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ORIGINAL RESEARCH

A Bibliometric Analysis of Exosomes Therapy in the Treatment of Osteoarthritis from 2012 to 2022

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Purpose: Osteoarthritis (OA) is a common clinical disease characterized by the destruction of articular cartilage, subchondral ossification, cystic degeneration and osteophyte formation. Recently, more and more scholars draw attention to exosomes in the field of OA, and exciting breakthroughs have been achieved in recent years. However, bibliometric analysis of the literature in this research field is lacking. Considering its potential in treatment of OA, this article aimed to analyze the research status and identify future hotspots of exosomes in osteoarthritis in recent 10 years by bibliometrics tools.

Methods: Relevant publications in this field from 2012 to 2022 was retrieved from the Web of Science core collection database (WOSSCC). And we used Vosviewers, CiteSpace, an online analysis platform and the R package "Bibliometrix" for bibliometric analysis.

Results: A total of 484 publications (including 319 articles and 165 reviews) from 51 countries, 720 institutions, were included in this study. IRCCS Ist Ortoped Galeazzi, Shanghai Jiao Tong University, and Sun Yat-sen University are the leading research institutions in this field. *International Journal of Molecular Sciences* contributed the largest number of articles, and *Osteoarthritis and Cartilage* is the most co-cited journal. Of the 2664 scholars who participated in the study, Ragni E, De Girolamo L, Orfei CP, and Colombini A had the largest number of articles. Zhang, SP is the most co-cited author. "Mesenchymal stem cell", "biomaterials", "Inflammation" and "regenerative medicine" are the keywords in the research.

Conclusion: This is the first bibliometric analysis of exosomes in osteoarthritis. We explored current research status in recent years and identified frontiers and hot spots in this research field. We highlight the significant roles of mesenchymal stem cell-derived exosomes (MSC-Exos) in the treatment of osteoarthritis, and identified exosomal biomaterials as frontier in this research domain, which can provide reference for the researchers who focus on this research field.

Keywords: exosomes, osteoarthritis, bibliometric analysis, CiteSpace, VOSviewer, R package "bibliometrix"

Introduction

Osteoarthritis (OA) is a common clinical disease, characterized by the degeneration of articular cartilage, subchondral osteosclerosis, cystic degeneration and osteophyte formation. The main risk factors, including aging, obesity, genetic, traumatic joint injury, play vital roles in the development of OA.[1] Advanced osteoarthritis often leads to persistent pain and disability, and the rising incidence worldwide in recent years has placed an even greater economic burden on society[2].Due to the unclear mechanism of OA, it remains a challenge to repair and regenerate the degenerated articular cartilage in OA. Symptom-relieving drugs (including analgesics and non-steroidal anti-inflammatory drug etc.), which are available as options for the treatment, have many side effects associated with long-term use. And surgery

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intervention, including knee or hip arthroplasty, is often the last resort for the advanced OA.[3] Finding secure and practical alternatives for the promising developments of OA is therefore crucial.

Exosomes are a type of extracellular vesicle that ranges in size from 30 to 150 nm and contains proteins, cytokines, lipid molecules, DNA, and other compounds.[4,5] Almost all cells in the body can secrete exosomes, including Mesenchymal stem cell, dendritic cell, and T cells. Exosomes have an important role in pathogenesis of osteoarthritis, according to an increasing number of academics in this field,[6–12] exosomes are essential in the treatment of OA due to their stable properties, lack of heterologous danger, ease of storage, and transportation. Exciting breakthroughs have been achieved in recent years.

In light of quantitative and visual analysis, bibliometrics is a method of literature analysis that examines the output and status of literature in a research subject. It is now frequently utilized in the medical field,[13] such as orthopaedics,[14,15] oncology,[16,17] and thoracic surgery,[18] etc. We may obtain comprehensive data on countries, institutions, journals, authors, keywords, and references in the research fields with the help of bibliometrics tools like CiteSpace,[19] VOSviewer,[20] and the R package "Bibliometrix",[21] and we can also visualize these results.[22]

Although scholars have done bibliometric studies on exosomes in many diseases, such as diabetes[23] and cardiovascular diseases,[24] there are no bibliometric studies on exosomes in osteoarthritis. This study conducted a bibliometric analysis of the publications on exosomes in osteoarthritis published in the recent ten years (2012–2022) to summarize the state of the research, assess the trends in the field, and forecast future research priorities.

Materials and Methods

Search Strategy

We selected the Web of Science Core Collection (WoSCC) database to conduct a literature search on 28 Dec.2022. The search terms is as follows: #1:TS=(exosome* OR exosomes OR exosomal OR "extracellular vesicle" OR "extracellular vesicles" OR "extracellular particle" OR "extracellular particles" OR "microvesicle" OR "microvesicles" OR "Shedding Microvesicle" OR "Shedding Microvesicles" OR "Secretory Vesicle" OR "Secretory Vesicles" OR "Cell-Derived Microparticle" OR "Cell-Derived Microparticles"), #2:TS=(Osteoarthritides OR Osteoarthrosis OR Osteoarthroses OR Arthritis, Degenerative OR Arthritides, Degenerative OR Degenerative Arthritides OR Degenerative Arthritis OR Arthrosis OR Arthroses OR Osteoarthrosis Deformans OR osteoarthritis), final=#1 AND #2. LA = (English), the date of search was from 1 January 2012 to 28 Dec. 2022, and the type of documents was set to "articles" and "review". Following the initial retrieval, we screened the titles and abstracts to confirm the eligibility of the articles based on predefined inclusion and exclusion criteria. The flowchart of the screening process is shown in Figure 1.

Data Analysis

Subsequent to the data collection process, we extracted relevant bibliometric information from the selected publications, including publication year, authorship, affiliations, countries, research domains, journal titles, and citation counts. For the analysis and visualization of the bibliometric data, we employed four advanced tools: VOSviewer (Version 1.6.18), R package "bibliometrix" (version 3.2.1) (https://www.bibliometrix.org), CiteSpace (Version 6.1. R1) and an online analysis platform (https://bibliometric.com).

VOSviewer (version 1.6.18) is a widely used bibliometric analysis software,[20] we can generate visualizations of cooperative, co-citation, co-occurrence networks by using VOSviewer. In this study, we utilized VOSviewer to carry out the following analyses: co-occurrence analysis of keywords, country, journal and co-cited journal, author and co-cited author, institution. In the visual network generated by VOSviewer, each node represents the country, institution, journal, and author category being analyzed. The nodes' size and color, respectively, represent the number and categorization of the examined categories. The degree of cooperation or co-citation between the nodes is indicated by the thickness of the links between them.

CiteSpace (version 6.1. R1) is another bibliometric analysis and visualization software developed by Professor Chen Meichao, Drexel University.[19] The "co-citation analysis theory" postulates that a co-citation relationship is formed when two papers are both listed in the references of a third cited article. Investigating these co-citation connections can uncover

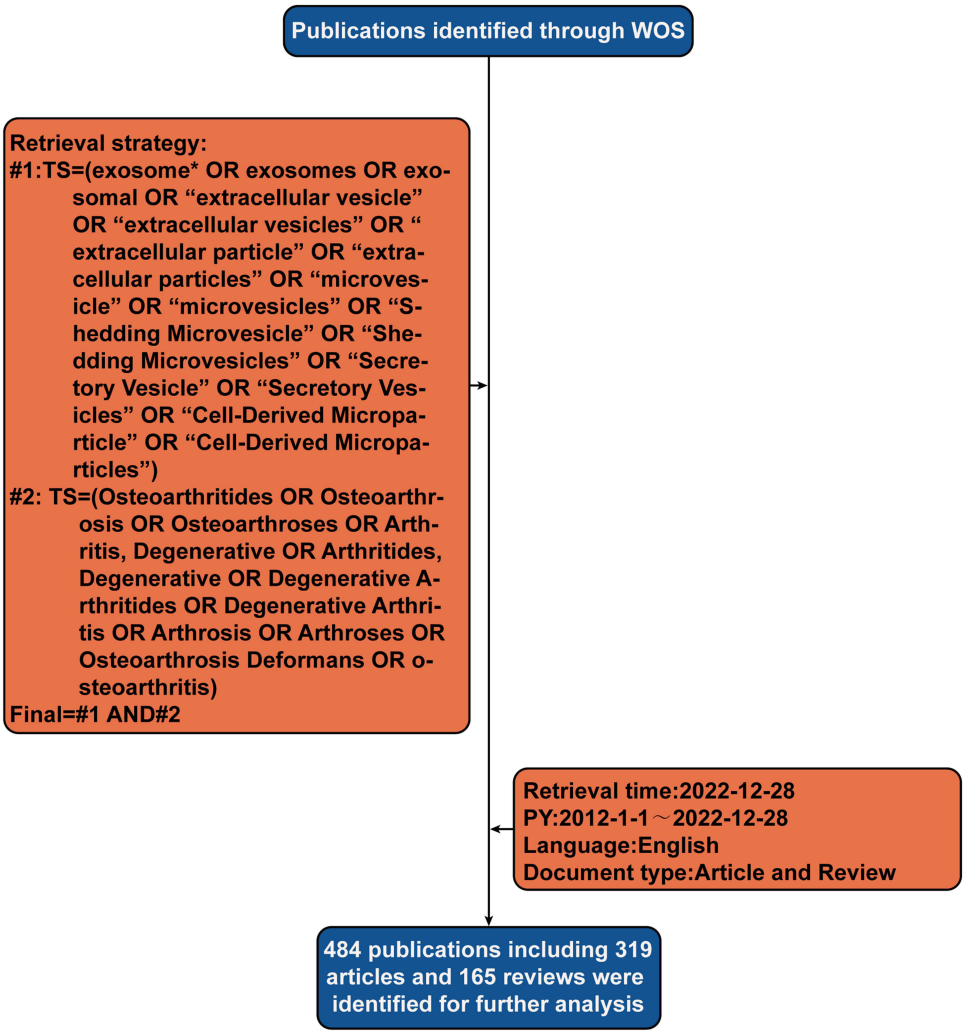


Figure 1 Flowchart of literature identification and analysis process.
Abbreviations: TS, Topic; WOS, Web of science; PY, Year Published.

pivotal transitions, the progression of keywords, and the forefront of associated research disciplines. In this study, CiteSpace was employed to visualize cooperation networks of institutions (Figure 2A), create dual-map overlays for journals (Figure 3C) and identify references (Figure 4C) and keywords (Figure 5A) with significant citation bursts.

We used the R package "Bibliometrix"[21](version 3.2.1) (https://www.bibliometrix.org) to display publication production across countries (Figure 6B), illustrate international collaboration among countries (Figure 6E), and present a three-field plot analysis (Figure 5C) as well as trend topic analysis (Figure 5D). Additionally, we visualized the annual output of the top 5 institutions (Figure 2B), journals (Figure 3B), and top 10 authors (Figure 7B).

Additionally, we also used GraphPad prism (version 9.5.0) to conduct quantitative analysis of all the data. (Figure 6A). The integration of these sophisticated tools enabled a multi-faceted examination of the roles of exosomes in osteoarthritis, providing a robust foundation for the evaluation of the field's current state and prospects.

Results

Quantitative Analysis of Publication

The annual output of the literature reflects trends in research development in the field, our search strategy identified 484 publications of exosomes in osteoarthritis in the last 10 years, including 319 article and 165 review. As shown in Figure 6A, from 2011 to 2015, there were little research manuscripts concerning the roles of exosomes in the

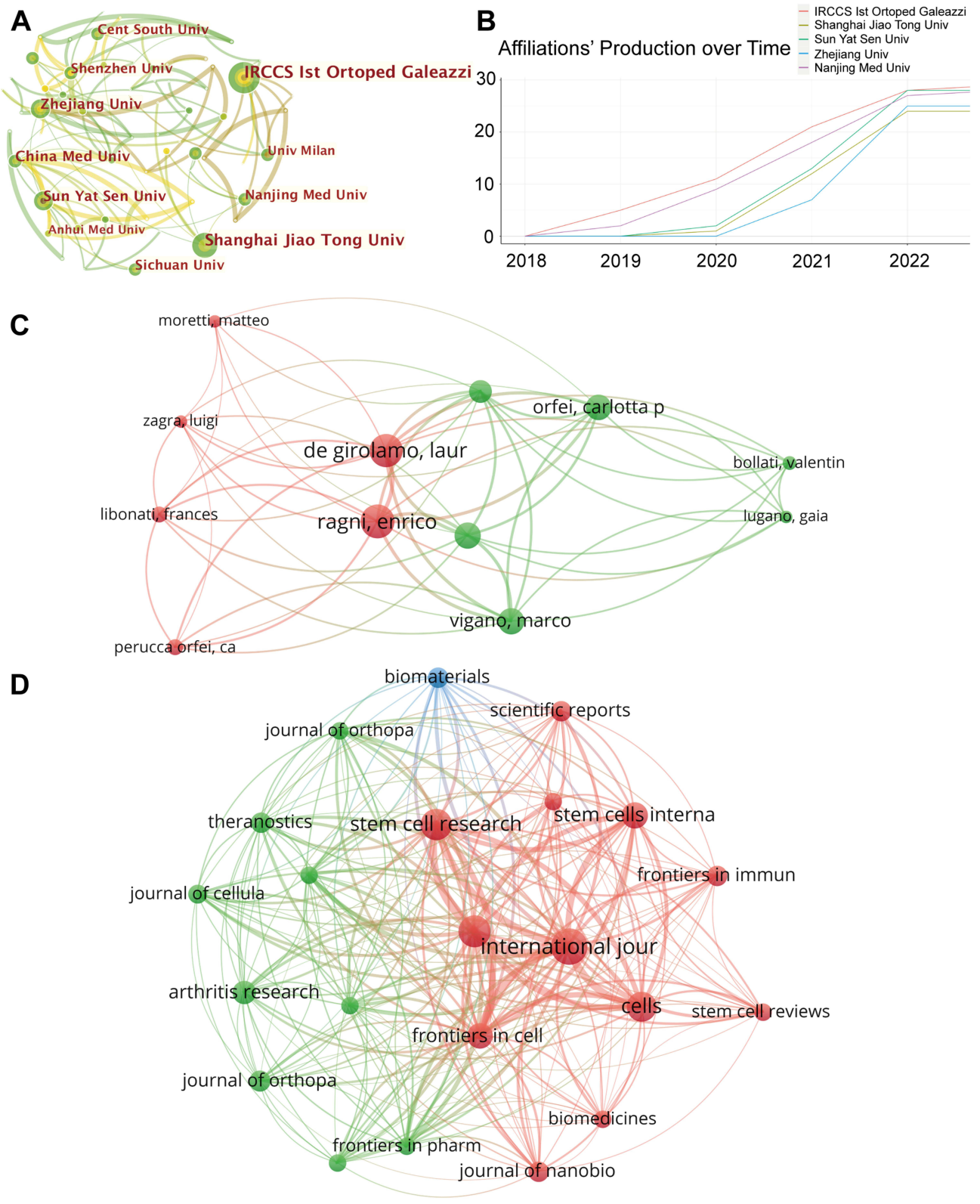


Figure 2 (**A**) The visualization of institutions cooperation networks based on CiteSpace. (**B**) Top 5 institutions' production over time. (**C**) Map of authors' cooperative relationship and (**D**) visualization of journals on the research of exosomes in osteoarthritis based on VOSviewer.

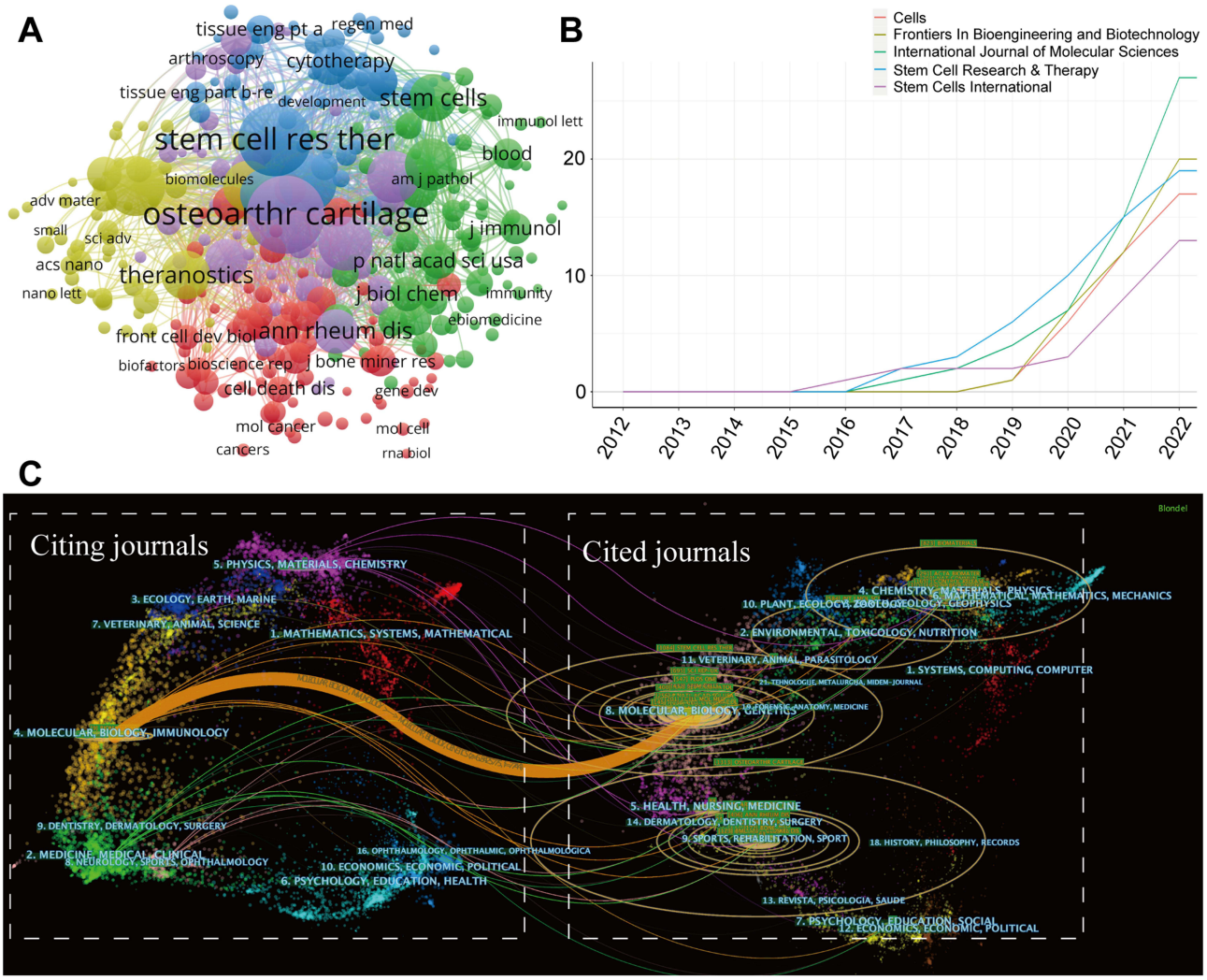
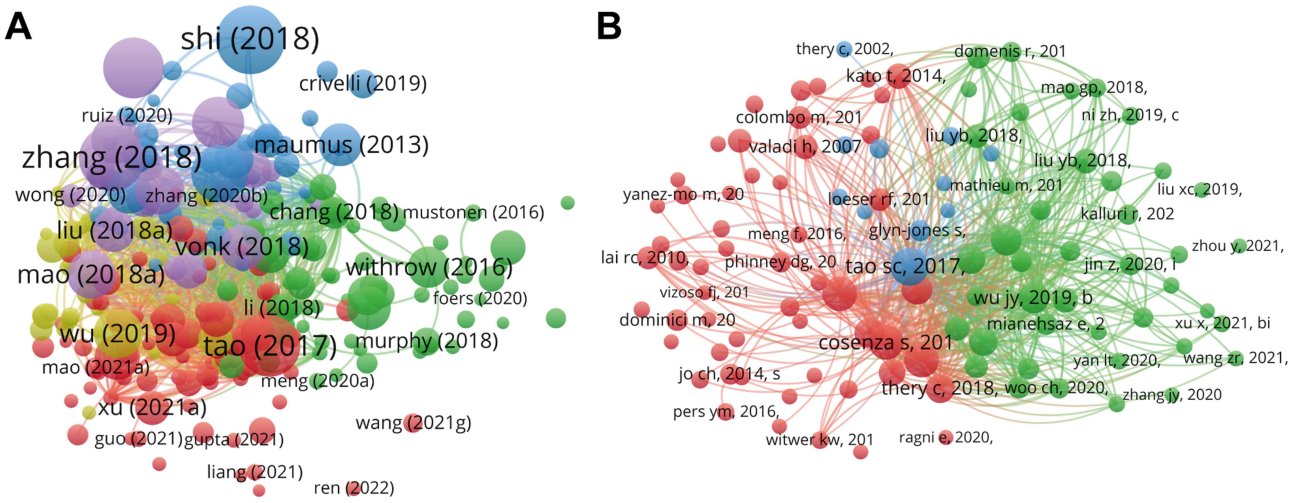


Figure 3 (**A**) Network map of journals that were co-cited in more than 20 citations. (**B**) Top 5 journals' publication overtime. (**C**) The dual-map overlay of journals related to exosomes in orthopedics.

osteoarthritis domain. Subsequent to 2016, the quantity of research manuscripts in this discipline has exhibited a consistent annual augmentation, with the publication count escalating from 9 in 2016 to 162 in 2022. This evinces that exosomes research has gained considerable recognition from osteoarthritis investigators in recent years. Manifestly, the utilization of exosomes in osteoarthritis therapy harbors immense potential, and the research trend is likely to continue.

Analyses of Institutions and Countries

All publications were produced by 720 institutions, 217 journals, and 51 nations. According to geographical network map in Figure 6E, the top 10 nations were spread over Asia, Europe, and the North America. As delineated in Table 1, publications originating from China (248) and the United States (56) predominate, with both countries jointly accounting for 62.81% of the aggregate global publications. Succeeding these two nations are the Italy (N = 52, 10.74%), South Korea (N = 29, 5.99%), and England (N = 23, 4.75%).As indicated in Table 1, the overall citation frequency is highest for publications from China (6736), trailed by the United States (1926), Italy (885), and France (733).In Figure 6C, the lines show the frequency of international academic collaboration, and the size of the node symbolizes the number of publications published in that country. As portrayed in Figure 6C and D, research collaboration amongst disparate countries is notably robust, with active cooperation existing between the United States and China, as well as Italy.



C

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2018 - 2022
Kato T, 2014, ARTHRITIS RES THER, V16, P0, DOI 10.1186/ar4679, DOI	2014	7.31	2018	2019	
Glyn-Jones S, 2015, LANCET, V386, P376, DOI 10.1016/S0140-6736(14)60802-3, DOI	2015	6.28	2018	2020	
Zhang B, 2014, STEM CELLS DEV, V23, P1233, DOI 10.1089/scd.2013.0479, DOI	2014	5.62	2018	2019	
Colombo M, 2014, ANNU REV CELL DEV BI, V30, P255, DOI 10.1146/annurev-cellbio-101512-122326, DOI	2014	5.06	2018	2019	
Zhang S, 2016, OSTEOARTHR CARTILAGE, V24, P2135, DOI 10.1016/j.joca.2016.06.022, DOI	2016	5.01	2018	2020	
Rani S, 2015, MOL THER, V23, P812, DOI 10.1038/mt.2015.44, DOI	2015	4.8	2018	2020	
Withrow J, 2016, ARTHRITIS RES THER, V18, P0, DOI 10.1186/s13075-016-1178-8, DOI	2016	4.63	2018	2019	
Kordelas L, 2014, LEUKEMIA, V28, P970, DOI 10.1038/leu.2014.41, DOI	2014	3.93	2018	2019	
Headland SE, 2015, SCI TRANSL MED, V7, P0, DOI 10.1126/scitranslmed.aac5608, DOI	2015	3.69	2018	2020	
Song J, 2015, CLIN EXP MED, V15, P121, DOI 10.1007/s10238-013-0271-4, DOI	2015	3.37	2018	2019	
Jo CH, 2014, STEM CELLS, V32, P1254, DOI 10.1002/stem.1634, DOI	2014	3.37	2018	2019	
Casado JG, 2017, FRONT VET SCI, V4, P0, DOI 10.3389/fvets.2017.00039, DOI	2017	2.95	2018	2020	
Cross M, 2014, ANN RHEUM DIS, V73, P1323, DOI 10.1136/annrheumdis-2013-204763, DOI	2014	2.81	2018	2019	
Kolhe R, 2017, SCI REP-UK, V7, P0, DOI 10.1038/s41598-017-01905-y, DOI	2017	2.67	2018	2019	
Hofer HR, 2016, STEM CELL RES THER, V7, P0, DOI 10.1186/s13287-016-0394-0, DOI	2016	2.58	2018	2020	
Nakamura Y, 2015, FEBS LETT, V589, P1257, DOI 10.1016/j.febslet.2015.03.031, DOI	2015	2.21	2018	2020	
Pers YM, 2015, OSTEOARTHR CARTILAGE, V23, P2027, DOI 10.1016/j.joca.2015.07.004, DOI	2015	2.21	2018	2020	
Kowal J, 2016, P NATL ACAD SCI USA, V113, P0, DOI 10.1073/pnas.1521230113, DOI	2016	2.21	2018	2020	
Ding JP, 2016, STEM CELL TRANSL MED, V5, P1079, DOI 10.5966/sctm.2015-0263, DOI	2016	2.21	2018	2020	
Yanez-Mo M, 2015, J EXTRACELL VESICLES, V4, P0, DOI 10.3402/jev.v4.27066, DOI	2015	5.8	2019	2020	
Vizoso FJ, 2017, INT J MOL SCI, V18, P0, DOI 10.3390/ijms18091852, DOI	2017	3.02	2019	2020	
Guo SC, 2016, INT J BIOL SCI, V12, P1262, DOI 10.7150/ijbs.16150, DOI	2016	2.9	2019	2020	
Baglio SR, 2015, STEM CELL RES THER, V6, P0, DOI 10.1186/s13287-015-0116-z, DOI	2015	2.9	2019	2020	
Loeser RF, 2016, NAT REV RHEUMATOL, V12, P412, DOI 10.1038/nrrheum.2016.65, DOI	2016	2.19	2019	2020	
Robinson WH, 2016, NAT REV RHEUMATOL, V12, P580, DOI 10.1038/nrrheum.2016.136, DOI	2016	2.46	2020	2022	

Figure 4 (**A**) Network map of citation analysis of documents with more than 5 citations. (**B**) Network map of co-citation analysis of references. (**C**) Top 25 references with strongest citation bursts of publications regarding exosomes in osteoarthritis.

Additionally, Italy and England demonstrate a close collaboration. However, China's multiple country publication (MCP) research constitutes merely a small fraction of its domestic research output (as depicted in Figure 6B), signifying a paucity of intimate academic cooperation between China and other nations and continents in this research sphere.

Employing Citespace software, we undertook a visual analysis of the 720 institutions encompassed in this study (Figure 2A). With respect to publication rankings, Table 1 presents the top 10 institutions contributing the most. IRCCS Ist Ortoped Galeazzi leads the list with 23 publications, followed by Shanghai Jiao Tong Univ with 20 publications, while Sun Yat Sen Univ claims the third position, boasting 16 publications. As we can see, there was no significant difference in the volume of publications from these institutions.

Figure 2A displays the inter-institutional collaboration network diagram, illustrating a robust cooperative relationship among the various institutions, as we can see in Figure 2A, there is close cooperation between IRCCS Ist Ortoped Galeazzi and the University of Milan, and active collaboration between Sun Yat Sen University and China Med University. It is worth noting that collaboration between institutions is often limited within their own country, while

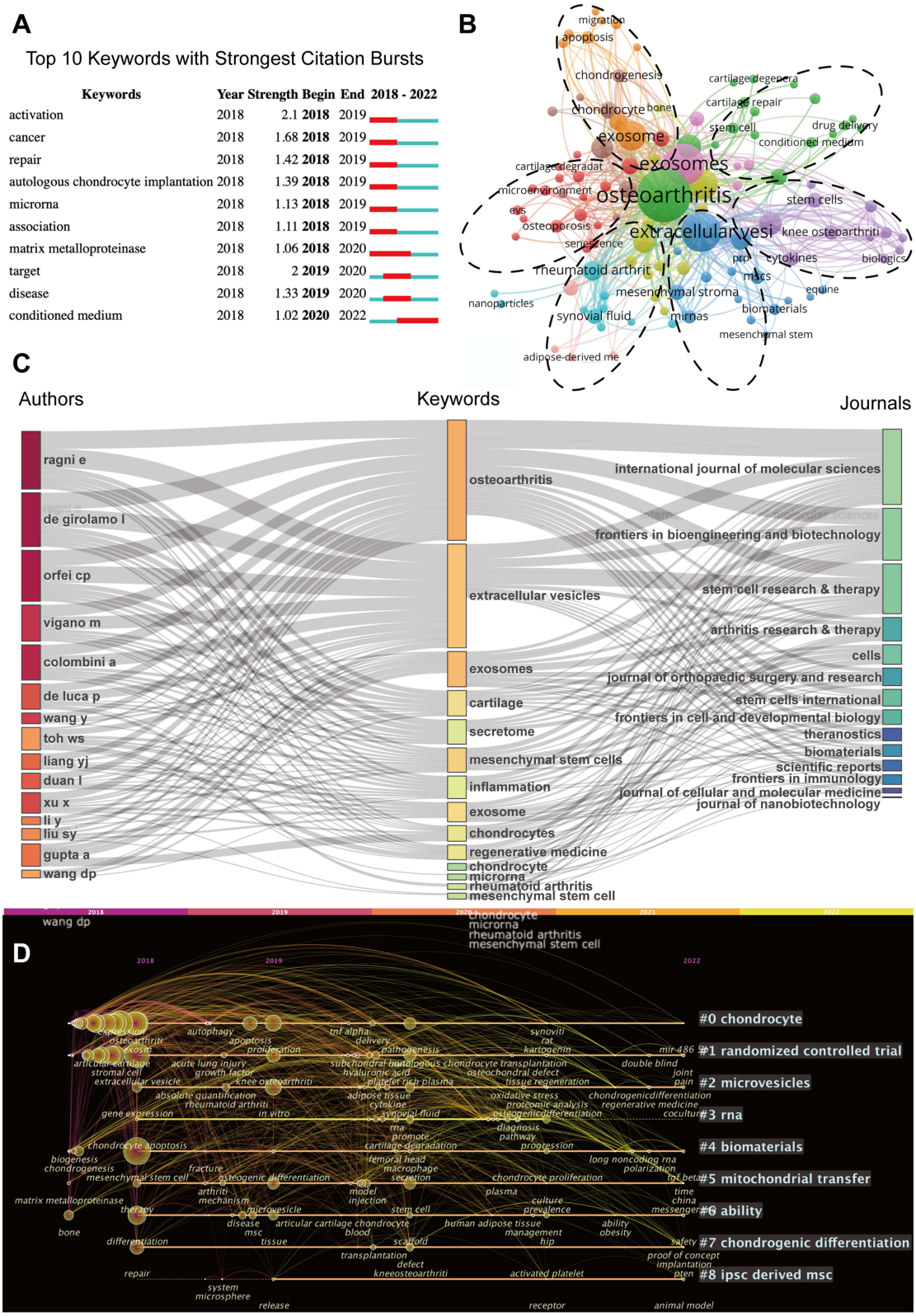


Figure 5 (**A**) Top 15 keywords with the strongest citation bursts based on Citespace. (**B**) overlay visualization of the keyworks network based on Vosviewer. (**C**) Three-field plot of the Keywords analysis base on R package "bibliometrix" and (**D**) The timeline view of keywords conducted by CiteSpace.

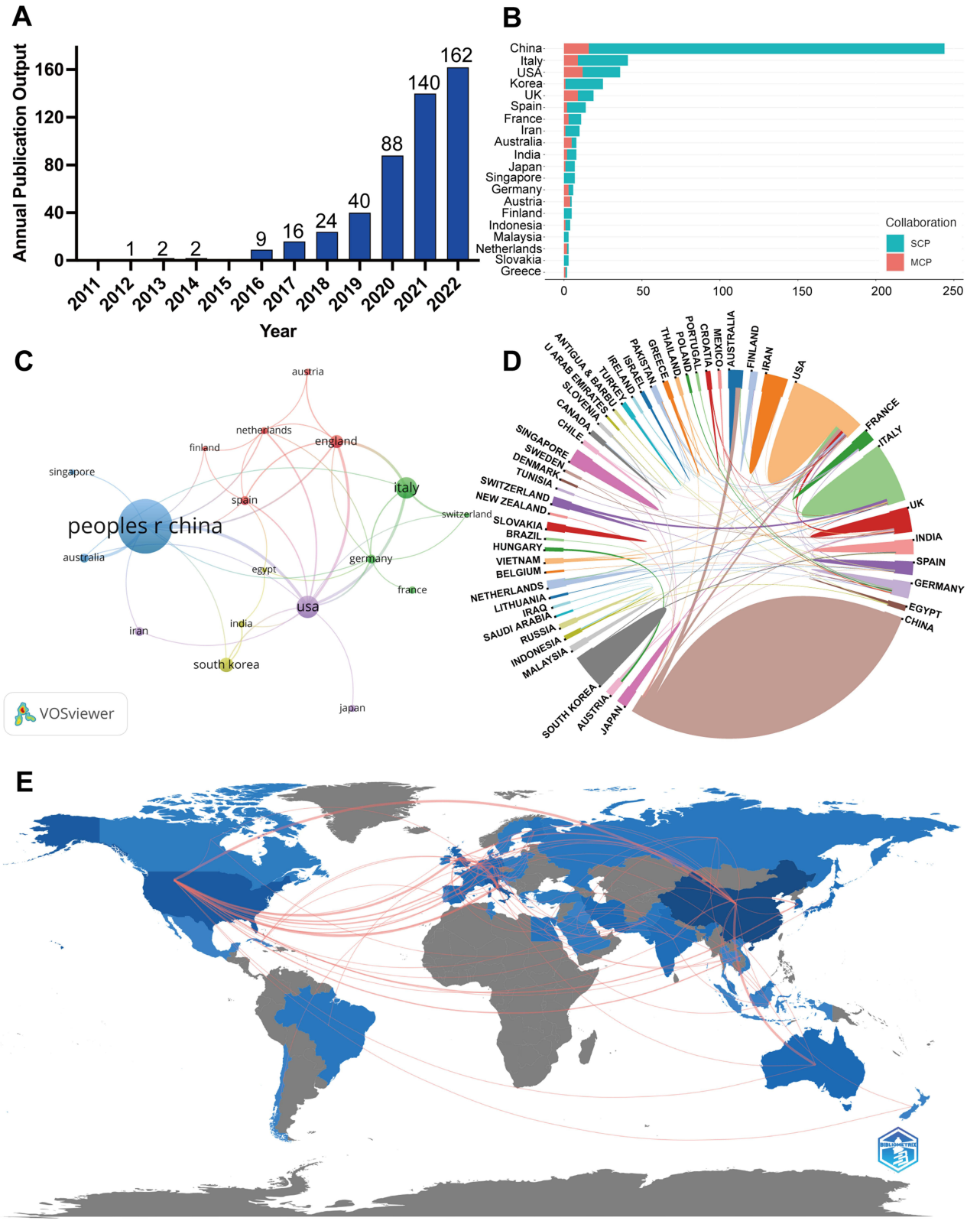


Figure 6 (**A**) Annual outputs of publications regarding exosomes in osteoarthritis field. (**B**) TOP 20 Corresponding Author's countries that produced the largest number of literature. (**C**) The overlay visualization map of country co-authorship analysis conducted by VOSviewer. (**D**) The international cooperation analysis among different countries. (**E**) The geographical network map of exosomes in osteoarthritis.
Abbreviations: SCP, Single Country Publications; MCP, Multiple Country Publications.

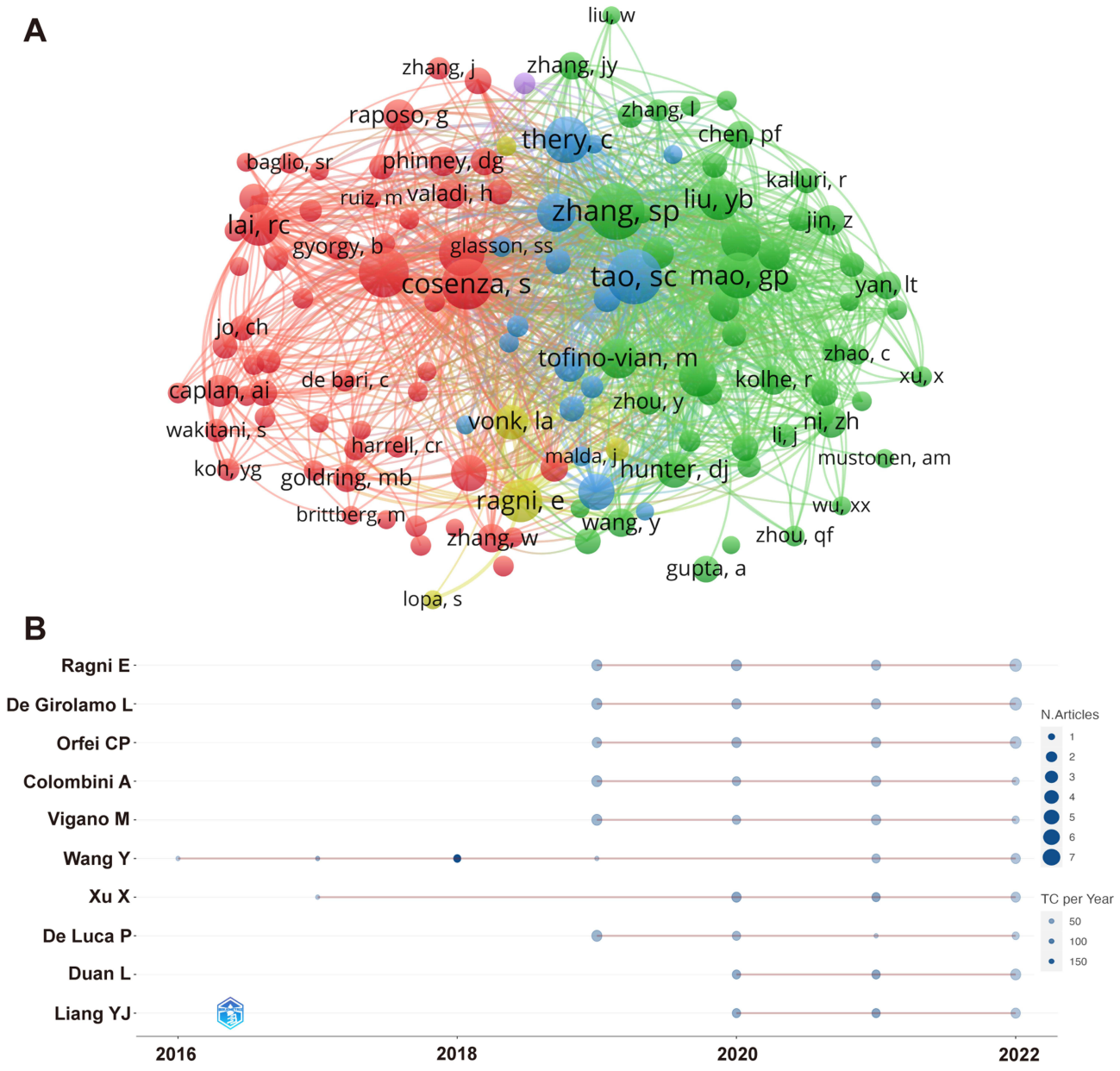


Figure 7 (**A**) Network visualization diagram of the co-cited authors regarding exosomes in osteoarthritis.(**B**) Top 10 authors' production over time.
Abbreviation: TC, total citation.

there is a noticeable lack of active academic cooperation between institutions from different countries. As depicted in Figure 2B, the yearly publication output from the top 5 institutions has exhibited a steady upward trend in recent years.

Journals and Co-Cited Journals

Utilizing VOSviewer, we conducted a visual representation of journals and co-cited journals within this research domain. A total of 217 journals were encompassed, and Figure 2D incorporated 22 journals with a minimum publication threshold of 5, the magnitude of the nodes exemplifies the publication volume of each journal. Figure 3A presents a network map of co-cited journals, featuring those with a minimum of 20 citations. As portrayed in Figure 3A, 319 co-cited journals were manifested in the aggregate link strength. The top 5 journals with the most robust total link strength were as follows: *Stem Cell Res Ther* (total link strength = 103,852 times), *Osteoarthr Cartilage* (total link strength = 103,796 times), *Biomaterials* (total link strength = 66,818 times), *Sci*

Table 1 Top Ten Nations and Institutes for Exosome Research in Osteoarthritis

Rank	Country	Articles	Citation	Institution	Counts
1	China	248(51.24%)	6736	IRCCS Ist Ortoped Galeazzi	23(4.75%)
2	USA	56(11.57%)	1926	Shanghai Jiao Tong Univ	20(4.13%)
3	Italy	52(10.74%)	885	Sun Yat Sen Univ	16(3.31%)
4	South Korea	29(5.99%)	463	Zhejiang Univ	15(3.09%)
5	England	23(4.75%)	271	Nanjing Med Univ	13(2.68%)
6	Spain	16(3.31%)	468	Cent South Univ	13(2.68%)
7	Australia	14(2.89%)	287	China Med Univ	13(2.68%)
8	Germany	12(2.48%)	227	Sichuan Univ	13(2.68%)
9	France	12(2.48%)	733	Shenzhen Univ	12(2.48%)
10	Iran	11(2.27%)	267	Univ Milan	10(2.06%)

Rep-UK (total link strength = 66,681 times), and *Arthritis Res Ther* (total link strength = 53,495 times). As delineated in Figure 3B, the publication output of the leading 5 journals in this research field has witnessed consistent growth in recent years.

Table 2 enumerates the top 10 most prolific and co-cited journals incorporated in this investigation. *International Journal of Molecular Sciences* (impact factor = 6.20, 2022) emerged as the foremost publisher, with 31 publications. Additionally, there were 20 publications in *Frontiers In Bioengineering and Biotechnology* (IF = 6.06, 2022), 19 publications in *Stem Cell Research and Therapy* (IF = 7.66, 2022), 17 publications in *Cells* (IF =

Table 2 Top 10 Journals and Co-Cited Journals for Studies Exosomes in Osteoarthritis

Ranks	Journals	Count	IF	Q	Co-Cited Journals	Co-Citation	IF	Q
1	International Journal of Molecular Sciences	31	6.20	Q1	Osteoarthritis and Cartilage	1366	7.50	Q1
2	Frontiers In Bioengineering and Biotechnology	20	6.06	Q1	Stem Cell Research and Therapy	1178	8.08	Q1
3	Stem Cell Research and Therapy	19	7.66	Q2	Biomaterials	797	15.30	Q1
4	Cells	17	8.07	Q1	Sci Rep-UK	742	4.99	Q2
5	Stem Cells International	13	6.08	Q1	Arthritis Res Ther	661	5.60	Q1
6	Frontiers In Cell And Developmental Biology	13	5.13	Q2	PLoS One	616	3.75	Q2
7	Biomaterials	10	15.30	Q1	Arthritis Rheum-US	614	15.48	Q1
8	Arthritis Research and Therapy	10	5.60	Q1	Int J Mol Sci	580	6.20	Q1
9	Journal Of Orthopaedic Surgery And Research	8	2.67	Q2	J Extracell Vesicles	542	17.33	Q1
10	Frontiers In Immunology	8	8.78	Q1	Theranostics	504	11.60	Q1

8.07, 2022), and 13 articles in *Stem Cells International* (IF = 6.08, 2022). 7 of the top 10 journals were classified in the Q1 JCR region.

The collection of all the previous literature represented by the cited literature is the basis and evidence of the research frontier of a discipline. The dual map overlay of journals pertinent to exosomes in osteoarthritis was illustrated in Figure 3C utilizing CiteSpace. The clusters on the left of the orange line indicate citing journals, while the cluster on the right of the orange path indicates co-cited journals. The primary path reveals that articles published in the fields of molecular/ biology/ genetics are mainly cited by researchers in molecular/ biology/ immunology journals. The results of dual-map overlay of journals may indicate that the current exosomes-osteoarthritis research is focused on the Molecular Biology and Immunology.

Authors and Co-Cited Authors

In the study of exosomes in osteoarthritis, 2664 authors took part. The leading 10 authors collectively contributed to 143 publications, which constituted approximately 29% of the total publications within this domain (Table 3). Ragni E emerged as the most prolific author, having published 21 studies, followed by De Girolamo L with 20 publications, and Orfei CP with 18 publications (Table 3). The H-index, a metric that signifies a researcher who has authored H papers each with a minimum of H citations, was established to evaluate the influence of scientific research, as shown in Table 3, Ragni E and De Girolamo L distinguished themselves as the authors with the highest H-index. Figure 7B delineates the annual outputs of the top 10 authors spanning from 2016 to 2022. Wang Y has been focused on this field for 6 years, while the major of top 10 authors began their research after 2019. VOSviewer provides a visualization of the interconnections among authors, as exhibited in Figure 2C. Authors within the same country tend to collaborate more often, exhibiting robust connections. Nevertheless, the links between authors from distinct countries remain insufficient.

The co-citation analysis assessed the relevance of items according to their co-citation frequency. Utilizing VOSviewer, a total of 189 authors with a minimum number of 20 citations were examined, as depicted in Figure 7A. As demonstrated in Figure 7A, there was a close cooperation between Mao GP and Zhang SP, so did Tao SC and Cosenza S. As shown in Table 3, Zhang SP is the most co-cited author (co-citation = 226), followed by Tao SC (co-citation = 213), and Cosenza S (co-citation = 184), out of the 15,978 co-cited writers, six authors were co-cited more than 150 times.

Table 3 Top10 Authors and Co-Cited Authors on Exosomes Studies in Osteoarthritis

Rank	Authors	Counts	H-Index	Co-Cited Authors	Citations	Total Link Strength
1	Ragni E	21	11	Zhang SP	226	5853
2	De Girolamo L	20	11	Tao SC	213	5450
3	Orfei CP	18	10	Cosenza S	184	4897
4	Colombini A	14	10	Toh WS	178	4026
5	Vigano M	14	10	Thery C	151	3515
6	Wang Y	12	8	Mao GP	150	4860
7	Xu X	12	9	Zhang S	149	3979
8	De Luca P	11	9	Ragni E	132	2674
9	Duan L	11	7	Lai RC	124	3098
10	Liang YJ	10	7	Liu YB	122	3470

Highly Valuable Papers

To evaluate the publications' influence on osteoarthritis research, we evaluated regional citations. A cumulative total of 336 articles within this field garnered more than 5 citations each (Figure 4A). The most frequently cited paper, "Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases", amassed 519 citations.[25] This review examined our present knowledge regarding the immune-regulatory processes of MSCs, along with the challenges associated with their therapeutic usage, and highlighted immunoregulatory effects of exosomes derived from MSCs on various immune cells. While the second-ranked article, "MSC exosomes mediate cartilage repair by enhancing proliferation, attenuating apoptosis and modulating immune reactivity", obtained 464 citations.[26] This article illustrated how the effective regeneration of osteochondral tissue via MSC-exosomes was accomplished by the harmonized engagement of various cell types and stimulation of numerous cellular activities. The third most cited article was "Exosomes derived from miR-140-5p-overexpressing human synovial mesenchymal stem cells enhance cartilage tissue regeneration and prevent osteoarthritis of the knee in a rat model", which accrued 395 citations and highted the manifest potential of modified SMSC-exosomes in cartilage regeneration.[27]

The co-citation network conducted by VOSviewer (Figure 4B) highlighted three primary clusters, each comprising numerous references. This implies a broad interconnectivity among these references. As shown in Figure 4B, "tao sc, 2017, theranostics, v7, p180" have close co-cited relationships with "Zhang sp, 2018, biomaterials, v156, p16" and "mao gp, 2018, stem cell res ther, v9". Table 4 lists the top 10 co-cited references on exosomes studies in osteoarthritis, "tao sc, 2017, theranostics, v7, p180", which was shown above as the third most-cited article, ranks first among these references with 134 co-citations.

Additionally, references that were extensively cited by academics over time in a certain topic are known as references with citation bursts. They serve as a valuable metric, highlighting the references that have piqued researchers' interest within a specific field during a given period. In this study, CiteSpace identified the top 25 references with the most robust citation bursts, which are exhibited in Figure 4C. Among these, the 2014 article authored by Kato T, "Exosomes from IL-1β stimulated synovial fibroblasts induce osteoarthritic changes in particular chondrocytes", held the highest rank (strength = 7.31).[28] Ranking secondly, Glyn-Jones et al reviewed the pathogenesis, diagnosis, and treatment of osteoarthritis, and summarized the current challenges in the treatment of osteoarthritis.[29] Zhang et al explored the immunological activity of MSC-exosomes both in vitro and in vivo.[26]

Analysis of Keywords

The algorithm employed by CiteSpace was utilized to identify keyword bursts through burst detection. The top 10 keywords with the most substantial burst strength are illustrated in Figure 5A. The keyword with the most significant

Table 4 Top10 Co-Cited References on Exosomes Studies in Osteoarthritis

Rank	Co-Cited Reference	Citations
1	Tao SC, 2017, theranostics, v7, p180[27]	166
2	Zhang S, 2016, osteoarthr cartilage, v24, p2135[53]	138
3	Cosenza S, 2017, sci rep-uk, v7[54]	138
4	Zhang SP, 2018, biomaterials, v156, p16[26]	136
5	Wu JY, 2019, biomaterials, v206, p87[55]	105
6	Mao GP, 2018, stem cell res ther, v9[41]	103
7	Zhu Y, 2017, stem cell res ther, v8[56]	102
8	Toh WS, 2017, semin cell dev biol, v67, p56[57]	100
9	Wang YF, 2017, stem cell res ther, v8[58]	91
10	Thery C,2018, j extracell vesicles, v7[59]	88

citation outbreaks was "activation" (strength = 2.1), followed by "cancer" (1.68) and "repair" (1.42). The keyword with the most extended burst time was "matrix metalloproteinase", spanning two years from 2018 to 2020. Notably, the keyword "conditional medium" experienced the most recent citation bursts (2020–2022). Conditioned medium is a type of culture medium that contains various bioactive molecules secreted by cells, including exosomes. It is typically used in the study of intercellular communication and interactions, particularly in stem cell research and regenerative medicine. This suggests that exploring the use of exosome-enriched conditioned medium to stimulate cartilage repair could be a future research hotspot.

The co-occurrence analysis of keywords allows us to quickly identify hotspots in a research area. Table 5 lists the top 20 high-frequency terms in this area. The top 4 keywords ranked by co-occurrence analysis are as follows: osteoarthritis (occurrences, 250), exosomes (occurrences, 137), extracellular vesicles (occurrences, 124), Mesenchymal stem cells (occurrences, 65). Mesenchymal stem-cells, cartilage, and regenerative medicine appear more than 30 times, which represent the main focus of exosome research in osteoarthritis.

Out of a total of 1251 keywords, we excluded keywords with less than 2 co-occurrences, and included 358 keywords to perform keyword clustering analysis (Figure 5B) through VOSviewer. The thickness of connections between keywords is shown by the lines connecting nodes. As depicted in Figure 5B, the identified keywords can be categorized into six distinct clusters, each symbolizing a unique research trajectory. The red cluster encompasses keywords such as osteoporosis, microenvironment, and cartilage degradation, all of which are intricately tied to the pathophysiological development of osteoarthritis. Meanwhile, the blue cluster comprises keywords like mesenchymal stem cells, mesenchymal stroma, miRNA, and biomaterials, suggesting a potential link to the implementation of exosome-related regenerative medicine and cellular therapies in osteoarthritis management. The purple cluster is characterized by the presence of keywords such as stem cells, knee osteoarthritis, cytokines, and biologics, indicating a focus on fundamental research and therapeutic approaches to osteoarthritis, particularly with respect to stem cells and biologics. The green cluster's keywords, namely conditioned medium, drug delivery, cartilage repair, and cartilage degeneration, hint at a concentration on therapeutic strategies for osteoarthritis, notably in the realms of cartilage repair and exosome-facilitated drug delivery. Lastly, the orange cluster encapsulates keywords like migration, apoptosis, and chondrogenesis, suggesting an emphasis on research concerning the involvement of exosomes in cellular activities and chondrogenesis within the context of osteoarthritis.

Figure 5C represents a tri-field graph in which authors, keywords, and journals were interconnected. This tri-field graph allowed the observation of the relationships between the primary components, with the connection link strength directly exhibiting these relationships. The most frequently used keywords were äosteoarthritis", "extracellular vesicles",

Table 5 Top 20 Keywords on Research of Exosomes in Osteoarthritis

Rank	Keywords	Occurrences	Rank	Keywords	Occurrences
1	Osteoarthritis	250	11	Rheumatoid arthritis	24
2	Exosomes	137	12	Mesenchymal stem cell	21
3	Extracellular vesicles	124	13	microRNA	19
4	Mesenchymal stem cells	65	14	Chondrocyte	17
5	Exosome	63	15	Cartilage regeneration	16
6	Cartilage	38	16	Extracellular vesicle	16
7	Regenerative medicine	33	17	Regeneration	15
8	Chondrocytes	32	18	Mesenchymal stromal cells	14
9	Inflammation	31	19	miRNA	14
10	Secretome	25	20	Synovial fluid	14

"exosomes", and "cartilage", which align with the keywords presented in Figure 5B. The authors Ragni E, De girolamo L, and Orfei CP are strongly associated with the keywords "osteoarthritis" and "extracellular vesicles" establishing the most robust links. Concurrently, the most substantial links were related to the journal *International Journal of Molecular Sciences*. Furthermore, it is evident that *International Journal of Molecular Sciences* encompassed most of the papers related to the keywords "osteoarthritis", "extracellular vesicles", and "exosomes".

Analyzing the timeline of keywords provides valuable insight into the progression and evolving focal points within a field of research. As depicted in Figure 5D, there are 8 categories, including #0 chondrocyte, #1 randomized controlled trial, #2 microvesicles, #3 RNA, #4 biomaterials, #5 mitochondrial transfer, #6 ability, #7 chondrogenic differentiation, #8 ipsc derived msc. The early emergence of keywords such as chondrocyte apoptosis, articular cartilage, and differentiation (dating back to 2018), suggests that the investigation into cartilage repair and differentiation were among the initial areas of interest within this domain. Although the interest in exosomal RNA appears to be declining in recent years, the focus on mesenchymal stem cells and stem cells has remained constant. It's worth highlighting that there's a noticeable increase in the frequency of the keyword clust "biomaterials" in recent times. This trend may signal a shift towards the development of exosomal biomaterials, potentially marking it as an upcoming area of emphasis in osteoarthritis treatment research.

Discussion

This investigation implemented sophisticated bibliometric analysis principles and advanced visualization techniques, utilizing tools such as VOSviewer, Citespace, the R package "bibliometrix", and an online analysis platform. In exploring the therapy roles of exosomes within the realm of orthopedics, we executed comprehensive assessments of annual publication volume, geographic regions, and institutions, contributing authors and cited authors, academic journals and referenced journals, and pertinent keywords to unveil prevailing research focal points and tendencies in this domain.

Upon examination of the geographic regions and institutions, the United States and China emerge as the two nations exhibiting the most prolific publication output. Nevertheless, a discernible paucity of international collaboration between these countries persists. It is imperative for China to actively participate in increased global cooperation, fostering the collective advancement of this particular domain. Among the top ten institutions in terms of publication volume, those from China account for a relatively high proportion. However, these institutions predominantly engage in collaborations with fellow domestic counterparts. Consequently, we aspire to witness an augmentation in cooperation amongst diverse nations and institutions, thereby fostering the collaborative progression of this research sphere.

Pertaining to the journals and co-cited journals delineated in Table 2, *International Journal of Molecular Sciences* exhibited the highest number of publications. The average impact factor of the top ten journals in 2022 was 7.155, with *Biomaterials* possessing the highest impact factor (15.30). Moreover, 90% of journals had an impact factor exceeding 5, and 70% of journals were classified as Q1 (JCR). *J Extracell Vesicles* boasted the highest impact factor among co-cited journals (IF = 17.33), while *Osteoarthritis and Cartilage* emerged as the most co-cited journal. Additionally, 8 of the top 10 co-cited journals belonged to Q1. These findings indicate that this area has garnered academic interest from high-impact journals in the field of orthopaedics, biology, and biomaterials.

As to authors, Ragni E and De Girolamo L published the most papers and distinguished themselves as the authors with the highest H-index. The examination of the author collaboration network (Figure 2C) indicates active collaborations between them. Their most cited article presents a novel therapeutic approach involving the use of bioactive factors and extracellular vesicles (EVs) secreted by adipose-derived stem cells (MSCs) for the treatment of inflammatory and degenerative diseases.[30] This therapeutic method is referred to as the "secretome". The article describes how to extract the secretome from MSCs and how to enhance its anti-inflammatory properties using IFNγ pretreatment. Furthermore, the paper details how bioinformatics can be employed to predict the regulatory effects of the secretome on articular cartilage and synovial macrophages, and discusses the clinical potential and limitation of secretome applications. In light of the novel therapeutic approach, extracting methodology, bioinformatics application mentioned in the paper, this article could serve as a significant reference for research into the roles of extracellular vesicles in osteoarthritis.

Regarding the analysis of the cited authors, Zhang SP was the most co-cited author. His most cited article suggests that extracellular vehicles (EVs) secreted by MSCs can alleviate temporomandibular joint osteoarthritis by mitigating inflammation and restoring matrix homeostasis, providing fresh insights for the treatment of other types of osteoarthritis.[26] Additionally, the article also introduces methods for the preparation and application of MSC-derived EVs, which holds significant implications for the future development of a wider range of exosome-based therapeutic strategies.

The most cited document and reference have already been discussed in detail above, along with their significance to this field of research. Therefore, we will not repeat them here.

Hotspots and Frontiers

References and keywords experiencing citation bursts serve as indicators of trending topics within a specific research field, as they have been frequently referenced by scholars in recent times. Upon examining the primary research areas of these rapidly cited references and keywords, we discover that current major themes within this field revolve around understanding the biological function and pathogenesis of exosomes in osteoarthritis and exploring the therapeutic use of exosomes in osteoarthritis treatment. The exogenous exosomes of interest come from a variety of cell sources, including, as highlighted in this study, mesenchymal stem cells (MSCs), or are engineered exosomes, such as those loaded with miRNA.

Keywords serve as effective tools to swiftly grasp the distribution and progression of focal points within the research domain of exosomes in osteoarthritis. Based on the keyword clustering analysis and timeline view (refer to Figure 5), Based on the keyword clustering analysis and timeline view, we can infer the evolution of research topics over time. We have noticed that the trend in recent years has begun to focus on the possible translational pathway from basic research to clinical practice. This includes the integration of disciplines such as biomaterials science and nanotechnology with exosome research. This trend suggests a burgeoning interest in the practical application of exosomal research findings, aiming to bring the benefits of these discoveries directly into the clinical setting. We can infer that research concerning exosomes in osteoarthritis is predominantly centered around the following aspects:

Hotspots-MSCs Derived Exosomes

Among cells producing exosomes, Mesenchymal Stem Cells (MSCs) have captured the interest of numerous researchers.[31–35] MSCs boast potent tissue repair capabilities and can be readily sourced from bone marrow, adipose tissue, blood, and the umbilical cord among others. The MSCs can execute a myriad of functions, encompassing immunomodulation, homing, and differentiation.[36] Moreover, MSCs can secrete a range of growth factors and cytokines.[37] With their anti-inflammatory and immunomodulatory effects,[38] MSCs can create an optimal regenerative microenvironment for severely inflamed, damaged tissue, facilitating the restoration of the inflammatory balance.[39] In recent times, cell therapies, epitomized by Mesenchymal Stem Cells, have yielded promising results in clinical trials aimed at treating cartilage injuries, rheumatic diseases, and fractures. Compared to MSCs, exosomes derived from Mesenchymal stem cell (MSC-Exos) have similar biological functions, while more stable and better avoiding the body's immune rejection reaction or vascular embolism or other adverse reactions.

Compared with traditional cell therapy or single-factor drugs (small molecule drugs, biological agents, etc.), due to its ability to transport different macromolecules, such as DNA, miRNA, and lncRNA, MSC-Exos has a wide range of therapeutic targets, and thus it has stronger efficacy of immunomodulatory and tissue repairing. For example, bone marrow-derived Mesenchymal stem cell exosomes (BMSC-Exos) suppress chondrocyte pyroptosis and reduce osteoarthritis by targeting HDAC3 and STAT1//NF-κB p65 via the delivery of miR-326 to recipient chondrocytes.[40] By targeting WNT5A, MSC-Exos overexpressing miR-92a-3p stimulate cartilage synthesis and prevent cartilage degeneration,[41] Xia et al found that miR-125a-5p-overexpressing MSC-Exos inhibited cartilage degradation and alleviated osteoarthritis by targeting E2F2.[42] MSC-Exos overexpressing miR-155-5p, which increases chondrocyte proliferation, decreases chondrocyte apoptosis, and controls the release of extracellular matrix secretion, have been shown to prevent osteoarthritis.[43]

Despite these promising in vivo outcomes, there are still challenges with MSC-Exos preparation and separation. Prior to being put on trial, MSC-Exos needs to be purified and quantified. To further establish the route of administration, dose,

timing, interval between treatments, and long-term safety of MSC-Exos in the treatment of OA, more high-quality studies are required.

Frontiers-Exosomal Biomaterials

Biomaterials play a pivotal role in osteoarthritis research,[44] encompassing applications such as drug delivery systems, bone defect repair, and cartilage regeneration.[45] For instance, biodegradable polymers, bioactive glasses, and nanomaterials have been extensively utilized in drug delivery systems to optimize drug release and enhance the bioavailability of drugs.[46–48] Furthermore, biomaterials are employed in the design and fabrication of bioactive bone substitutes to stimulate bone defect repair and bone regeneration. Despite some progress, current biomaterials still struggle to meet all the demands of osteoarthritis treatment, such as target specificity, durability, and biocompatibility.

In the context of osteoarthritis, exosomal biomaterials have been explored for their therapeutic potential due to several unique properties.[47] Firstly, exosomes can function as natural vehicles for the delivery of therapeutic molecules,[49] including anti-inflammatory agents, growth factors, and even genetic material like miRNA or siRNA, to target cells.[50–52] This makes them an ideal platform for drug delivery, as they can potentially overcome many limitations associated with traditional drug delivery systems, such as poor target specificity, low bioavailability, and unwanted side effects.

Given the inherent advantages of exosomal biomaterials and the growing interest in this field, it is anticipated that further advancements will be made in the coming years, which may eventually lead to the development of effective and safe exosome-based therapies for osteoarthritis.

Conclusion

In conclusion, bibliometric analysis of the literature on exosome research in osteoarthritis reveals a vibrant and rapidly growing field of study, reflecting its potential for significant impact on our understanding and treatment of this debilitating disease. We observed that mesenchymal stem cell-derived exosomes, cartilage repair, inflammation management, and the "secretome" were among the dominant themes, highlighting the current focus on harnessing the regenerative and anti-inflammatory properties of exosomes.

Notably, the emergence of "exosomal biomaterials" as a key theme suggests an exciting direction for future research. The integration of biomaterials with exosome-based therapeutics could potentially overcome some of the limitations of current treatment approaches, such as poor target specificity and low bioavailability, and pave the way for the development of more effective and safer therapies for osteoarthritis.

Therefore, researchers, clinicians, and policymakers should closely monitor this field and support its continued development, as it holds significant potential for improving the lives of osteoarthritis patients worldwide.

Data Sharing Statement

The raw data can be directly obtained from the Web of Science Core Collection (WoSCC) database.

Ethics Approval and Informed Consent

This study did not include any patient information. Thus, the requirement for ethics approval was waived.

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Disclosure

The authors report no conflicts of interest in this work.

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