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Research landscape and trends of human umbilical cord mesenchymal stem cell-derived exosomes

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Abstract

Background Human umbilical cord mesenchymal stem cell-derived exosomes (hUCMSC-Exos) have gained significant attention for their potential in cellular regeneration and functional rehabilitation. Nevertheless, the rapid expansion of research in this field makes it challenging for emerging trends and strategic priorities, potentially impeding scientific advancement. This study employs bibliometric analysis to systematically evaluate the research landscape and highlight pivotal research trajectories of hUCMSC-Exos.

Methods Publications on hUCMSC-Exos from 2012 to 2024 were retrieved from the Web of Science Core Collection (WoSCC). Quantitative bibliometric analysis was implemented through integrated utilization of VOSviewer, CiteSpace, and Bibliometrix analytical tools.

Results China and its institutions led global publication output, with Qian Hui from Jiangsu University identified as the most prolific author. *STEM CELL RESEARCH & THERAPY* emerged as a high-impact journal in this domain. Current research predominantly focuses on immunomodulation, regenerative medicine, pharmaceutical delivery systems, and clinical model development. Future research directions are expected to explore angiogenesis, spinal cord injury, and immunomodulation.

Conclusions This study maps the evolving landscape of hUCMSC-Exos research, emphasizing its applications in regenerative medicine. By synthesizing current and emerging paradigms, these findings provide insights into therapeutic potential, novel mechanisms, and pathways for clinical translation.

Keywords Human umbilical cord, Mesenchymal stem cell, Exosomes, Angiogenesis, Spinal cord injury, Immunomodulation, Bibliometric analysis

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Introduction

Mesenchymal stem cell (MSC)-based therapy has been widely recognized for its substantial therapeutic potential in various diseases, including hepatic insufficiency, hepatoma, stroke, and spinal cord injury (SCI) [1, 2]. Notably, MSCs, owing to their remarkable self-renewal and multipotency, demonstrate therapeutic efficacy in enhancing split liver transplantation outcomes by mitigating postoperative complications and accelerating graft regeneration [3, 4]. MSCs originating from the human umbilical cord (hUC) demonstrate superior proliferative capacity and enhanced differentiation plasticity, positioning them as a promising candidate for tissue repair [5, 6]. Despite encouraging therapeutic outcomes, the underlying mechanisms of hUC-MSCs-based treatment, specifically their contributions to proliferation, differentiation, immunomodulation, and apoptosis, remain incompletely elucidated [7, 8]. Consequently, most clinical trials employing hUC-MSCs have progressed only to phase I/II stages [9], underscoring the need for robust preclinical validation. Despite these challenges, hUC-MSCs are distinguished by their low immunogenicity, negligible tumorigenicity, minimal graft rejection, and high proliferative capacity, prompting extensive research into their clinical translation [10, 11].

Exosomes (Exos) are a key mechanism by which hUC-MSCs deliver therapeutic benefits in disease management [12]. hUCMSC-derived Exos (hUCMSC-Exos) exhibit superior proliferative capacity and reduced immunogenicity compared to Exos derived from other MSC origins and can be obtained by noninvasive methods [13, 14]. The therapeutic efficacy of hUCMSC-Exos is influenced by disease-tailored cellular dynamics (e.g., regeneration, inflammation, cell death, and oxidative stress) and key intracellular signaling pathways, such as mitogen-activated protein kinase (MAPK), wingless-related integration site (Wnt)/β-catenin, and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways [15–18]. Moreover, hUCMSC-Exos serve as an effective vehicle for therapeutic compounds, enhancing bioavailability and reducing adverse effects [6]. Currently, hUCMSC-Exos are being explored in regenerative medicine for various conditions, including hepatic diseases (e.g., NCT05871463), cardiovascular diseases (e.g., NCT05669144), and SCI (e.g., IRCT20200502047277N1).

Given the growing interest in hUCMSC-Exos, the volume of scholarly publications has increased significantly, complicating the identification of emerging research trends and critical developments. This surge in literature, coupled with the absence of comprehensive reviews and meta-analyses, necessitates a synthesized overview of the field's current and future directions. A bibliometric synthesis is essential for analyzing and predicting the trajectory of a particular research field, offering a comprehensive landscape of scholarly discourse and employing quantitative methodologies to elucidate research hotspots and emerging trends, a methodology widely used in medical research.

Despite its significance, there is currently no bibliometric study that provides a comprehensive examination of hUCMSC-Exos research. In this study, we aim to fill this gap by conducting a systematic literature search and employing bibliometric methods to highlight key milestones, pinpoint focal points of interest, anticipate forthcoming avenues of inquiry, and encapsulate the evolution of hUCMSC-Exos research through the year 2024.

Materials and methods

Data source

A total of 1066 scholarly publications were systematically retrieved from the Clarivate Analytics of Science Citation Index Expanded (SCI-Expanded) within the Web of Science Core Collection (WoSCC). The search strategy employed was: TS = ("umbilical cord mesenchymal stem cells" OR "umbilical cord mesenchymal stromal cells") AND TS = ("extracellular vesicles" OR "exosomes"). The temporal scope spanned from September 3, 2012 (the date of the inaugural publication on hUCMSC-Exos) to October 19, 2024. Inclusion criteria were limited to English-language peer-reviewed articles (original research and reviews). Following rigorous screening (Fig. 1), the final dataset was compiled on October 19, 2024. Moreover, this bibliometric study required no ethical approval as it involved no human or animal experimentation.

Data processing

The bibliometric analysis was systematically conducted using VOSviewer (v1.6.20), CiteSpace (v6.4.R1), and the bibliometrix package in RStudio (v4.1.2). VOSviewer generated bibliometric maps using network, overlay, and density visualizations, facilitating structural and evolutionary analysis of the research networks [19]. Specifically, VOSviewer was employed to analyze international/institutional collaborations, co-citation networks, and keyword clusters. CiteSpace employed citation pattern analysis and burst detection to identify intellectual transitions and disciplinary trends [20]. Additionally, it conducted reference burst detection and keyword emergence analysis, revealing temporal patterns in conceptual evolution. The bibliometrix package performed multidimensional analysis of scholarly datasets through scientific mapping techniques [21], visualizing geographic collaboration patterns to elucidate research network dynamics.

Results

Bibliometric analysis of publication output

Original research articles constituted 78.61% of publications in the hUCMSC-Exos field, outnumbering review

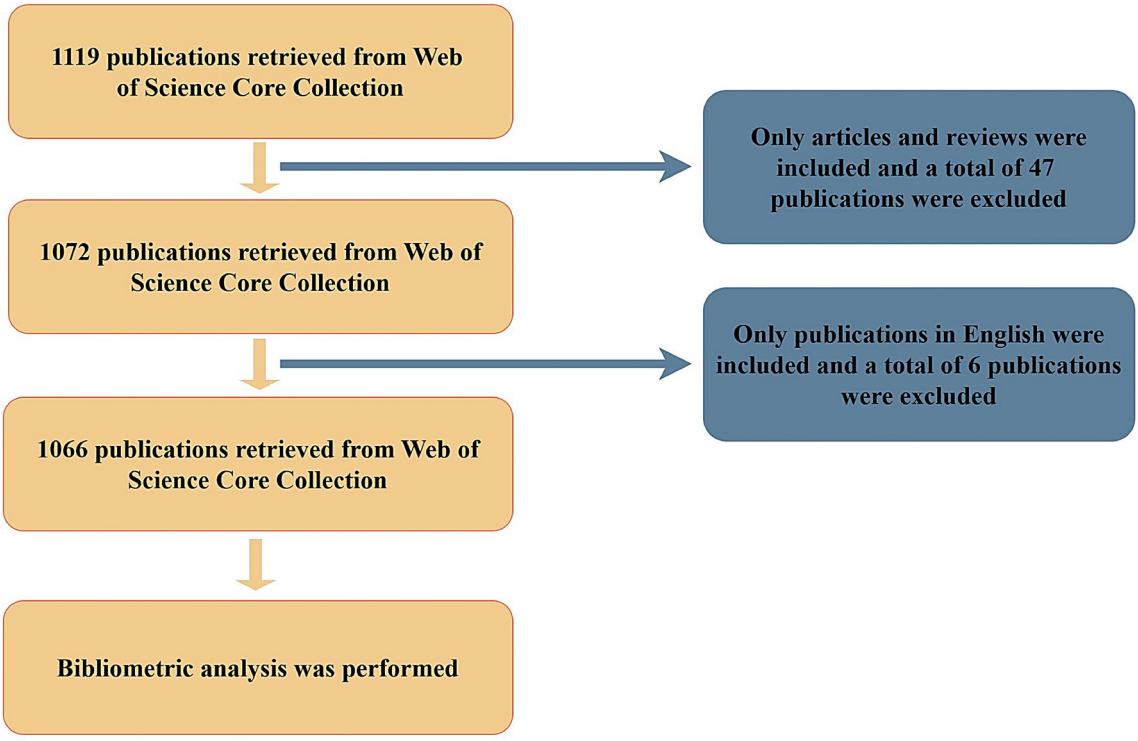


Fig. 1 Flow diagram illustrating the inclusion and exclusion criteria for the study

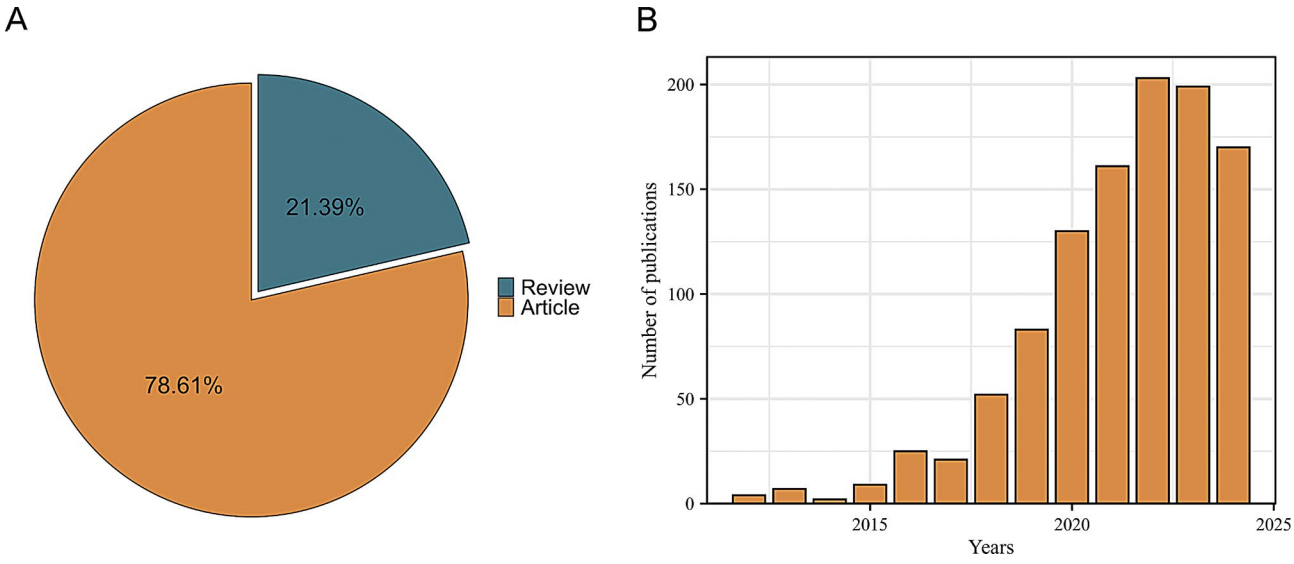


Fig. 2 (**A**) Classification of publication types involving human umbilical cord mesenchymal stem cell-derived exosomes (hUCMSC-Exos); (**B**) Annual production volume of hUCMSC-Exos

articles by a factor of three (Fig. 2A). The inaugural study emerged in 2012, marking the onset of scientific exploration in this domain. Temporal distribution analysis (2012–2024) revealed three developmental epochs: the foundational phase (2012–2014; $n = 13$), the developmental phase (2015–2018; $n = 107$), and the exponential growth phase (2019–2024; $n = 946$). Since 2018, publication output has exhibited sustained exponential growth, reflecting the maturation and increasing significance of the field (Fig. 2B).

Bibliometric analysis of countries/regions

China led scholarly output in hUCMSC-Exos research, producing 684 publications (64.17%) with cumulative citations reaching 24,171 (average article citations, AACs = 35.34), thereby solidifying China's global

scientific preeminence (Table 1). This dominance highlights a stark contrast in research investment compared to other nations, with the USA ranking second ($n = 96$, 9.01%). Network analysis of international collaboration identified China's centrality despite limited transnational partnerships (Fig. 3A). Citation-based collaboration networks exhibited radial connectivity patterns centered on China (Fig. 3B). Geospatial collaboration network analysis confirmed the strongest China-USA cooperation (Fig. 4), with China exerting intellectual influence across multiple bibliometric indicators.

Bibliometric analysis of institutions

Institutional productivity analysis (Table 2) further reinforced Chinese dominance in hUCMSC-Exos research, with Jiangsu University leading both in publications ($n = 60$) and citation metrics (total citations, TCs = 5,611), followed by Nanjing Medical University (TCs = 1,657; $n = 30$). Inter-institutional collaboration networks (Fig. 5A) revealed three primary clusters: (1) The dominant blue cluster centered on Jiangsu University; (2) the red cluster featuring Shandong University; and (3) the green cluster anchored by Central South University. Core institutions including Soochow University, Nanjing Medical University, and Shanghai Jiao Tong University exhibited dense co-authorship linkages, while peripheral nodes like Sichuan University, Nantong University, and Capital Medical University demonstrated weaker collaborative ties. Citation network analysis (Fig. 5B) confirmed Jiangsu University's epistemic authority, maintaining radial connections to other network nodes and indicating its significant impact and collaborative reach within the academic network.

Bibliometric analysis of authors

Scholarly output metrics identified Qian Hui as the most prominent contributor ($n = 34$, TCs = 4,772) among the top 10 authors (Table 3), followed by Xu Wenrong ($n = 30$, TCs = 4,632) and Yan Yongming ($n = 24$, TCs = 3,407), respectively. Notably, all leading contributors were affiliated with China, highlighting the country's dominant role in advancing hUCMSC-Exos research. The co-authorship network (Fig. 6A) revealed distinct clusters led by prominent authors, including Qian Hui, Xu Wenrong, and Yan Yongming. The citation network (Fig. 6B) confirmed Qian Hui's scholarly influence, indicating both his significant scholarly impact and extensive collaborations in the hUCMSC-Exos research field. Peripheral authors demonstrated limited collaborative propensity, suggesting more independent research trajectories.

Bibliometric analysis of journals

Journal productivity analysis (Table 4) revealed that *STEM CELL RESEARCH & THERAPY* is the leading journal in the field ($n = 78$; TCs = 3,821), thereby demonstrating its scholarly preeminence. While the *INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES* ranked second in output ($n = 40$), it paradoxically exhibited the lowest citation frequency (TCs = 639; AACs = 15.98). *STEM CELLS* secured the second citation rank (TCs = 1,391; AACs = 107.00), with *STEM CELLS TRANSLATIONAL MEDICINE* closely following in third place (TCs = 1,387; AACs = 115.58), confirming their status as key knowledge repositories. Significantly, the journal citation network analysis (Fig. 7) reinforced the pivotal role of *STEM CELL RESEARCH & THERAPY* as the central hub, exhibiting extensive connectivity with other major journals, such as the *INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES* and *STEM CELLS INTERNATIONAL*. This further emphasized their collective contribution to the hUCMSC-Exos research domain.

Bibliometric analysis of references

Table 5 summarized the top 10 most-cited publications in the hUCMSC-Exos domain. The seminal work by Li Tingfen et al. (2013) achieved the highest citation count ($n = 661$) in *STEM CELLS AND DEVELOPMENT*,

Table 1 The number of documents published and cited at country level

Rank	Top 10 Most Productive Countries/Regions			Most Cited Countries/Regions		
	Country/Region	Record	Percentage (%)	Country/Region	TCs	AACs
1	China	684	64.17	China	24,171	35.34
2	USA	96	9.01	USA	4,160	43.33
3	Italy	39	3.66	Germany	1,206	44.67
4	Iran	38	3.56	Italy	966	24.77
5	South Korea	31	2.91	Austria	881	62.93
6	Spain	29	2.72	Japan	842	56.13
7	Germany	27	2.53	England	825	37.50
8	England	22	2.06	Iran	801	21.08
9	India	19	1.78	India	792	41.68
10	Canada	16	1.50	Spain	781	26.93

TCs: Total citations; AACs: Average article citations

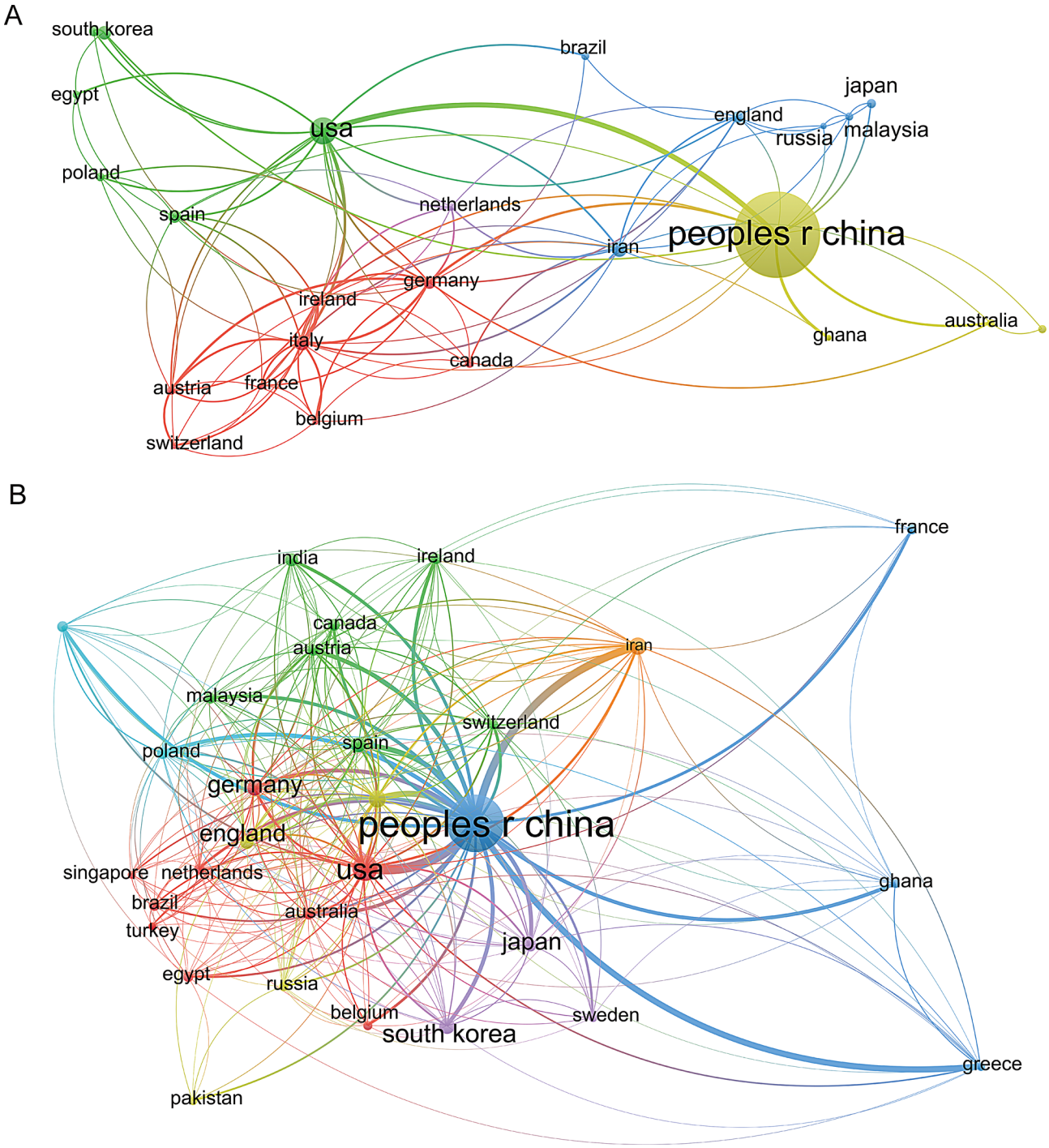


Fig. 3 Knowledge visualization maps examining country-level collaboration and citation patterns: (**A**) Collaborative network map of countries; (**B**) Citedness distribution map of countries

elucidating hUCMSC-Exos' therapeutic efficacy against hepatic fibrosis. Lee et al. (2012) ranked second ($n = 628$ citations) in *CIRCULATION*, investigating MSC-derived exosome-mediated cytoprotection in hypoxic pulmonary hypertension models. These landmark studies collectively underscore the translational potential of MSC research. The citation network visualization (Fig. 8A) employed node sizing proportionate to citation frequency. Moreover, burst detection analysis identified 25 pivotal references (Fig. 8B) with citation bursts, revealing periods of intensified scholarly interest (denoted by red zones). Pioneering researchers such as Li Tingfen, Zhang Bin, Zhou Ying, and Thery Clotilde emerged as leading

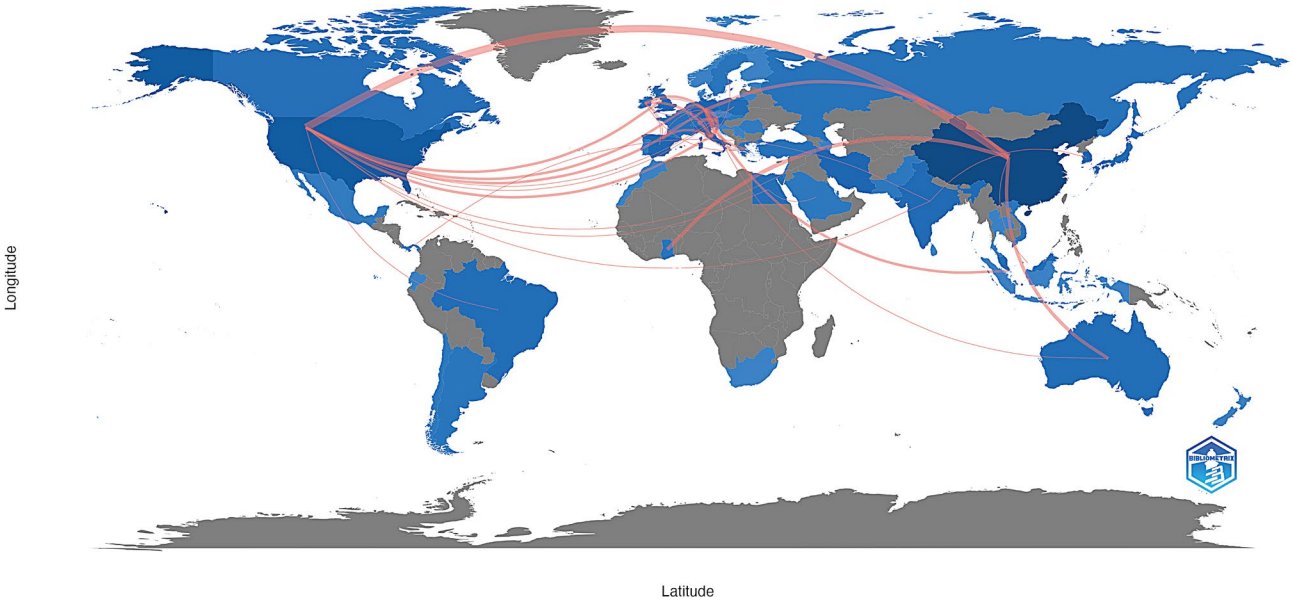


Fig. 4 Knowledge visualization map for international collaboration

Table 2 Top 10 most productive institutions

Top 10 Most Productive Institutions			Most Cited Institutions			
Name	**Record**	**Country/Region**	**Name**	**Country/Region**	**TCs**	**AACs**
Jiangsu Univ	60	China	Jiangsu Univ	China	5,611	93.52
Shandong Univ	32	China	Nanjing Med Univ	China	1,657	55.23
Nanjing Med Univ	30	China	Second Mil Med Univ	China	1,343	134.30
Central South Univ	29	China	Shandong Univ	China	1,031	32.22
Shanghai Jiao Tong Univ	28	China	Shanghai Jiao Tong Univ	China	1,025	36.61
Sun Yat Sen Univ	28	China	Soochow Univ	China	978	46.57
Tongji Univ	27	China	Southern Med Univ	China	921	38.38
Chinese PLA General Hosp	24	China	Southeast Univ	China	839	83.90
Southern Med Univ	24	China	Guangzhou Med Univ	China	836	49.18
Soochow Univ	21	China	Tongji Univ	China	821	30.41

TCs: Total citations; AACs: Average article citations

contributors, laying the foundation for MSC-Exos mechanisms and therapeutic applications [22–25].

Bibliometric analysis of keywords

Keyword analysis revealed the shifting academic focus of hUCMSC-Exos research, elucidating prevailing investigative priorities and emerging research directions. Through synonym consolidation, 3,822 distinct keywords were extracted from 1,066 publications, with 20 high-frequency terms (≥75 occurrences) identified (Table 6). Network visualization delineated the structural composition of the research domain (Fig. 9A), categorizing keywords into four major clusters: green (predominantly "versus-host-disease" and "immunomodulation"), blue ("angiogenesis", "cellular proliferation", and "microRNAs"), yellow ("regeneration" and "wound healing"), and red ("inflammation", "SCI", "acute lung injury", "transplantation", "fibrosis", "delivery", and "therapy"). Notably, key nodal elements including "angiogenesis", "immunomodulation", "inflammation", "regeneration", "delivery", "pathway", and "SCI" exhibited heightened centrality and interconnectivity, reflecting their critical relevance to hUCMSC-Exos research priorities.

Temporal mapping enabled chronological analysis of disciplinary progression, revealing phase-specific research priorities and developmental trajectories within hUCMSC-Exos studies (Fig. 9B). Distinct clustering patterns emerged around terms including "cancer", "autophagy", "macrophages", "osteoarthritis", and "inflammation", indicating a consistent scholarly emphasis on therapeutic applications and mechanistic explorations across diverse pathologies. Burst detection analysis identified 19 temporally significant keywords (Fig. 10), with "stromal cells" (Strength: 8.64) and "microvesicles" (Strength: 9.06) emerging as prominent focal points. The marked surge in "extracellular vesicle" research since 2021 highlighted its

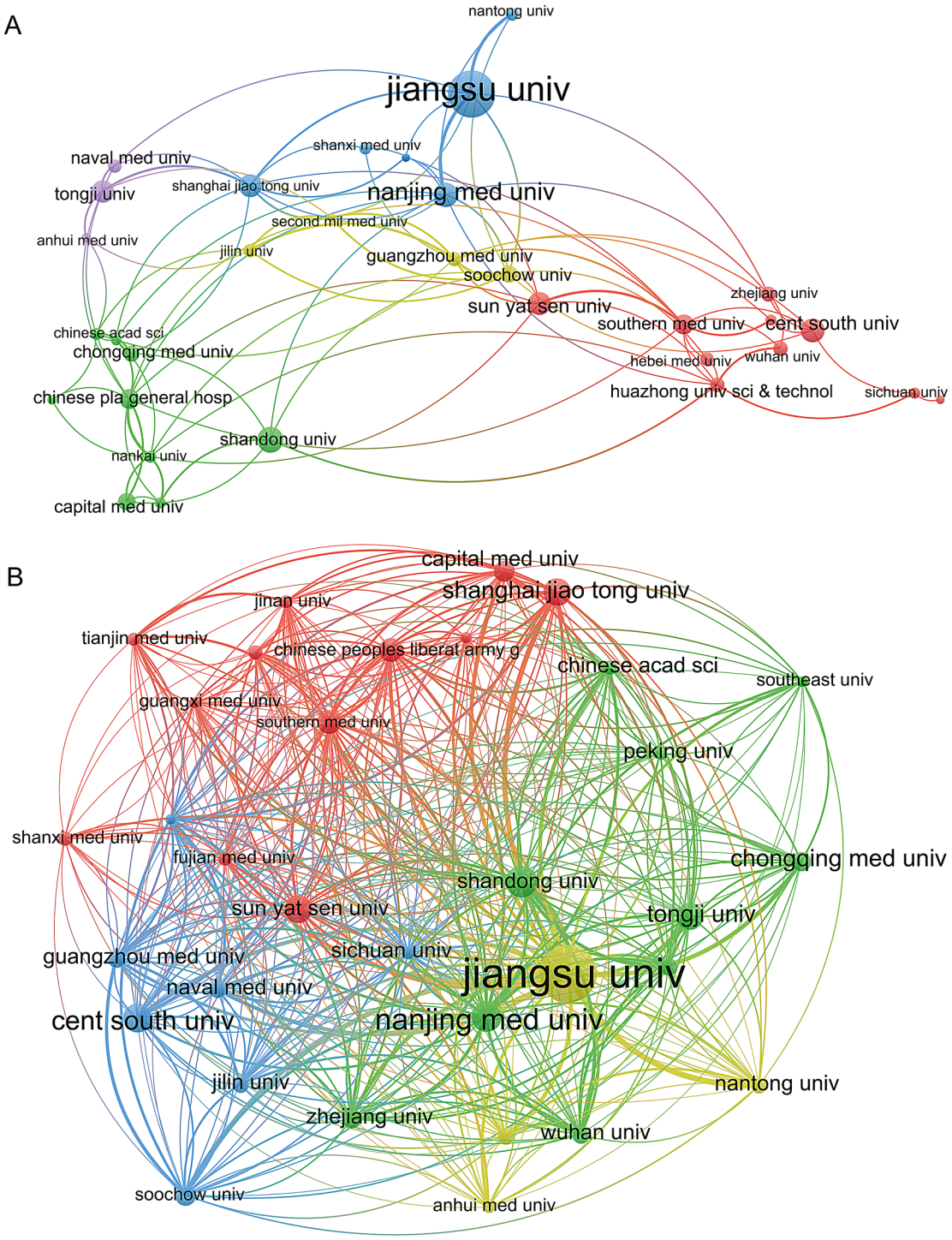


Fig. 5 Knowledge visualization maps for institutional collaboration and citation analysis: (**A**) Institutional collaboration network map; (**B**) Citedness distribution map of institutions

Table 3 Productivity based on number of articles at author level

Rank	Top 10 Most Productive Authors			Most Cited Authors			
	Name	Record	Country/Region	Name	Country/Region	TCs	AACs
1	Qian Hui	34	China	Qian Hui	China	4,772	140.35
2	Xu Wenrong	30	China	Xu Wenrong	China	4,632	154.40
3	Yan Yongmin	24	China	Yan Yongmin	China	3,407	141.96
4	Zhang Xu	23	China	Zhang Xu	China	3,068	133.39
5	Mao Fei	22	China	Zhu Wei	China	3,031	202.07
6	Zhang Bin	17	China	Zhang Bin	China	2,503	147.24
7	Zhu Wei	15	China	Mao Fei	China	2,171	98.68
8	Li Yang	11	China	Wang Mei	China	1,955	279.29
9	Zhang Yu	10	China	Shi Hui	China	1,613	179.22
10	Shi Hui	9	China	Li Wei	China	919	131.29

TCs: Total citations; AACs: Average article citations

emergence as a contemporary investigative priority with growing academic relevance.

Discussion

To our current understanding, this investigation marks the inaugural application of bibliometric methodologies to systematically quantify and characterize the hUCMSC-Exos research corpus. We identified pivotal research foci and developmental trajectories of hUCMSC-Exos studies, providing a comprehensive framework that elucidated the evolutionary trends in the domain.

Countries/institutions cooperation

The findings demonstrate that hUCMSC-Exos research represents an emergent scientific frontier, with exponential growth in publication volume. Geographical distribution patterns revealed the top 10 contributing nations spanning three major scientific regions: Asia, Europe, and North America. Strikingly, China has emerged as the leading contributor, surpassing the USA in both productivity and citation influence. While academic engagement continued to intensify, international collaborative efforts remained constrained, indicating substantial potential for enhanced global scientific partnerships. The institutional analysis identified Jiangsu University and Shandong University as key players, both distinguished by their outstanding performance in publication output and academic influence. Notably, all top-tier productive institutions were based in China, which further reinforced the country's dominance in hUCMSC-Exos research.

Citation landscape

Analysis of author productivity revealed that eight of the top 10 most prolific researchers maintained affiliations with Jiangsu University, underscoring robust intra-institutional collaboration and confirming the university's leadership position in this field. Xu Wenrong has produced multiple seminal publications that have fundamentally shaped the field's trajectory. His 2012 breakthrough study in *STEM CELLS AND DEVELOPMENT* [22] first established the therapeutic potential of hUCMSC-Exos in hepatic fibrosis management, providing the conceptual framework for subsequent mechanistic and translational investigations. This foundational work was expanded in 2013 through *STEM CELL RESEARCH & THERAPY* [24], where Xu's team demonstrated hUCMSC-Exos' efficacy in counteracting cisplatin-induced nephrotoxicity, thereby proposing a novel therapeutic strategy for chemotherapy-associated renal complications. Collaborative research led by Xu has further elucidated hUCMSC-Exos applications across diverse pathologies including cutaneous regeneration [23], SCI [26], type 2 diabetes mellitus [27], and inflammatory bowel disease [28], substantially broadening the technology's clinical relevance.

Bibliometric evaluation identified stem cell-specific journals as principal knowledge dissemination channels, notably *STEM CELL RESEARCH & THERAPY*, *STEM CELLS INTERNATIONAL*, and *STEM CELLS*. *STEM CELLS TRANSLATIONAL MEDICINE*, a high-impact journal, has published works with the highest mean citation rates. In contrast, *STEM CELL RESEARCH & THERAPY*, despite leading in publication volume, has demonstrated comparatively lower citation metrics, highlighting the imperative of focusing on breakthrough research to enhance its academic standing.

Research hotspots and frontiers

The hUCMSC-Exos research domain has witnessed substantial investigation into tissue regeneration [29–33], employing methodologies that span transplantation protocols, cellular therapeutics, and biomaterial applications. Despite these advancements, the development of optimized clinical regimens remains an unresolved challenge, particularly in achieving sustained therapeutic efficacy and safety profiles within complex pathophysiological microenvironments [34–36]. Nevertheless, pioneering investigations in this research domain have garnered significant scholarly attention due to their pivotal role

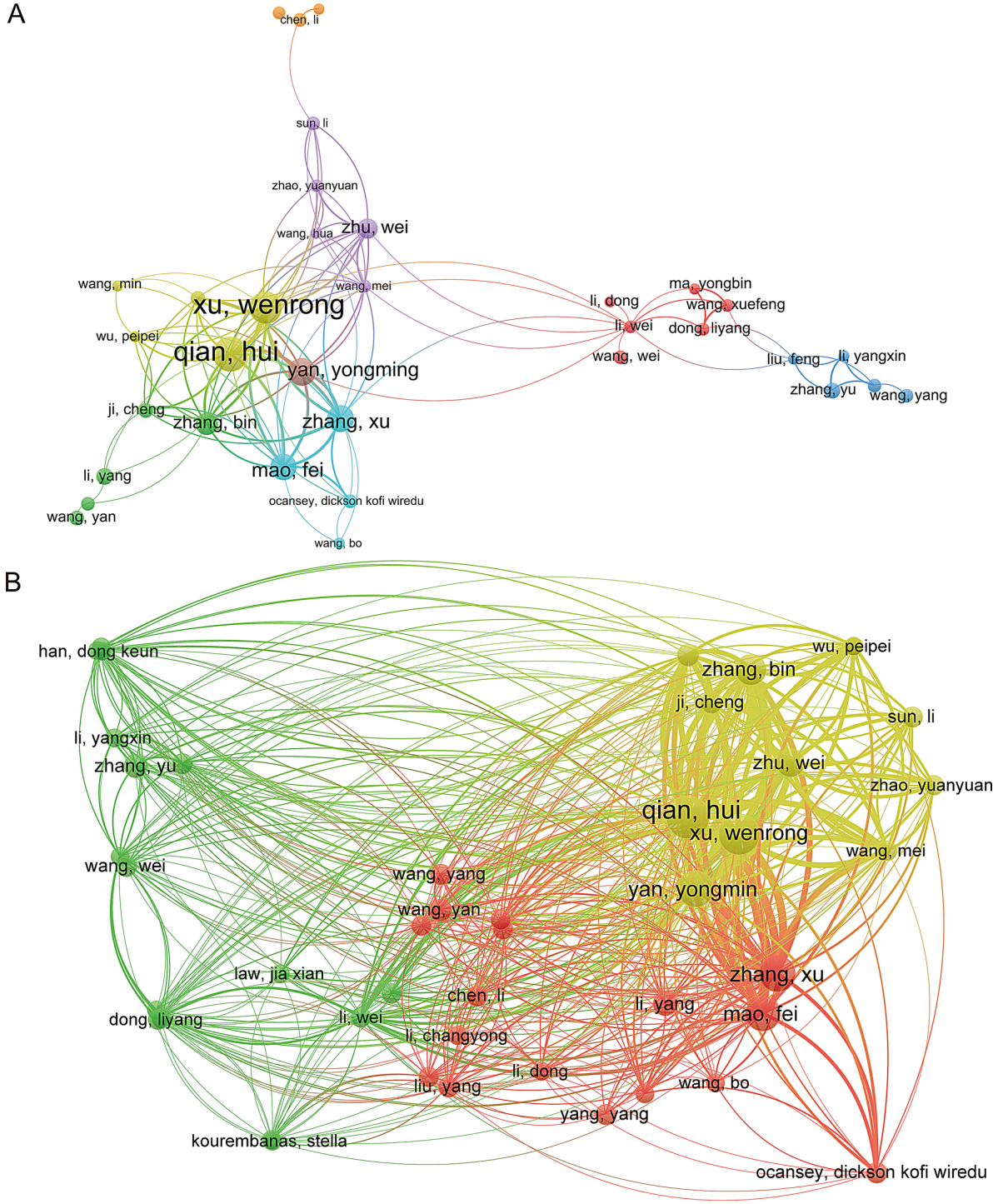


Fig. 6 Knowledge visualization maps focusing on author collaboration and citation trends: (**A**) Authors' collaboration network map; (**B**) Citedness distribution map of authors

in tissue repair mechanisms. The research scope encompasses the following areas: hepatic fibrosis suppression [22], protective mechanisms against hypoxic stress [37], cisplatin-induced cellular damage [24, 37], and promotion of dermal tissue regeneration [23]. These preliminary findings have delineated promising trajectories for clinical translation applications.

While these translational potentials are being explored, hUCMSC-Exos are emerging as a multifaceted regenerative strategy, with key properties such as immunomodulation, angiogenesis, and

Table 4 The number of documents published and cited at journal level

Rank	Top 10 Most Productive Journals			Top 10 Most Cited Journal			
	Journal	Record	IF (2024)	Journal	TCs	AACs	IF (2024)
1	STEM CELL RESEARCH & THERAPY	78	7.1	STEM CELL RESEARCH & THERAPY	3,821	48.99	7.1
2	INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES	40	4.9	STEM CELLS	1,391	107.00	4.0
3	STEM CELLS INTERNATIONAL	35	3.8	STEM CELLS TRANSLATIONAL MEDICINE	1,387	115.58	5.4
4	STEM CELL REVIEWS AND REPORTS	25	4.5	STEM CELLS INTERNATIONAL	1,248	35.66	3.8
5	CELLS	24	5.1	STEM CELLS AND DEVELOPMENT	938	93.80	2.5
6	FRONTIERS IN BIOENGINEERING AND BIOTECHNOLOGY	23	4.3	CELLS	710	29.58	5.1
7	JOURNAL OF NANOBIOTECHNOLOGY	22	10.6	CELL DEATH & DISEASE	703	100.43	8.1
8	INTERNATIONAL IMMUNOPHARMACOLOGY	15	4.8	THERANOSTICS	698	87.25	12.4
9	FRONTIERS IN CELL AND DEVELOPMENTAL BIOLOGY	14	4.6	STEM CELL REVIEWS AND REPORTS	661	26.44	4.5
10	STEM CELLS	13	4.0	INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES	639	15.98	4.9

IF (2024): 2024 Journal Impact Factor. TCs: Total Citations. AACs: Average article citations

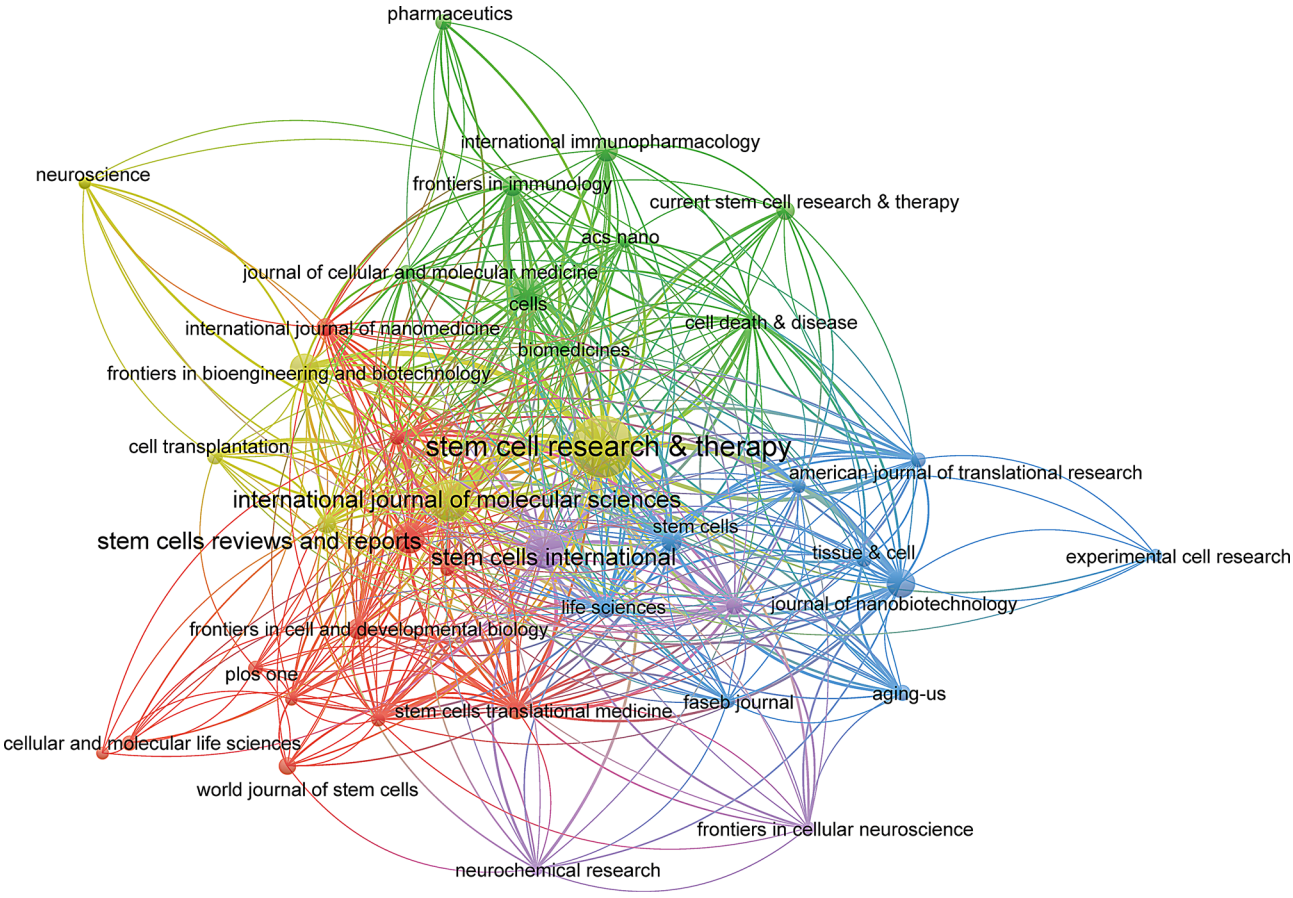


Fig. 7 Knowledge visualization map analyzing journal-level citation patterns

anti-apoptosis [38]. Angiogenesis serves as a pivotal determinant of tissue repair efficacy [39–42]. Notably, multiple clinical trials are committed to employing MSCs to ameliorate ischemic diseases, such as ischemic heart disease (NCT01781390 and NCT00877903), ischemic retinopathy (NCT03011541 and NCT01920867), critical limb ischemia (NCT04104451 and NCT05078385), and ischemic stroke (NCT03384433). The proangiogenic attributes of hUCMSC-Exos present a strategic therapeutic avenue to address the persistent clinical challenge of optimizing regenerative responses in ischemic tissue microenvironments.

Table 5 Ranking of the top 10 highest cited documents

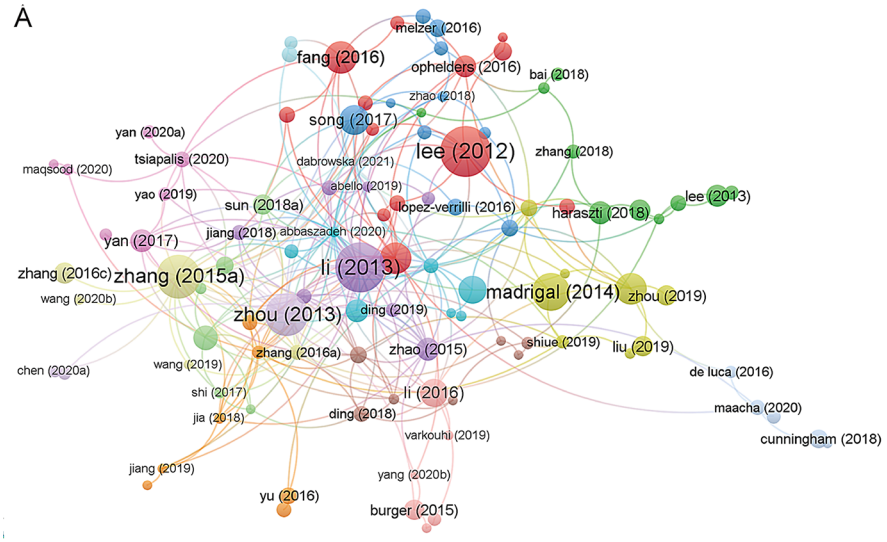
Rank	Title	First Author	Corresponding author	PY	Journal	TCs	Type
1	Exosomes Derived from Human Umbilical Cord Mesenchymal Stem Cells Alleviate Liver Fibrosis	Li, Tingfen	Xu, Wenrong	2013	STEM CELLS AND DEVELOPMENT	661	Article
2	Exosomes Mediate the Cytoprotective Action of Mesenchymal Stromal Cells on Hypoxia-Induced Pulmonary Hypertension	Lee, ChangJin	Kourembanas, Stella	2012	CIRCULATION	628	Article
3	HucMSC-Exosome Mediated-Wnt4 Signaling Is Required for Cutaneous Wound Healing	Zhang, Bin	Xu, Wenrong	2015	STEM CELLS	578	Article
4	Exosomes released by human umbilical cord mesenchymal stem cells protect against cisplatin-induced renal oxidative stress and apoptosis in vivo and in vitro	Zhou, Ying	Xu, Wenrong	2013	STEM CELL RESEARCH & THERAPY	502	Article
5	A review of therapeutic effects of mesenchymal stem cell secretions and induction of secretory modification by different culture methods	Madrigal, Marialaura	Madrigal, Marialaura	2014	JOURNAL OF TRANSLATIONAL MEDICINE	439	Review
6	Umbilical Cord-Derived Mesenchymal Stem Cell-Derived Exosomal MicroRNAs Suppress Myofibroblast Differentiation by Inhibiting the Transforming Growth Factor-beta/SMAD2 Pathway During Wound Healing	Fang, Shuo	Xing, Xin	2016	STEM CELLS TRANSLATIONAL MEDICINE	404	Article
7	Isolation, cultivation, and characterization of human mesenchymal stem cells	Mushahary, Dolly	Charwat, Verena	2018	CYTOMETRY PART A	368	Review
8	Human Umbilical Cord Mesenchymal Stem Cell Exosomes Enhance Angiogenesis Through theWnt4/beta-Catenin Pathway	Zhang, Bin	Xu, Wenrong	2015	STEM CELLS TRANSLATIONAL MEDICINE	356	Article
9	Exosomal miR-146a Contributes to the Enhanced Therapeutic Efficacy ofInterleukin-1-PrimedMesenchymal Stem Cells Against Sepsis	Song, Yuxin	Hou, Yayi	2017	STEM CELLS	347	Article
10	Exosome Derived From Human Umbilical Cord Mesenchymal Stem Cell Mediates MiR-181c Attenuating Burn-induced Excessive Inflammation	Li, Xiao	Yin, Huinan	2016	EBIOMEDICINE	333	Article

PY: Publication year; TCs: Total citations

Burst analysis further identified SCI as a consistent investigative priority within hUCMSC-Exos research. Mechanistic studies demonstrate their multi-target therapeutic actions: microRNA (miR)-146a-5p-mediated nuclear factor kappa-B (NF-κB) axis suppression mitigates post-traumatic neuroinflammation and promotes neural repair, while Wnt/β-catenin pathway modulation reduces apoptosis and enhances locomotor recovery [43–46]. Clinically, intrathecal administration of UCMSCs/UCMSC-Exos has shown preliminary efficacy in enhancing sensorimotor outcomes in SCI patients, despite the absence of standardized therapeutic protocols [47–49]. This therapeutic ambiguity necessitates comprehensive clinical validation through rigorously designed trials to establish evidence-based treatment paradigms.

hUCMSC-Exos have been established as pivotal immunomodulatory agents, with their therapeutic primacy substantiated through our results and experimentally validated multimodal mechanisms. hUCMSC-Exos orchestrate bidirectional immunomodulation in both innate and adaptive immunity across heterogeneous disease models [50–52]. Specifically, hUCMSC-Exos exhibit multimodal immunomodulation through: (1) macrophage repolarization via NF-κB inhibition [53], (2) pharmacological synergy (e.g., arsenic trioxide-enhanced macrophage polarization in acute graft-versus-host disease management) [54], (3) neuroinflammatory modulation (regulation of expressed interleukin (IL)-6/IL-1β/IL-10) [55], and (4) regulatory T cell expansion [56]. These coordinated mechanisms collectively validate their therapeutic efficacy across immune disorders.

While methodologically rigorous, this study has limitations including exclusive reliance on WoSCC data (excluding PubMed), which risks selection bias. Through multidimensional analysis (geographic-institutional-author metrics, citation networks, thematic evolution), we mapped hUCMSC-Exos research priorities and forecasted key trajectories: SCI management, vascularization



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Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2012 - 2024
Gatti S, 2011, NEPHROL DIAL TRANSPL, V26, P1474, DOI 10.1093/ndt/gfr015, DOI	2011	6.91	2013	2016	
Li TF, 2013, STEM CELLS DEV, V22, P845, DOI 10.1089/scd.2012.0395, DOI	2013	15.24	2015	2018	
Zhou Y, 2013, STEM CELL RES THER, V4, P0, DOI 10.1186/scrt194, DOI	2013	12.96	2015	2018	
Bian SY, 2014, J MOL MED, V92, P387, DOI 10.1007/s00109-013-1110-5, DOI	2014	6.32	2015	2019	
Zhang B, 2015, STEM CELLS, V33, P2158, DOI 10.1002/stem.1771, DOI	2015	15.15	2016	2020	
Kordelas L, 2014, LEUKEMIA, V28, P970, DOI 10.1038/leu.2014.41, DOI	2014	8.06	2016	2019	
Zhu YG, 2014, STEM CELLS, V32, P116, DOI 10.1002/stem.1504, DOI	2014	7.5	2016	2018	
Doeppner TR, 2015, STEM CELL TRANSL MED, V4, P1131, DOI 10.5966/sctm.2015-0078, DOI	2015	7.31	2016	2020	
Liang XT, 2014, CELL TRANSPLANT, V23, P1045, DOI 10.3727/096368913X667709, DOI	2014	6.54	2016	2019	
Rani S, 2015, MOL THER, V23, P812, DOI 10.1038/mt.2015.44, DOI	2015	10.5	2017	2020	
Zhao YY, 2015, STEM CELLS INT, V2015, P0, DOI 10.1155/2015/761643, DOI	2015	10.09	2017	2020	
Lener T, 2015, J EXTRACELL VESICLES, V4, P0, DOI 10.3402/jev.v4.30087, DOI	2015	8.64	2018	2020	
Li X, 2016, EBIOMEDICINE, V8, P72, DOI 10.1016/j.ebiom.2016.04.030, DOI	2016	7.25	2018	2021	
Squillaro T, 2016, CELL TRANSPLANT, V25, P829, DOI 10.3727/096368915X689622, DOI	2016	5.68	2018	2021	
Fang S, 2016, STEM CELL TRANSL MED, V5, P1425, DOI 10.5966/sctm.2015-0367, DOI	2016	10.4	2019	2021	
Yan YM, 2017, MOL THER, V25, P465, DOI 10.1016/j.ymthe.2016.11.019, DOI	2017	7.85	2019	2021	
Zhang SP, 2018, BIOMATERIALS, V156, P16, DOI 10.1016/j.biomaterials.2017.11.028, DOI	2018	6.58	2020	2021	
Zhu LP, 2018, THERANOSTICS, V8, P6163, DOI 10.7150/thno.28021, DOI	2018	6.19	2020	2021	
Witwer KW, 2019, J EXTRACELL VESICLES, V8, P0, DOI 10.1080/20013078.2019.1609206, DOI	2019	7.46	2021	2022	
Wu PP, 2018, CYTOTHERAPY, V20, P291, DOI 10.1016/j.jcyt.2017.11.002, DOI	2018	5.75	2021	2022	
Vizoso FJ, 2017, INT J MOL SCI, V18, P0, DOI 10.3390/ijms18091852, DOI	2017	5.75	2021	2022	
Théry C, 2018, J EXTRACELL VESICLES, V7, P0, DOI 10.1080/20013078.2018.1535750, DOI	2018	10.67	2022	2024	
Abbaszadeh H, 2020, J CELL PHYSIOL, V235, P706, DOI 10.1002/jcp.29004, DOI	2020	6.87	2022	2024	
Yang JY, 2020, INT J NANOMED, V15, P5911, DOI 10.2147/IJN.S249129, DOI	2020	6.87	2022	2024	
Shi YF, 2018, NAT REV NEPHROL, V14, P493, DOI 10.1038/s41581-018-0023-5, DOI	2018	6.67	2022	2024	

Fig. 8 Knowledge visualization map of document-level citation metrics: (**A**) Citedness distribution map of documents; (**B**) Temporal analysis map of document-level citation bursts

mechanisms, and immune homeostasis regulation. This synthesized overview provides critical guidance for future research and frontier exploration.

Conclusion

This systematic bibliometric mapping delineates the evolutionary trajectory of hUCMSC-Exos research, characterizing its academic influence, conceptual focal points, and disciplinary progression. Contemporary research efforts put emphasis on four aspects: immunomodulatory mechanisms, regenerative medicine, therapeutic delivery systems, and clinical model development. Notably, the therapeutic potential of hUCMSC-Exos reveals particular promise in SCI repair, ischemic diseases intervention, and immune disorder management. This analysis provides a structured framework for navigating

Table 6 Ranking of the top 20 keywords

Rank	Keyword	Counts	Rank	Keyword	Counts
1	Exosomes	643	11	Inflammation	113
2	Extracellular vesicles	384	12	Apoptosis	112
3	Mesenchymal stem cells	378	13	Expression	110
4	Stromal cells	219	14	Umbilical-cord blood	101
5	Bone-marrow	178	15	Umbilical cord	100
6	Human umbilical cord mesenchymal stem cells	148	16	Proliferation	97
7	Stem cells	136	17	Mesenchymal stromal cells	90
8	Angiogenesis	130	18	Differentiation	88
9	In-vitro	115	19	Injury	81
10	Therapy	114	20	Transplantation	75

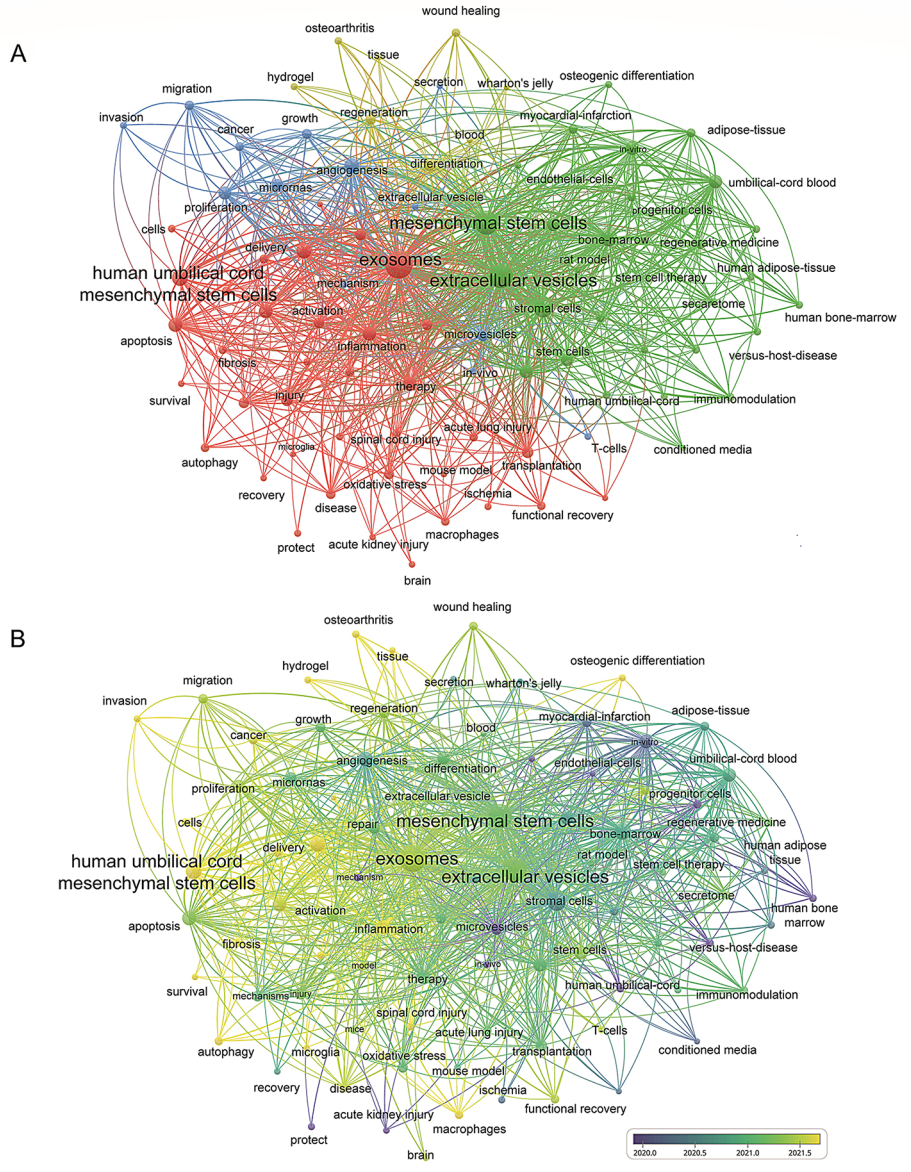

Fig. 9 Knowledge visualization map examining keyword-related research trends: (**A**) Clustered keywords visualization map; (**B**) Keywords timeline map

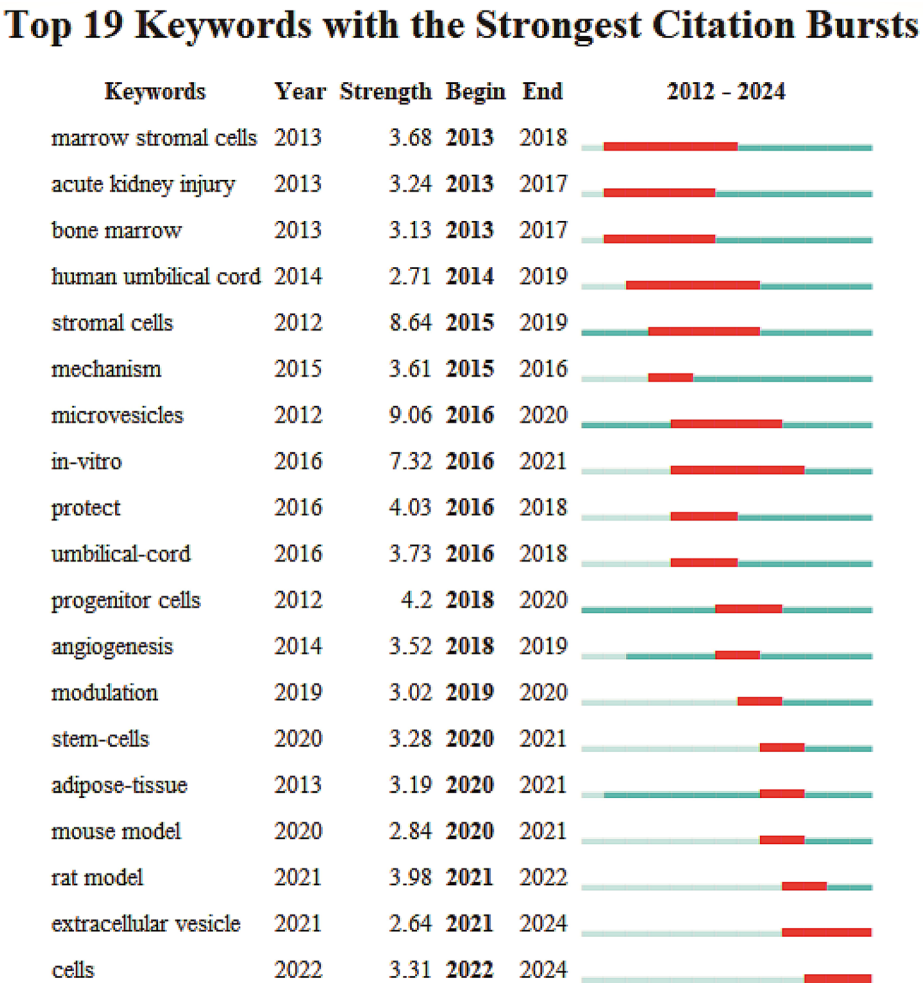

Fig. 10 Knowledge visualization map examining keyword-related research trends: Top 19 keywords with the strongest citation bursts

academic research in the hUCMSC-Exos field, clarifying intellectual frameworks. Furthermore, this study identifies key areas for mechanistic exploration and therapeutic innovation.

Abbreviations

Exos	Exosomes
hUC	Human umbilical cord
hUCMSC-Exos	Human umbilical cord mesenchymal stem cell-derived exosomes
MSC	Mesenchymal stem cell
SCI	Spinal cord injury
WoSCC	Web of science core collection
MAPK	Mitogen-activated protein kinase
Wnt	Wingless-related integration site
JAK/STAT	Janus kinase/signal transducer and activator of transcription
IL	Interleukin
miR	microRNA
KLF5	Krüppel-like factor 5
EFNA3	Ephrin-A3
Traf6	Tumor necrosis factor receptor-associated factor 6
Irak1	Interleukin-1 receptor-associated kinase 1
NF-κB	Nuclear factor kappa-B
TCs	Total citations
AACs	Average article citations
IF	Impact factor
NCT	National clinical trial
IRCT	Iranian registry of clinical trials

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions

Data analysis, data interpretation, and manuscript drafting were conducted by D.C., Z.C., J.Y., and G.C. Investigation and visualization were performed by Y.C. and K.H. The conception, design, revision of the manuscript, and acquisition of funding were led by Y.Y., L.Y., and Y.H.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors have given their consent for publication.

Competing interests
All authors declare that they have no competing interests.

AI usage
The authors declare that they have used artificial intelligence to polish the grammar of the manuscript.

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