of cocited references. A: Visualization of cocited references. Nodes represent cocited references, with red circles representing citation bursts references; B: Timeline graph of cluster analysis; C: Top 17 references with the strongest citation bursts.

This suggested that for some patients who do not have other options for vascular reconstruction, stem cell therapy can be considered an alternative to amputation. The most explosive reference was the paper published by Maxson *et al*[38] in *Stem Cells Translational Medicine*. This article delineated the function of mesenchymal stem cells (MSCs) in the process of wound healing and elucidated their ability to attract additional host cells and release growth factors and matrix proteins to orchestrate the mending mechanism.

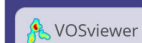
In the clustering analysis of cocited references, there were modules related to occlusive dressing, low-level laser, and exosomes, among others. With the use of advanced techniques, there have been some breakthroughs in the research on stem cells in the field of DF science. Exosomes derived from MSCs carry forward the robust functions of their originating cells. These functions include tasks such as managing inflammation and immune responses, fostering angiogenesis, facilitating cell proliferation and movement, mitigating oxidative stress, and regulating the equilibrium of collagen remodeling[53]. They can potentially avoid the potential risks associated with direct stem cell transplantation. Stem cell-derived exosomes may be a future research trend.

In chronic wounds, stem cell survival without scaffold support is short-lived. Multifunctional hydrogel wound dressings play a crucial role in the healing of skin wounds, as they can sustain stem cell viability for an extended period, provide moisture, and prevent electrolyte and fluid loss in DFUs[54]. Furthermore, photobiomodulation may also play an important role in stem cell applications. The combination of stem cells and photobiomodulation has shown the potential to accelerate the healing process of diabetic wounds[47].

Hotspots and frontiers

Keywords summarize the research topics and core content. Based on keyword co-occurrence analysis, it is possible to understand the distribution and development of various research hotspots in a specific field[55]. The keyword clustering ultimately identified eight possible research directions, including “diabetes mellitus,” “expression,” “chronic wounds,” “adipose-derived stem cells,” “diabetic foot,” “diabetic wound healing,” “double-blind,” and “biological therapies.” The most common keywords were “diabetic foot ulcers,” “wound healing,” “mesenchymal stem cells,” “stem cells,” and “angiogenesis.” In addition, the most frequently mentioned keywords, included “repair,” “skin,” “venous leg ulcers,” “efficacy,” and “mechanisms.” The aforementioned words indicate that the use of stem cells in DF has not only been examined in basic research studies but has also been investigated in clinical translation studies.

A growing body of research indicates that MSCs are capable of enhancing angiogenesis and epithelial remodeling, engaging in immune regulation, mitigating inflammation, and ultimately contributing to the facilitation of DFU repair. They have become an effective therapeutic approach for treating DF[56]. It is worth noting that controlled studies conducted using animal models indicated that combining stem cells with biostimulants (such as photobiomodulation) can reduce biofilm formation and expedite the healing of infected diabetic wounds[57]. Multiple randomized controlled trials have confirmed that stem cell therapy is a promising treatment for DF, as it can improve healing rates and reduce the amputation rate[58]. There is good clinical evidence promoting the clinical application and translation of stem cell therapy for DF. When selecting clinical stem cell types, considerations should be given to the availability and supply of stem cells, such as ease of acquisition, good manufacturing practices, and broad *in vitro* proliferative capacity[59]. Because of their convenient procurement, uncomplicated extraction methods, and documented safety profile, adipose-derived stem cells and other stem cell variants have become increasingly popular. Consequently, they have emerged as pivotal areas of concentration within research endeavors[60]. Beyond their regenerative characteristics and capacity to stimulate blood vessel development, stem cells sourced from adipose tissue exhibit a greater content when contrasted with bone



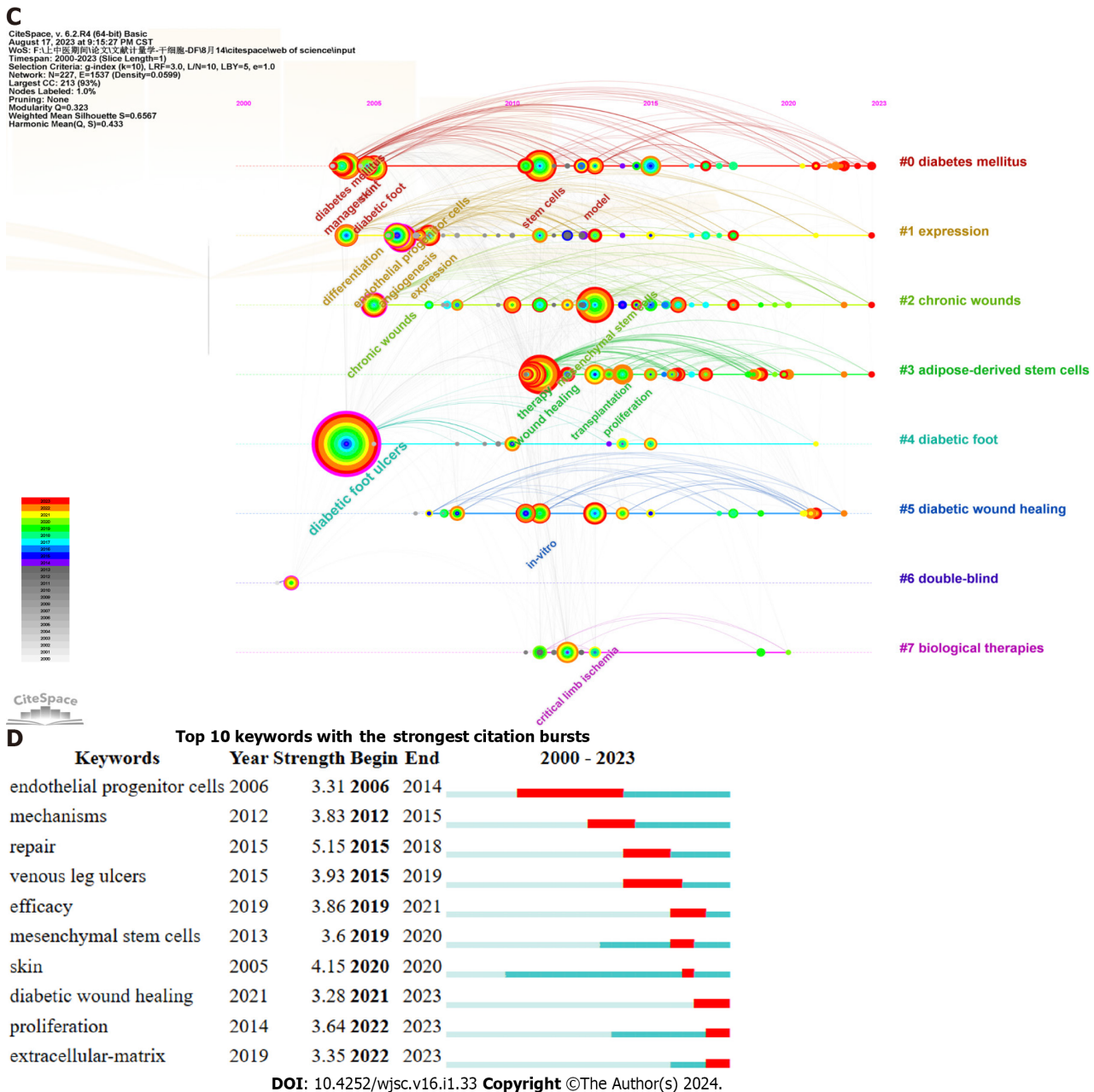


Figure 8 Analysis of keywords. A: Co-occurrence and clustering of keywords; B: Density map of keywords co-occurrence; C: Top 8 cluster timeline distributions; D: Top 17 cocited references with the most citation burstiness.

marrow aspirate-derived stem cells[59].

Through the utilization of bibliometric analysis, this study systematically presented the body of research concerning stem cell therapy in DF cases while also identifying focal points and burgeoning trends within this domain. Therefore, we have also depicted the potential mechanism diagram of stem cell research in the field of DF in Figure 9. Nevertheless, there are certain limitations associated with this study. First and foremost, the study's scope was confined to the WoSCC database for literature screening, potentially resulting in the omission of pertinent articles. This is due to the limitations of current bibliometric software, which makes it difficult to analyze multiple databases simultaneously. Additionally, this study utilized only a few tools, such as VOSviewer, CiteSpace, and R bibliometrics package, which may not fully explain the data. In future research, we intend to explore the use of other tools, such as artificial neural networks, to further analyze and interpret the data.

CONCLUSION

The bibliometric analysis indicated that research on stem cell therapy in DF has been rapidly progressing and holds great prospects for the future. The United States and China are scientific hubs for the research of stem cells in DF. In this field, Iran's Shahid Beheshti University Medical Sciences demonstrated the highest productivity, with Dr. Bayat from the same

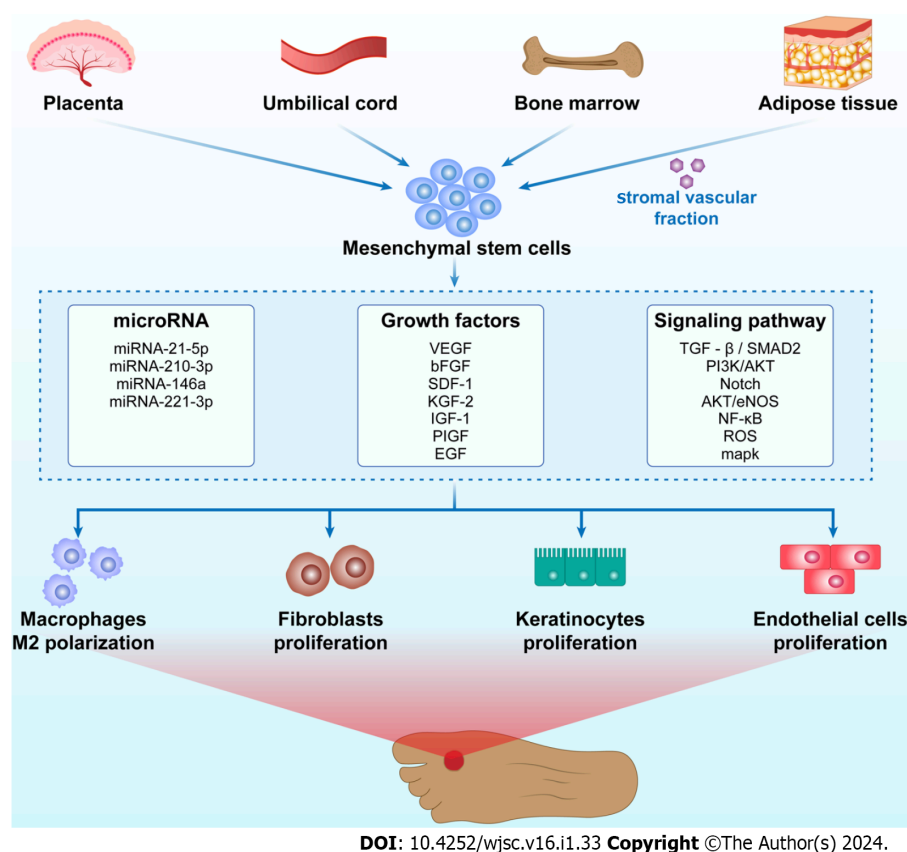


Figure 9 Mechanism diagram of stem cell research in the field of diabetic foot. bFGF: Basic fibroblast growth factor; EGF: Epidermal growth factor; eNOS: Endothelial nitric oxide synthase; IGF: Insulin-like growth factor; KGF: Keratinocyte growth factor; NF-κB: Nuclear factor-kappa B; PI3K: Phosphatidylinositol 3-kinase; PIGF: Phosphorylated insulin-like growth factor; ROS: Reactive oxygen species; SDF: Stromal cell derived factor; TGF-β: Transforming growth factor-β; VEGF: Vascular endothelial growth factor.

university being an outstanding researcher in this domain. The priority topics revolved around dressings, extracellular vesicles, wound healing, and adipose stem cells. The results of these analyses will help researchers understand the current research status and provide hopeful directions for future studies. Future research will also focus on the clinical translation of stem cell therapies for DF.

ARTICLE HIGHLIGHTS

Research background

Stem cell therapy has shown great potential for treating diabetic foot (DF).

Research motivation

There is currently a lack of comprehensive research in this field.

Research objectives

The purpose of this study was to conduct a bibliometric analysis of studies on the use of stem cell therapy for DF over the past two decades, with the aim of depicting the current global research landscape, identifying the most influential research hotspots, and providing insights for future research directions.

Research methods

We searched the Web of Science Core Collection database for all relevant studies on the use of stem cell therapy in DF. Bibliometric analysis was carried out using CiteSpace, VOSviewer, and R (4.3.1) to identify the most notable studies.

Research results

A search was conducted to identify publications related to the use of stem cells for DF treatment. A total of 542 articles published from 2000 to 2023 were identified. The United States had published the most papers on this subject. In this field, Iran's Shahid Beheshti University Medical Sciences demonstrated the highest productivity. Furthermore, Dr. Bayat from the same university has been an outstanding researcher in this field. *Stem Cell Research & Therapy* was the journal

with the highest number of publications in this field. The main keywords were “diabetic foot ulcers,” “wound healing,” and “angiogenesis.”

Research conclusions

This study systematically illustrated the advances in the use of stem cell therapy to treat DF over the past 23 years. Current research findings suggested that the hotspots in this field included stem cell dressings, exosomes, wound healing, and adipose-derived stem cells.

Research perspectives

Future research should also focus on the clinical translation of stem cell therapies for DF.

FOOTNOTES

Author contributions: Liu GB, Yang X, and Fan WJ proposed the research design; Shi HS and Yuan X conducted the literature search, publication screening, and data extraction; Shi HS carried out the data analysis; Wu FF and Li XY conducted manuscript revisions; Hu XM made important contributions to the editing and illustration of this manuscript; The authors collectively contributed to and endorsed the final version of the article.

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