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Emerging Molecular Insights in Stem Cell Therapy for Osteoarthritis: Decade of Bibliometric Analysis

Osteoartrit için Kök Hücre Terapisinde Ortaya Çıkan Moleküler Görüşler: Bibliyometrik Analizin On Yılı

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ABSTRACT Objective: Osteoarthritis (OA) a chronic degenerative joint disease that significantly challenges quality of life. Traditional treatments largely focus on symptom management, leaving a gap for therapies that can modify the disease process. Mesenchymal stem cells (MSCs) have gained attention as a potential therapeutic option due to their regenerative and immunomodulatory properties, leading to an increase in research activity in this area. This study aims to provide a comprehensive bibliometric analysis of MSC research in OA, highlighting key trends, contributors, and emerging areas of interest. **Material and Methods:** This study conducted a bibliometric analysis of MSC research in OA from 2012 to 2024, using data from the Web of Science. Employing robust tools such as VOSviewer, CiteSpace, and RBibliometrix provides an in-depth exploration of publication trends, collaboration networks, and emerging research themes, including cutting-edge areas like MSC-derived exosomes. **Results:** The study revealed a significant increase in MSC research output after 2015, driven by advancements in stem cell technology and a deeper understanding of OA pathogenesis. China, the USA, and Korea were identified as the leading contributors in this field. The most cited journals include "American Journal of Sports Medicine" and "Stem Cell Research&Therapy". Additionally, the growing interest in MSC-derived exosomes as a promising research focus was highlighted. **Conclusion:** The potential of MSC-based therapies in OA treatment has garnered increasing attention, with a notable rise in publications since 2015. Novel approaches such as MSC-derived exosomes are emerging as promising therapeutic strategies in regenerative medicine. However, challenges remain, including variability in patient responses, the need for standardized protocols, and long-term clinical efficacy. Further advanced preclinical and clinical studies are necessary to fully establish the therapeutic potential of MSCs in OA treatment.

Keywords: Osteoarthritis; mesenchymal stem cell; exosomes; bibliometrics

ÖZET Amaç: Osteoartrit (OA), yaşam kalitesini önemli ölçüde zorlayan kronik dejeneratif bir eklem hastalığıdır. Geleneksel tedaviler büyük ölçüde semptom yönetimine odaklanır ve hastalık sürecini değiştirebilecek terapiler için bir boşluk bırakırlar. Mezenkimal kök hücreler [mesenchymal stem cells (MSC'ler)], rejeneratif ve immünomodülatör özellikleri nedeniyle potansiyel bir tedavi seçeneği olarak dikkat çekmiş ve bu alanda araştırma faaliyetlerinde artışa yol açmıştır. Bu çalışma, OA'daki MSC araştırmalarının kapsamlı bir bibliyometrik analizini sunmayı, temel eğilimleri, katkıda bulunanları ve ortaya çıkan ilgi alanlarını vurgulamayı amaçlamaktadır. **Gereç ve Yöntemler:** Bu çalışma, Web of Science'tan alınan verileri kullanarak 2012'den 2024 yılına kadar OA'da MSC araştırmasının bibliyometrik analizini gerçekleştirdi. VOSviewer, CiteSpace ve RBibliometrix gibi sağlam araçların kullanılması, MSC türevi eksozomlar gibi son teknoloji alanlar da dâhil olmak üzere yayın eğilimleri, iş birliği ağları ve ortaya çıkan araştırma temalarının derinlemesine bir incelemesini sağlar. **Bulgular:** Çalışma, 2015 yılından itibaren MSC araştırma çıktısında önemli bir artış olduğunu ortaya koymuştur. Bu artış, kök hücre teknolojisindeki gelişmeler ve OA patogenezinin daha iyi anlaşılması ile ilişkilidir. MSC araştırmalarının en çok gerçekleştirildiği ülkeler arasında Çin, ABD ve Kore bulunmaktadır. Literatüre katkı sağlayan en çok atıf alan dergiler, "American Journal of Sports Medicine" ve "Stem Cell Research&Therapy" olarak belirlenmiştir. MSC'lerin OA'da kullanımına dair yayınların 2015'ten sonra belirgin bir artış gösterdiği ve MSC kaynaklı eksozomların gelecek vadeden bir araştırma alanı olarak öne çıktığı gözlemlenmiştir. **Sonuç:** MSC araştırmalarının OA tedavisindeki potansiyeli artan ilgi görmektedir ve bu alandaki yayın sayısı 2015'ten sonra belirgin bir artış göstermiştir. MSC kaynaklı eksozomlar gibi yeni yaklaşımlar, rejeneratif tıp alanında umut vaat eden terapiler arasında yer almaktadır. Ancak hasta tepkilerindeki değişkenlik, protokollerin standardizasyonu ve uzun vadeli klinik etkinliğin belirlenmesi gibi engeller hâlen mevcuttur. Bu nedenle MSC temelli tedavilerin OA'daki kesin etkinliğini anlamak için ileri düzey preklinik ve klinik araştırmalar gereklidir.

Anahtar Kelimeler: Osteoartrit; mezenkimal kök hücre; eksozomlar; bibliyometri

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Osteoarthritis (OA) is a prevalent, chronic degenerative joint disease marked by the progressive deterioration of articular cartilage. This pathological condition profoundly diminishes the quality of life in affected individuals by inducing chronic pain, swelling, restricted range of motion, and ultimately joint deformities. The conventional therapeutic approach to OA has predominantly involved conservative management strategies, including nonsteroidal anti-inflammatory drugs and structured physical therapy regimens. These interventions aim to enhance joint function by fortifying the periarticular muscles and mitigating pain. Nonetheless, these traditional methodologies generally exhibit limited efficacy in decelerating the pathological progression of OA and primarily offer temporary symptom relief.[1,2]

Stem cell-based therapies offer a promising alternative to traditional treatments, addressing the therapeutic gaps in managing various diseases. Traditional treatments often focus on symptom management rather than addressing the root cause of diseases, which can lead to chronic conditions and limited recovery. Stem cell therapies, with their regenerative potential, aim to repair or replace damaged tissues, offering a more comprehensive approach to treatment. This potential is particularly significant in the context of non-communicable diseases, human immmunodeficiency virus (HIV), and degenerative conditions. Below are key aspects highlighting the therapeutic gap and the promise of stem cell-based therapies.

Traditional treatments for non-communicable diseases often involve long-term medication and lifestyle changes, which may not fully restore health or prevent disease progression.[3]

In the case of HIV, antiretroviral therapy manages the virus but does not eliminate it, leaving persistent viral reservoirs that can lead to disease resurgence.[4] Degenerative diseases and injuries often result in irreversible tissue damage, with current treatments unable to regenerate lost tissue function. Stem cell therapies have shown potential in regenerating damaged tissues, offering hope for conditions like OA, diabetes, and heart failure by addressing the underlying causes rather than just symptoms.[3,5] Advances in tissue engineering and stem cell research have demonstrated promising results in clinical trials, indicating the potential for widespread application in regenerative medicine.[6]

Despite their promise, stem cell therapies face challenges such as safety, efficacy, and ethical concerns, which need to be addressed through rigorous research and regulatory frameworks.[5,6] The development of stem cell therapies requires multidisciplinary collaboration and significant investment in research to overcome existing barriers and maximize therapeutic benefits.[6,7] While stem cell therapies hold transformative potential, it is crucial to address the challenges associated with their development and application. This includes ensuring safety and efficacy, navigating ethical considerations, and establishing robust regulatory frameworks to facilitate their integration into clinical practice.

Bibliometric analysis serves as a powerful tool to quantitatively assess research output and trends across various scientific fields. Its primary objectives include mapping the state of the art, identifying research gaps, and understanding the evolution of specific domains. This method is particularly relevant for understanding molecular advancements, as it provides a structured overview of existing literature, highlights influential works, and suggests future research directions. This study aims to provide a comprehensive bibliometric analysis of MSC research in OA, highlighting key trends, contributors, and emerging areas of interest.

MATERIAL AND METHODS

SEARCH STRATEGY

An extensive review of the literature on stem cell research related to OA was performed using the Web of Science Core Collection (WoSCC) on July 31, 2024. The search strategy included the themes: stem cell*, OA*, cartilage*, and therapy*, with document types restricted to Article, Review, Early Access, and Book Chapter, all in English. The search focused on publications from 2012 to 2024. After the search was completed, the specified data from the retrieved literature was saved as "Full Record and Cited References" and downloaded from the WoSCC database in text format for subsequent analysis. The literature details

comprised authors' names, publication year, institutions, countries, keywords, journals, citations, H-index, and other relevant information. This data was then imported into VOSviewer, Citespace, R Bibliometrix, and a bibliometric tool for further analysis.

DATA ANALYSIS AND VISUALIZATION

In all bibliometric analyses, the R package Bibliometrix, VOSviewer 1.6.20 software (Leiden University, Leiden, Netherlands), Microsoft Office Excel 2021, and Citespace 6.2.4 (Chen Meichao, Drexel University) were utilized to characterize the publications, with results presented in both tabular and graphical formats. Basic information about all publications, including the total number of publications, publication types, number of publications by authors, and number of publications by journals, was gathered using the R package Bibliometrix. VOSviewer was employed to create visual representations of networks linking authors, citations, institutions, and countries, as well as the occurrence of keywords. Furthermore, VOSviewer illustrates relationships and temporal distances between topics using various colors, allowing the software to effectively predict future research hotspots. Analysis of the strongest citation bursts, along with the most significant citation bursts of keywords and references, was conducted using CiteSpace to identify research hotspots across different time periods.

RESULTS

PUBLICATION SUMMARY

The workflow diagram for this research is presented in Figure 1A. The search strategy employed in this study yielded 944 publications related to stem cell research for OA from the WoSCC covering the years 2012 to 2024. After excluding 2 retracted publications, 11 conference proceedings, and 9 online publications, a total of 922 publications were kept for analysis. This collection consists of 871 articles, 20 book chapters, 19 early access papers, and 12 reviews, authored by 4,849 individuals.

Annual variations in the literature indicate trends in research progress within this domain, with publication volume serving as a critical marker for assessing hotspots. Figure 1B illustrates the annual scientific output between 2012-2024. As depicted, the number of publications was relatively low in 2012 (25), gradually increasing to 38 and 39 in 2013 and 2014, respectively. A significant growth phase commenced between 2015-2022, with publications escalating from 46 to 115.

ANALYSIS OF COUNTRIES' CONTRIBUTION

Table 1 summarizes the leading countries contributing to the field, detailing their total citations and av-

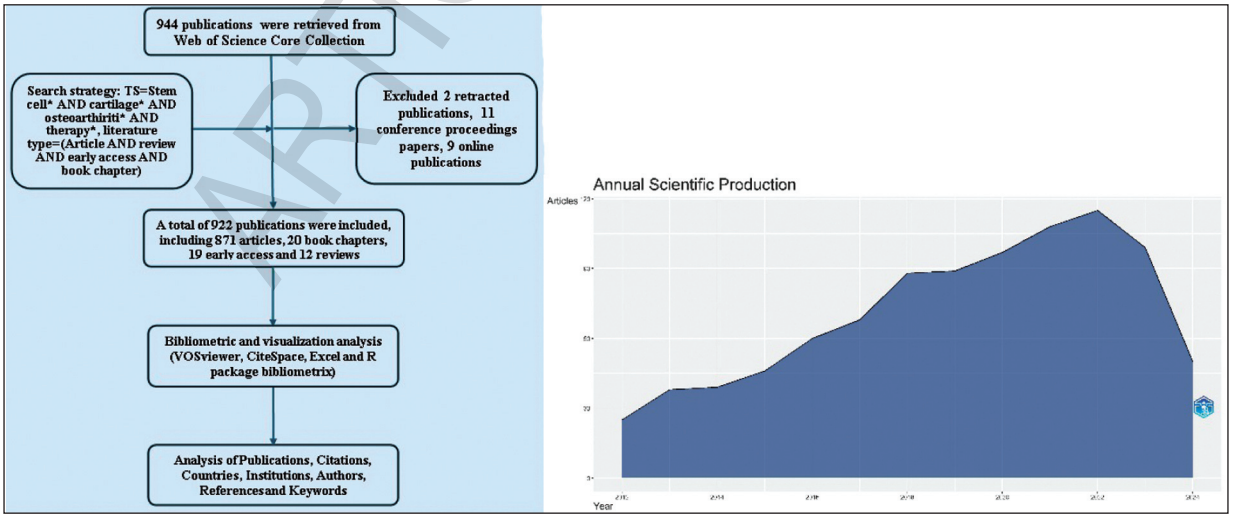

FIGURE 1: (A) Workflow diagram; **(B)** The annual number of scientific productions between 2012-2024

AND:

TABLE 1: The top contributing countries

Rank	Country	Articles	Freq	SCP	MCP	Total citations	Average article citations
1	Chiina	270	0.306	219	51	6,694	24.79
2	USA	146	0.165	104	42	5,209	35.68
3	Korea	70	0.079	63	7	3,271	46.73
4	Germany	45	0.051	24	21	775	17.22
5	Japan	41	0.046	34	7	968	23.61
6	Italy	29	0.033	18	11	1,270	43.79
7	Iran	28	0.032	21	7	753	26.89
8	United Kingdom	25	0.028	16	9	1,085	43.40
9	India	24	0.027	17	7	502	20.92
10	Australia	17	0.019	12	5	406	23.88

SCP: Single country publication; MCP: Multiple country publication

erage citations per article. Notably, China topped the list with a total of 270 publications, accounting for 29.3% of the total, followed by the United States with 146 publications (15.8%) and Korea with 70 publications (7.6%). In terms of citations, China maintained its leading position with 6,694 citations and an average of 24.79 citations per article. The United States ranked 2nd with 5,209 total citations and an impressive average of 35.68 citations per article, while Korea recorded 3,271 total citations, achieving an average of 46.73 citations per article. Interestingly, although Singapore had only 7 publications, it garnered an impressive 860 total citations, resulting in an average of 122.86 citations per article, which was the highest among all countries in this category (not included in Table 1).

Figure 2 showcases the map of country collaborations alongside the network map of these nations. The visual representation indicates that China was the most active country in this research area by a considerable margin, followed by the United States, Korea, Germany, Japan, and Italy-countries that could significantly impact stem cell research related to OA (Figure 2B). Furthermore, collaboration between the United States and China was prominent, with the United States also frequently partnering with other nations, particularly Japan and various Western European countries (Figure 2A).

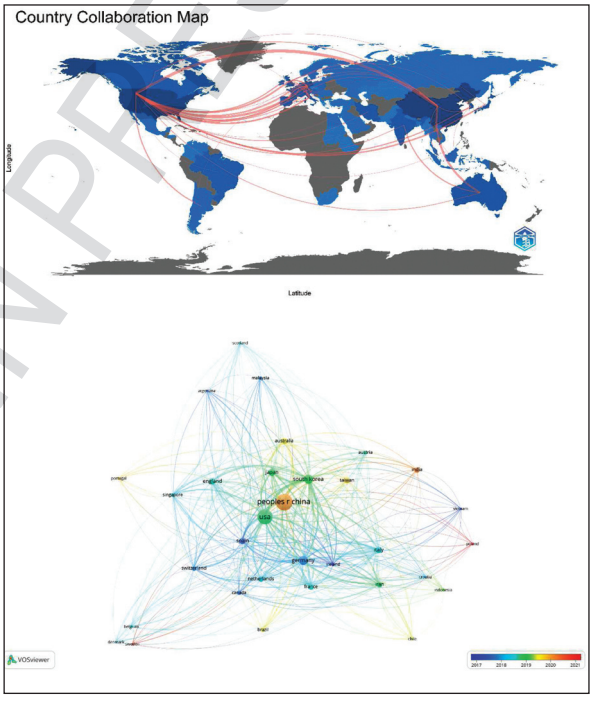

FIGURE 2: Analysis of Countries. **(A)** Country collaboration map, where the shades indicate the number of publications and the line thickness reflects the frequency of cooperation; **(B)** The network map of countries, where node size reflects the number of publications, and color denotes the average year of appearance.

ANALYSIS OF HIGHER-IMPACT JOURNALS

The journal analysis, which includes publications, citations, co-citation patterns, and core journals as per Bradford's Law, is depicted in Figure 3. Additionally, Table 2 provides an overview of the top 10 journals with the highest number of publications. The 922 articles evaluated for this study on stem cells for OA were published across 48 different journals from 2012 to 2024. Based on Bradford's Law, 20 core journals were identified, each with 9 or more publications (Figure 3C).

Table 2 shows that among the 48 journals publishing relevant articles, 17 journals produced 10 or more publications each. The American Journal of

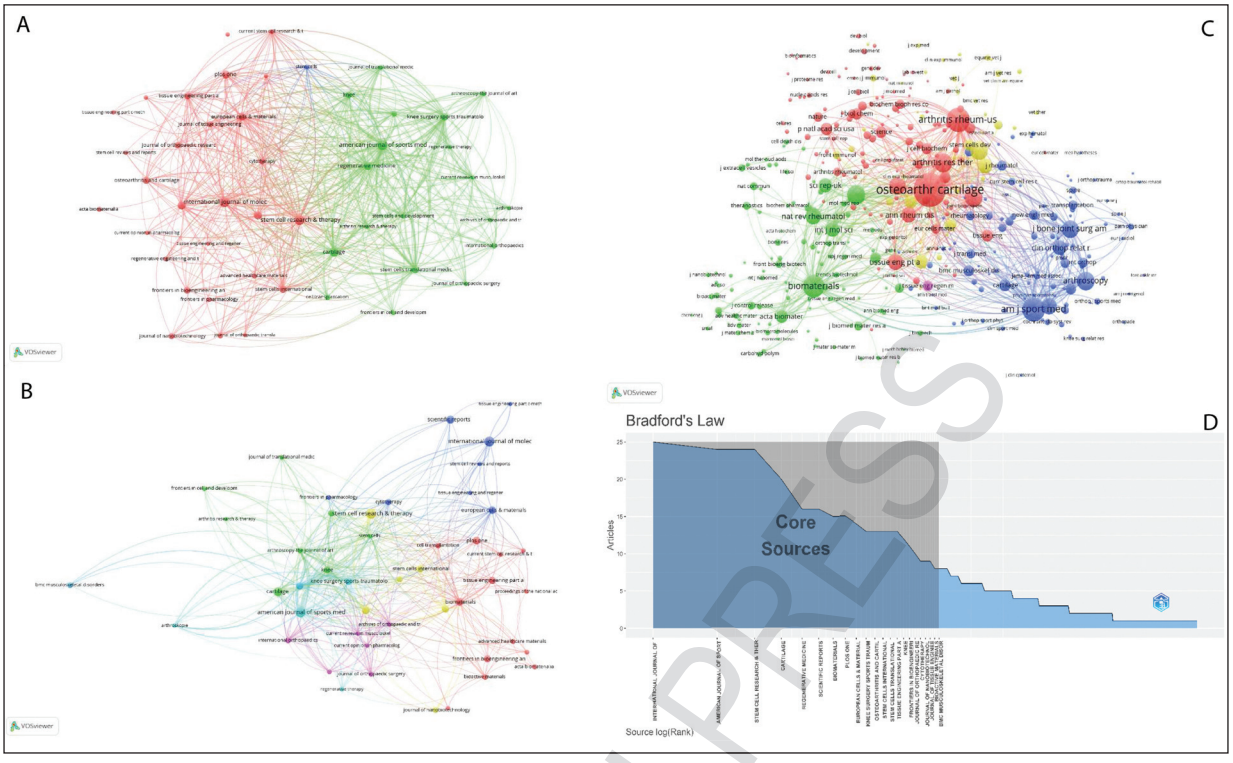

FIGURE 3: Journal analysis. **(A)** Analysis of publications, where node size reflects the publication counts of journals; **(B)** Citation analysis, with node size representing the total citations of journals; **(C)** Co-citation analysis of journals, where node size reflects the total citations of journals; **(D)** Core journals in accordance with Bradford's Law

TABLE 2: The general information of top 10 most productive journals

Rank	Sources	Articles	H-Index	G-Index	Total citations
1	American Journal of Sports Medicine	24	17	24	1,338
2	Stem Cell Research&Therapy	23	16	23	964
3	International Journal of Molecular Sciences	23	10	17	322
4	Cartilage	19	10	16	278
5	Biomaterials	15	12	15	1,047
6	Scientific Reports	15	12	15	893
7	Plos One	15	12	15	474
8	European Cells&Materials	14	12	14	807
9	Osteoarthritis and Cartilage	13	13	13	1,103
10	Stem Cells Translational Medicine	13	10	13	1,103

Sports Medicine emerged as the top journal, with the highest publication count (24) and an H-index of 17, which includes a total of 1,338 citations. It was followed closely by Stem Cell Research&Therapy, which published 23 articles and had an H-index of 16, along with 964 total citations, and the International Journal of Molecular Sciences, which also published 23 articles with an H-index of 10 and 322 total citations.

These findings illustrate that these journals are committed to high-quality research and are well-regarded in the field of stem cell research for OA. Notably, the American Journal of Sports Medicine (1,338 citations) and Biomaterials (1,047 citations) recorded the highest citation totals, further highlighting their significance in the field.

ANALYSIS OF INSTITUTIONS

The assessment of institutions, which includes citations, bibliographic coupling, and collaboration networks, is depicted in Figure 3. Additionally, Table 3 lists the top 10 institutions based on publication and

TABLE 3: The top 10 institutions based on number of publications and number of citations from the included publications on stem cell research for OA (n=91)

Rank	Institution	Publication	Citations	Avg. pub. year	Average citations
The top 10 institutions with most publications					
1	Shanghai Jiao Tong Univ, China	30	1,024	2020.70	34.13
2	Peking Univ, China	19	646	2020.16	34.00
3	Chinese Acad Sci, China	18	1,318	2018.83	73.22
4	Zhejiang Univ, China	18	687	2018.22	38.17
5	Sun Yat Sen Univ, China	17	254	2021.12	14.94
6	Hosp Special Surg, USA	15	455	2019.47	30.33
7	Southern Med Univ, China	15	365	2021.67	24.33
8	Tongji Univ, China	15	150	2021.07	10.00
9	Yonsei Univ, South Korea	14	1,177	2019.14	84.07
10	Nanjing Med Univ, China	13	1,024	2020.85	24.62
The top 10 institutions with most citation					
1	Chinese Acad Sci, China	18	1,318	2018.83	73.22
2	Yonsei Sarang Hosp, South Korea	10	1,195	2015.80	119.50
3	Yonsei Univ, South Korea	14	1,177	2019.14	84.07
4	Univ Hong Kong, China	6	1,089	2016.00	181.50
5	Harvard Univ, USA	6	1,070	2013.17	178.33
6	Johns Hopkins Univ, USA	7	1,052	2016.71	150.29
7	Shanghai Jiao Tong Univ, China	30	1,024	2020.70	34.13
8	Sichuan Univ, China	12	1,008	2018.67	84.00
9	Natl Univ Singapore, Singapore	8	989	2018.38	123.63
10	Univ Saarland, Germany	13	918	2014.23	70.62

OA: Osteoarthritis

citation counts. A total of 91 unique institutions contributed to the 922 articles published on stem cell research for OA, with universities and affiliated hospitals being the primary contributors, especially universities, which accounted for the largest share.

Among the institutions mentioned in Table 3, about 50% were located in China, while the remaining institutions were based in the United States, the United Kingdom, South Korea, Singapore, and Germany. The top 10 research institutions with the highest number of publications were as follows: Shanghai Jiao Tong University (30 publications), Peking University (19), Chinese Academy of Sciences (18), Zhejiang University (18), Sun Yat-sen University (17), Hospital for Special Surgery (15), Southern Medical University (15), Tongji University (15), Yonsei University (14), and Nanjing Medical University (13). According to the citation analysis in Table 3, articles from the Chinese Academy of Sciences had the highest citation count (1,318), followed by Yonsei Sarang Hospital (1,195) and Yonsei University (1,177).

Using VOSviewer software, bibliometric coupling network maps were constructed among institutions, excluding 8 publications, as illustrated in Figure 4A, Figure 4B. The results depict the collaboration landscape of more than 20 institutions in the network diagram (Figure 4C). In this visualization, the thickness of the lines indicates the strength of the coupling between institutions, while the size of the nodes reflects the number of publications. The analysis indicated that Shanghai Jiao Tong University had the highest total link strength (12,017), followed by Peking University (9,039), Monash University (9,008), and the Hospital for Special Surgery (8,294). Notably, Shanghai Jiao Tong University demonstrated considerable collaborative efforts with Nanjing Medical University and Tongji University.

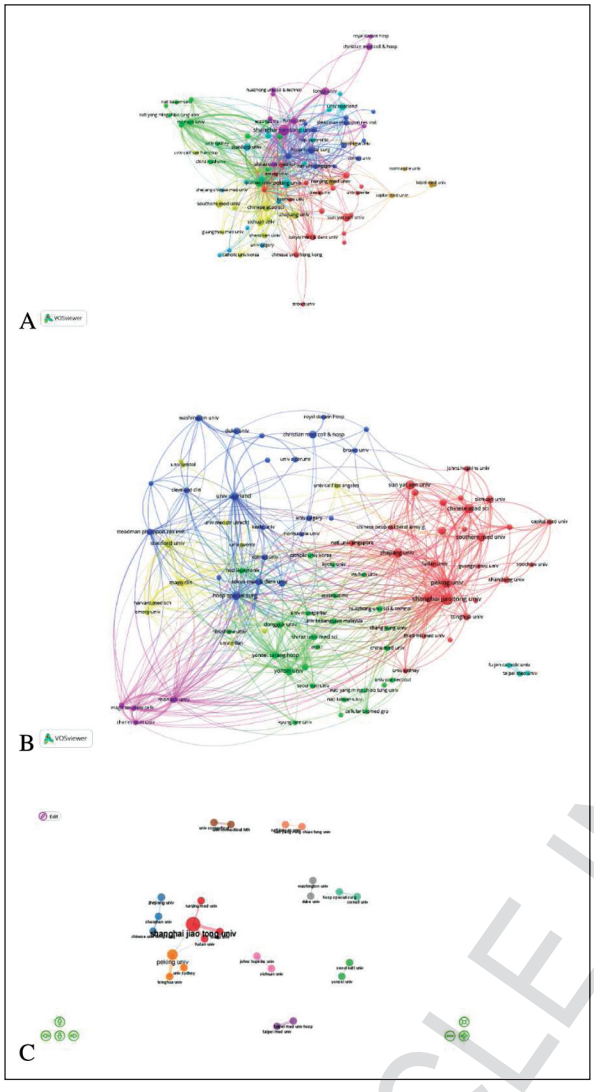

FIGURE 4: Analysis of Institutions. **(A)** The number of citations for institutions, with node size representing total citations; **(B)** Bibliographic coupling of institutions, where node size indicates the number of publications; **(C)** Collaboration network of institutions

ANALYSIS OF AUTHORS

To identify the most productive authors in the area of stem cell research for OA, a thorough analysis of author contributions was conducted using the R package Bibliometrix, along with VOSviewer and Citespace programs. The results, which include the network map of authors, citation analysis, bibliographic coupling among authors, and publication trends of top authors over time, are presented in Figure 5.

A total of 4,412 authors contributed to the publication of the 922 articles in this field. Table 4 highlights the ten authors with the highest publication counts. Na emerged as the leading author, with the highest number of publications (17 articles) and a G-index of 17. Following Na, Madry H. published 16 articles, achieving a G-index of 16, while Cucchiarini M. contributed 13 articles with a G-index of 13. Koh YG., who published 10 articles, was recognized as the most frequently cited author, amassing a total of 1,195 citations. The 2nd-most cited author was Choi, with 7 articles and a remarkable 1,130.673 citations (not shown in Table 4). Other noteworthy authors included Jorgensen C. (11 articles, 1,033 citations) and Cao (6 articles, 1,025 citations; not shown in Table 4).

TABLE 4: The top 10 authors with most publications

Rank	Author	Articles	H-Index	G-Index	Total citations
1	Na	17	12	17	469
2	Madry H.	16	13	16	970
3	Cucchiarini M.	13	10	13	685
4	Sekiya I.	12	10	12	447
5	Jorgensen C.	11	9	11	1,033
6	Vinod E.	11	7	10	110
7	Guilak F.	10	10	10	861
8	Kachroo U.	10	7	10	108
9	Koh YG.	10	10	10	1,195
10	Wang Y.	10	9	10	374

Figure 5A illustrates the author analysis, revealing a network with significant collaborations primarily among influential authors such as Madry H., Cucchiarini M., and REY-RICO A. However, it also indicates that collaboration among other authors in this field is relatively weak. This suggests a need for enhanced cooperation and more frequent collaboration among researchers to further advance stem cell research for OA.

ANALYSIS OF CITATIONS

The analysis of citations and co-citations in the realm of stem cell research for OA is depicted in Figure 6. This includes the network map of citations, the network map of co-cited references, the top references with the strongest citation bursts, and the most locally cited publications. Table 5 lists the top 10 most cited publications in this area of research. A total of 140 publications, each with 50 or more citations, were identified, with the most-cited articles published between 2012-2019.

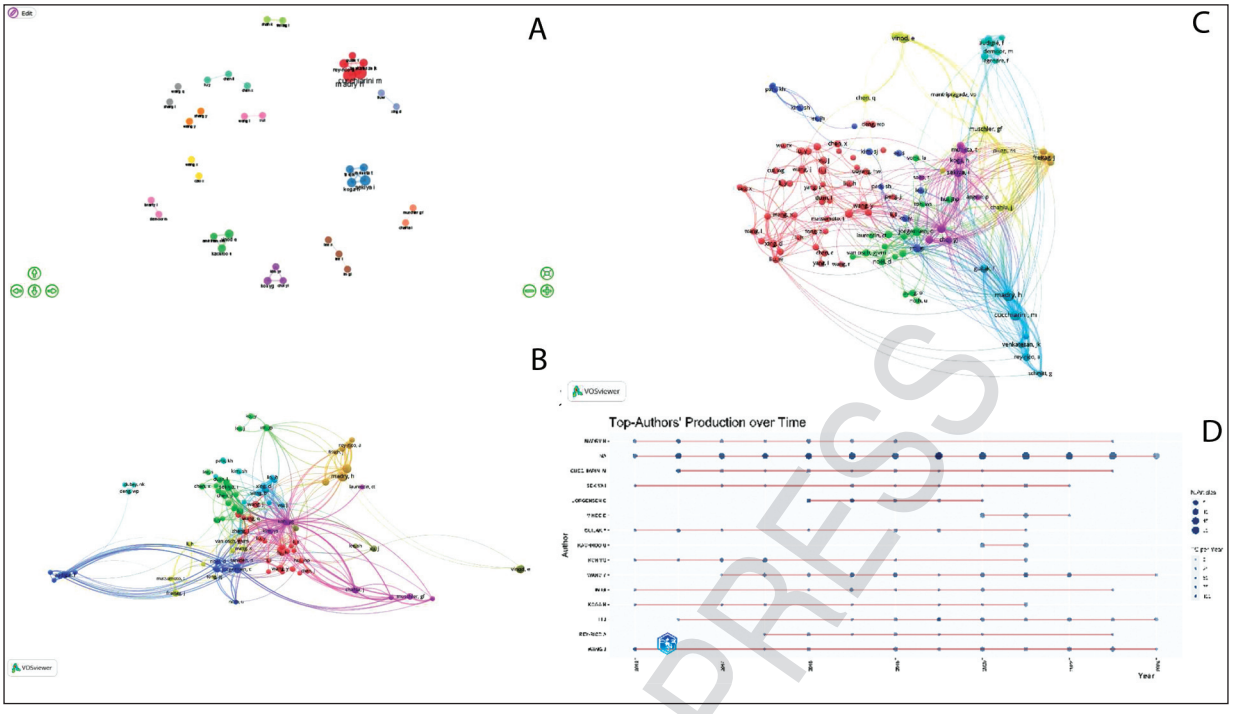

FIGURE 5: Author Analysis. **(A)** The network map of authors, where node size represents the number of publications; **(B)** Citation analysis of authors, with node size reflecting total citations; **(C)** Bibliographic coupling among authors, where node size indicates the number of publications; **(D)** Publication trends of top authors over time

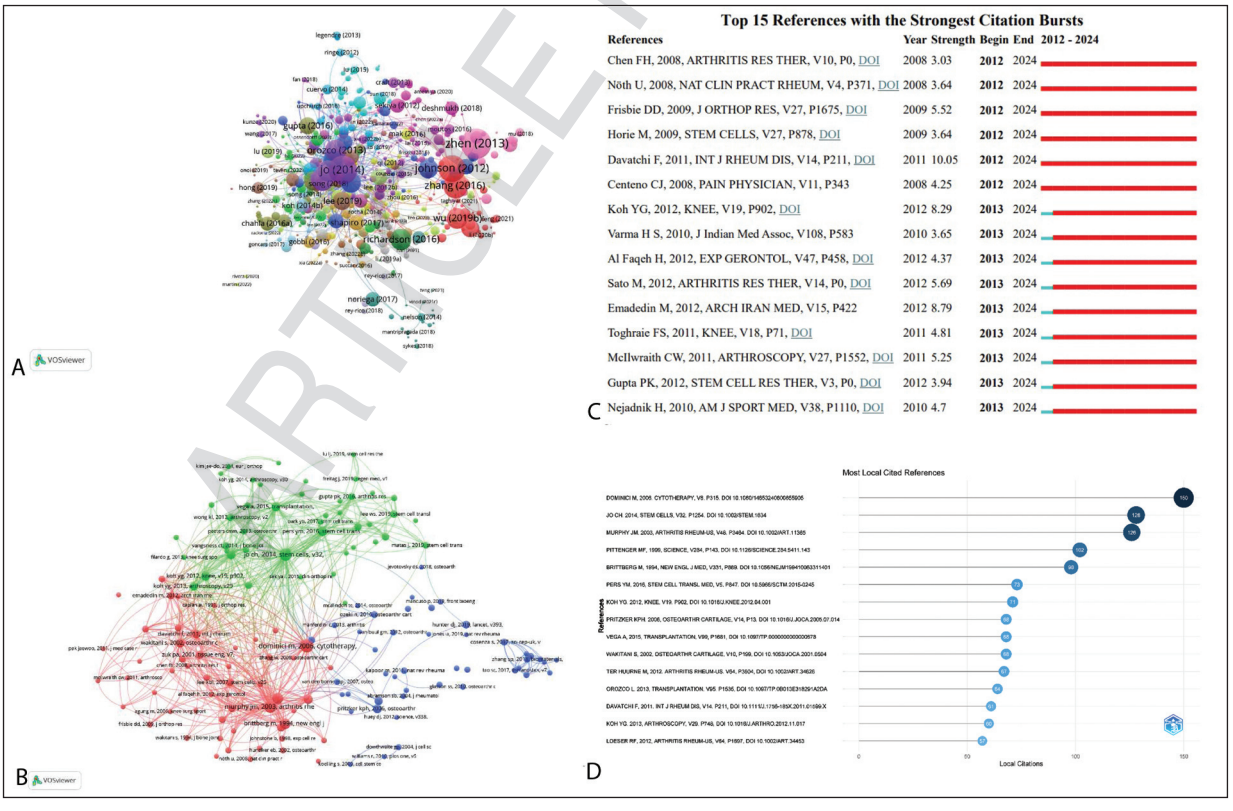

FIGURE 6: Citation and co-citation analysis. **(A)** Network map of total citations of publications; **(B)** Network map of co-cited references; **(C)** Top 15 references with the strongest citation bursts; **(D)** Most locally cited references

TABLE 5: The top 10 most cited publications (n=922)

Rank	Author	Year	Total citations
1	Zhen	2013	706
2	Jo	2014	626
3	Johnson	2012	551
4	Zhang	2016	459
5	Cosenza	2017	409
6	Vega	2015	405
7	Richardson	2016	341
8	Pers	2016	338
9	Orozco	2013	336
10	Wu	2019	326

Figure 6A presents the network map illustrating total citations for the studied publications. A thorough co-citation analysis was performed, involving 29,428 references, resulting in the corresponding network map of co-cited references shown in Figure 6B. It was found that 143 pieces of literature received more than 20 citations. Figure 6D highlights the top 15 most cited references, with Dominici's work published in 2006 receiving the most citations (150).[8] This is closely followed by Jo's publication from 2014, which garnered 128 citations, and Murphy's 2003 work with 126 citations.[9,10]

To identify emerging trends in the field, a citation burst analysis was conducted, measuring increases in citation frequency over specific time lapses to reflect areas of heightened academic interest.[11] The top 15 references with the strongest citation bursts are presented in Figure 6C, where dark blue bars indicate minor increases in citations, while red bars signify significant spikes. Most references experienced notable citation bursts between 2012-2024. Notably, the publication by Davatchi in 2011, featured in the International Journal of Rheumatic Diseases, demonstrated the highest burst strength (10.05), followed by Emadedin's 2012 work in Archives of Iranian Medicine (burst strength: 8.79) and Koh YG.'s 2012 publication in Knee (burst strength: 8.29).[14] Other significant references include Sato's 2012 article in Arthritis Research&Therapy (burst strength:

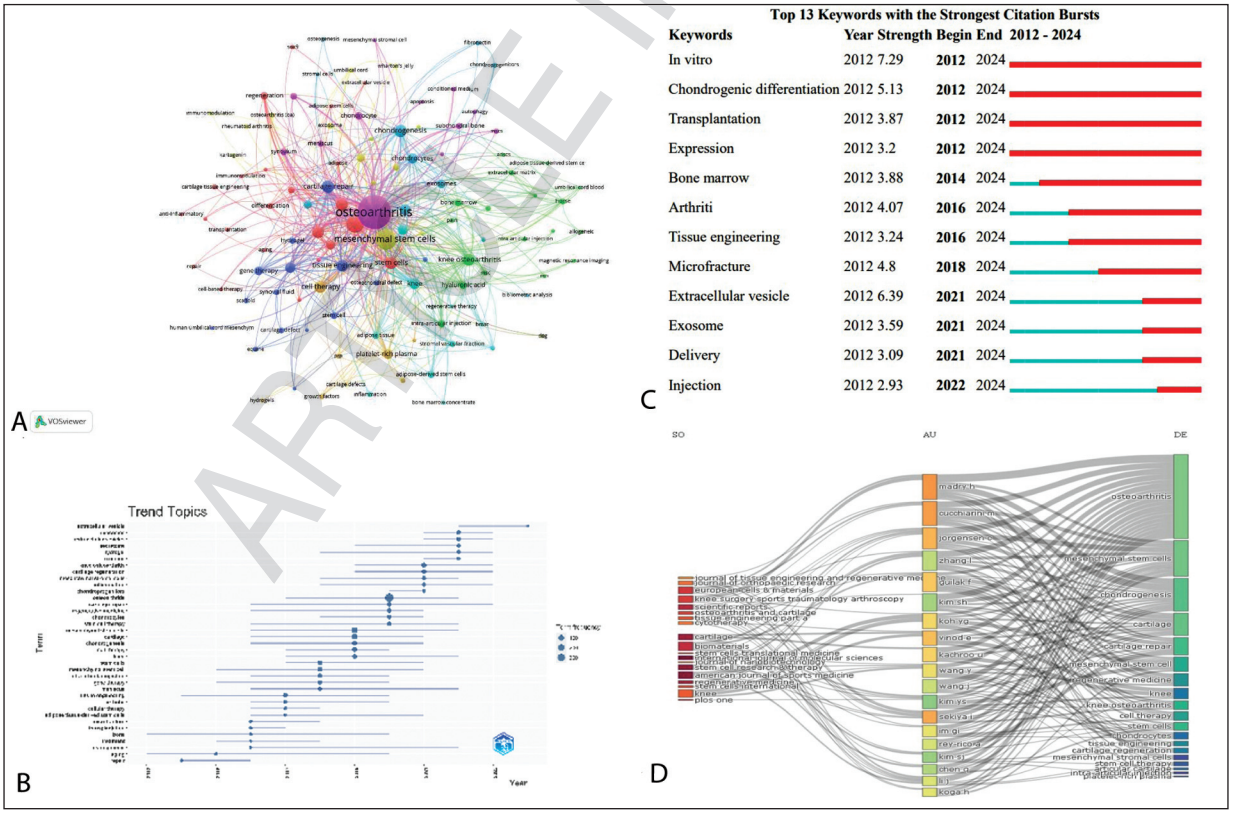

FIGURE 7: Keyword Analysis. **(A)** Network map of keywords, where node size represents frequency; **(B)** Trend topics based on keywords generated by the R package Bibliometrix; **(C)** Top 13 keywords with the strongest citation bursts; **(D)** Three-field plot of journals, authors, and keywords

5.69) and Frisbie's 2009 study in the Journal of Orthopaedic Research (burst strength: 5.52).[16,17] This comprehensive analysis reflects the evolving landscape of stem cell research in OA, emphasizing seminal references that continue to shape the field.

ANALYSIS OF KEYWORDS

The analysis of keywords, including the network map, trend topics based on keywords, top keywords with the strongest citation bursts, and a 3-field plot of journals, authors, and keywords, is presented in Figure 7. Table 6 shows the top 15 keywords by frequency in publications on stem cell research for OA.

From Figure 7A, the network analysis reveals that keywords like OA, mesenchymal stem cells (MSC), cartilage, chondrogenesis, cartilage repair, stem cells, knee OA, cell therapy, regenerative medicine, and tissue engineering were among the most frequently mentioned in this study. Figure 7B shows topic trends consistent with the visualizations in Figure 7A**.** The top 13 keywords with the strongest citation bursts were analyzed to highlight the historical research trends in this field (Figure 7C). Additionally, a 3-field plot depicting the relationships among journals, authors, and keywords was created (Figure 7D), revealing a close association between Madry H. and Cucchiarini M., whose research primarily focuses on OA and MSCs. The leading journals in this field were identified as European Cells and Materials, Journal of Orthopaedic Research, and Knee Surgery, Sports Traumatology, Arthroscopy.

The keyword burst detection algorithm helps identify keywords that have gained popularity within the academic community. This method presents results in 2 dimensions: burst value and burst time. Keywords with high burst values during specific periods indicate significant attention in the corresponding timeframe and reflect the research frontiers of the domain.[12] As shown in Figure 7C, the top 13 keywords with the highest burst values from 2012 to 2024 include *in vitro* (burst strength: 7.29), chondrogenic differentiation (5.13), transplantation (3.87), and expression (3.20). From 2015 to 2024, keywords such as bone marrow (3.88), arthritis (4.07), tissue engineering (3.24), and microfracture (4.80) were frequently cited. Finally, from 2020 to 2024, keywords like exosome, extracellular vesicle, delivery, and injection were commonly featured.

BIBLIOMETRIC ANALYSIS OF KEYWORD CO-OCCURRENCE

Keywords, serving as condensed representations of article themes, underwent co-occurrence analysis to determine research directions and highlights. Of the 112 keywords analyzed, 54 occurred more than 10 times. The co-occurrence network visualization, illustrated in Figure 7A, reveals that the top 5 keywords by occurrence weight were "OA" (391

TABLE 6: Top 15 keywords by frequency from the included publications on stem cell research for osteoarthritis (n=112)

Rank	Keyword	Total link strength	Occurrences	Avg. pub. year	Average citations
1	Osteoarthritis	844	391	2019.45	29.79
2	Mesenchymal stem cells	395	147	2018.95	36.05
3	Cartilage	289	105	2018.18	34.81
4	Chondrogenesis	134	54	2018.54	21.63
5	Cartilage repair	134	52	2019.21	21.35
6	Stem cells	151	52	2018.46	28.46
7	Knee osteoarthritis	117	50	2020.56	32.10
8	Cell therapy	140	49	2018.55	31.41
9	Regenerative medicine	150	48	2018.73	46.96
10	Tissue engineering	134	45	2017.47	44.96
11	Cartilage regeneration	89	42	2020.50	39.02
12	Knee	123	41	2018.95	47.51
13	Chondrocytes	100	37	2019.59	15.70
14	Articular cartilage	99	35	2019.11	44.71
15	Stem cell therapy	74	35	2019.20	39.03

occurrences; total link strength: 844), "MSCs" (147 occurrences; total link strength: 395), "cartilage" (105 occurrences; total link strength: 289), "chondrogenesis" (54 occurrences; total link strength: 134), and "cartilage repair" (52 occurrences; total link strength: 134) in descending order (as detailed in Table 6).

DISCUSSION

This bibliometric analysis provides critical insights into the evolving landscape of MSC research for OA, shedding light on publication trends, leading contributors, and emerging research themes. The findings underscore the increasing prominence of regenerative medicine and molecularly targeted therapies, highlighting both progress and existing challenges in translating MSC-based therapies into clinical practice**.**

ADVANCEMENTS IN RESEARCH TRENDS

The rapid increase in publications since 2015 reflects a shift in OA research from symptomatic management to regenerative approaches. This shift is particularly evident in the transition from traditional symptomatic relief methods to innovative cellular and molecular interventions aimed at cartilage regeneration and inflammation control. MSC-derived exosomes and extracellular vesicles have gained significant attention due to their potential to modulate the joint microenvironment and support cartilage repair without the risks associated with direct MSC implantation.[13,14] The bibliometric analysis indicates that these cell-free approaches are gaining traction, addressing the challenges of immune rejection, tumorigenicity, and ethical concerns linked to stem cell therapies.[10] Additionally, advancements in tissue engineering, gene therapy, and biomaterial scaffolds have expanded the potential applications of MSC-based treatments, providing a more targeted approach to OA management.

GLOBAL CONTRIBUTIONS AND COLLABORATION DYNAMICS

The analysis reveals that China and the United States are leading contributors to MSC research in OA, together accounting for a substantial portion of the published literature. China has the highest publication volume, while the United States produces higher-impact work in terms of citations per article. This difference suggests that while China is focusing on the expansion of research output, the United States is driving high-quality, impactful studies that shape the field's direction.[14,15]

Despite significant contributions from these leading nations, global collaboration remains suboptimal. The analysis highlights strong research ties between the United States and China, but broader international collaborations, particularly with European and other Asian countries, are relatively weaker. This lack of extensive cooperation may be attributed to differences in funding priorities, regulatory landscapes, and institutional policies governing stem cell research. Enhancing international collaboration through shared research initiatives, standardized protocols, and cross-border clinical trials could accelerate innovation and improve the reproducibility of findings across different populations.[16,17]

INSTITUTIONAL AND AUTHORIAL INFLUENCE

Key institutions such as Shanghai Jiao Tong University, the Chinese Academy of Sciences, and Peking University have emerged as central hubs of MSC research in OA. These institutions not only contribute to a high volume of publications but also play a pivotal role in shaping research directions through collaborative networks. The presence of influential hospitals and universities such as the Hospital for Special Surgery and Yonsei University further highlights the interdisciplinary nature of the field, bridging basic research with clinical applications.[13]

While some leading authors, such as Madry H. and Cucchiarini M., demonstrate strong research networks, the author collaboration network remains relatively fragmented. Many researchers work independently or within small groups, limiting knowledge exchange and the development of multidisciplinary solutions. Encouraging broader collaborations among researchers, particularly between clinical and basic science experts, could facilitate the translation of preclinical findings into effective clinical therapies.[18]

INSIGHTS FROM CITATION AND KEYWORD ANALYSES

The citation analysis underscores the enduring impact of foundational studies such as Dominici's 2006 work on MSC definitions, which continues to guide research and regulatory policies. Recent highly cited publications emphasize the growing interest in MSC-derived exosomes as a promising alternative to traditional cell-based therapies.[8,12]

Keyword analysis further reveals research priorities and emerging trends. Terms such as "cartilage repair", "tissue engineering", and "chondrogenesis" highlight the focus on regenerative mechanisms, while keywords like "inflammation" and "extracellular vesicles" indicate a shift toward understanding MSC paracrine effects in modulating OA pathophysiology.[14] Interestingly, the emergence of keywords such as "micro ribonucleic acid," "biomaterials," and "gene editing" suggests an increasing emphasis on enhancing MSC therapeutic efficacy through molecular modifications and scaffold-based delivery systems. These insights provide a roadmap for future research, indicating areas that warrant further exploration and investment.

CHALLENGES AND OPPORTUNITIES

Despite promising advancements, several critical challenges must be addressed for MSC-based therapies to reach their full potential in OA treatment. One major concern is the variability in patient responses to MSC treatments. Factors such as donor heterogeneity, cell passage number, and culture conditions significantly influence MSC function and therapeutic efficacy, leading to inconsistent clinical outcomes.[20,21] Standardizing MSC isolation, characterization, and application protocols is essential to ensure reproducibility and optimize clinical benefits.

Another key challenge is the regulatory landscape governing MSC-based interventions. Differences in approval pathways across regions create barriers to global implementation, slowing the transition from experimental studies to widely available treatments. Establishing harmonized regulatory guidelines would facilitate faster and safer clinical adoption of MSC therapies.[21]

Moreover, disparities in research funding and infrastructure between countries affect the field's progression. While developed nations have the resources to conduct large-scale, high-quality research, many developing regions struggle with limited access to advanced laboratory facilities and funding. Addressing these disparities through international funding programs and collaborative research initiatives could bridge the gap and promote more inclusive scientific progress.

FUTURE DIRECTIONS

To maximize the impact of MSC research in OA, the field must address these challenges while leveraging emerging opportunities. Key future directions include:

1. Standardization of MSC Therapies-Developing universally accepted guidelines for MSC isolation, characterization, and clinical application to ensure consistency across studies and trials.[23]

2. Advancement of Mechanistic Studies-Conducting in-depth research on the molecular pathways through which MSCs exert their therapeutic effects, particularly focusing on exosomal cargo and immunomodulatory mechanisms.[24]

3. Bridging Preclinical and Clinical Research-Strengthening the link between laboratory discoveries and patient-oriented applications through rigorously designed clinical trials with larger sample sizes and longer follow-up periods.[25]

4. Enhancing International Collaboration-Promoting interdisciplinary and multinational research initiatives to address regional disparities in funding, +-"infrastructure, and regulatory frameworks.[26]

5. Integration of Omics Technologies-Utilizing genomics, proteomics, and metabolomics to refine MSC therapies, identify biomarkers for patient stratification, and develop personalized treatment strategies.[27]

CONCLUSION

This bibliometric analysis provides a comprehensive overview of MSC research in OA, highlighting key trends, influential contributors, and emerging therapeutic directions. The study underscores the field's

transition toward molecularly targeted regenerative medicine, particularly through MSC-derived exosomes and extracellular vesicles. While significant advancements have been made, challenges such as standardization, variability in clinical outcomes, and research disparities must be addressed to facilitate broader clinical application. Future research should focus on refining MSC-based therapies through mechanistic studies, rigorous clinical trials, and enhanced international collaboration. By addressing these challenges and leveraging novel technological advancements, MSC-based therapies hold great promise for revolutionizing OA treatment, improving patient outcomes, and advancing regenerative medicine in musculoskeletal disorders.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Demet Tekdöş Demircioğlu, Seval Türk;* ***Design:*** *Demet Tekdöş Demircioğlu, Seval Türk;* ***Control/Supervision:*** *Demet Tekdöş Demircioğlu;* ***Data Collection and/or Processing:*** *Demet Tekdöş Demircioğlu;* ***Analysis and/or Interpretation:*** *Demet Tekdöş Demircioğlu, Seval Türk;* ***Literature Review:*** *Demet Tekdöş Demircioğlu, Seval Türk;* ***Writing the Article:*** *Demet Tekdöş Demircioğlu, Seval Türk;* ***Critical Review:*** *Demet Tekdöş Demircioğlu.*

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