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REVIEW

Global Research Trends on Exosome in Cardiovascular Diseases: A Bibliometric-Based Visual Analysis

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Background: Exosomes in cardiovascular diseases (CVDs) have attracted huge attention with substantial value and potential. Our bibliometrics is based on literature from the field of cardiovascular exosomes over the past 30 years, which has been visualized to display the development process, research hotspots, and cutting-edge trends of clinical practices, mechanisms, and management strategies related to psych cardiology.

Methods: We selected articles and reviews on exosomes in CVDs from the core collection of Web of Science, and generated visual charts by using CiteSpace and VOSviewer software.

Results: Our research included 1613 publications. The number of exosome articles in CVD fluctuates slightly, but overall shows an increasing trend. The main research institutions were Tongji University and Nanjing Medical University. The International Journal of Molecular Sciences has the highest publication volume, while the Journal of Cellular and Molecular Medicine has the highest citation count. Among all the authors, Eduardo Marban ranks first in terms of publication volume and H-index. The most common keywords are exosome, extracellular vesicles, and angiogenesis.

Conclusion: This is a bibliometric study on the research hotspots and trends of exosomes in CVD. Exosome research in the field of cardiovascular medicine is on the rise. Some exosome treatment methods may become the focus of future research.

Keywords: exosomes, cardiovascular diseases, bibliometric, citespace, VOSviewer

Introduction

Exosomes are common membrane-bound nanovesicles containing various biomolecules such as lipids, proteins, and nucleic acids.[1,2] They can be secreted by almost all types of cells under physiological and pathological conditions, which contribute to fundamental physiological processes, including neuronal communication,[3,4] antigen presentation,[5] immune responses,[6,7] organ development[8–10] and reproductive performances.[11] They play a central role in intercellular information exchange, which helps to regulate communication between different cells.[12,13] Thus, they are considerable in multicellular systems, such as the heart.[14,15]

In recent research, exosomes show immense potential in cardiovascular diseases.[16,17] For instance, they can prevent the cardiomyocyte apoptosis induced by HSP60 activating Toll-like receptor,[18,19] carry miRNA to orchestrate adaptive measures when myocardial infarction happens,[20,21] regulate differentiation, proliferation, and survival of cardiac progenitor cells, cardiomyocytes, and fibroblasts,[22–25] etc. Marban's group found that exosomes secreted by CDCs play a key role in cardiac regeneration. Their data showed that exosomes are involved in angiogenesis, survival and proliferation of cardiomyocytes.[26]

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Bibliometrics is an interdisciplinary science, covering mathematics and statistics, and carrying out quantitative analysis of all knowledge carriers which can describe or show relationships between published work.[27] This method can quantitatively measure the contour distribution, relationship, and clustering of the research field.[28] In order to study the hotspots and development trends of exosome research in CVD in the past 30 years, we used CiteSpace and VOSviewer software, and mapped the scientific knowledge.

Methods

Data Sources and Searches

Literature was extracted from the Web of Science. The search formula was as follows: TS = ("exosomes" OR "exosome" OR "exocrine") AND TS = ("high blood pressure" or hypertensi* or "peripheral arter*" disease* or "atrial fibrillat*" or tachycardi* or endocardi* or pericard* or ischem* or arrhythmi* or thrombo* or cardio* or cardiac* or "heart failure" or "heart beat" or "heart rate*" or "heart val*" or coronary* or angina* or ventric* or myocard*) AND DT = (Article OR Review) AND LA = (English) AND DOP = (1992–01-01/2023-08-31. The number of articles retrieved was 4479. According to our screening, 2866 unrelated literature were removed, and 1613 remained, including 1132 articles and 481 reviews. Then we carried out the following analysis work: general data, author and co-cited authors, journal and co-cited journal Institution, countries/regions, keywords, and co-cited reference. The detailed filtering process is demonstrated in Figure 1.

Data Analysis

VOSviewer is an important measurement network analysis software, which can visualize the analysis results, including the construction of network maps of academic publications, scientific journals, authors, research institutions, countries and keywords. The projects in these networks are connected by co-citation, co-occurrence, citation and bibliographic coupling. VOSviewer software provides three kinds of visual maps: network, overlay and density visualization.[29] It is suitable for large-scale data and can be drawn into graphs.[30] CiteSpace software is also an analysis software based on scientific measurement and data visualization.[31] Through the data mining, information analysis and Atlas drawing functions of the software, we can understand the structure, law and distribution of scientific knowledge. Knowledge

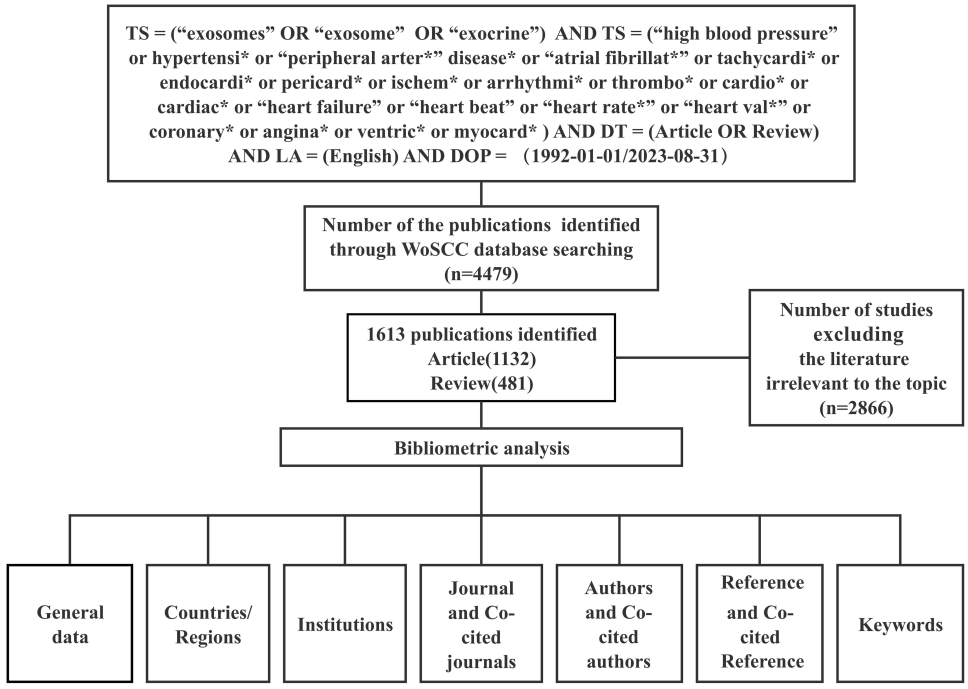

Figure 1 Flowchart of literature selection.

mapping is an important branch of information technology. It can intuitively visualize the research hotspots and evolution process, and predict the development trend of each field, which is often used in Bibliometric research.[30,32] We combined CiteSpace and VOSviewer software to visually analyze the distribution of countries/regions, authors and co-cited authors, journals and co-cited journals, co-cited references, keyword clustering analysis, and timelines.

Results

Annual Publication Outputs

The development trend of research in a field can be reflected by the number of papers published in a certain period (Figure 2). According to the figure, from 2001 to 2020, the number of research published on exosomes in CVDs showed a gradually increasing trend. Since the research and development of exosomes in cardiovascular science were infant before 2009, the number of published articles was relatively low. From 2010 to 2021, the number of published articles increased stably and rapidly, and reached its summit in 2021 of over 300 outputs. However, the number ushered in a decline in 2022 and 2023, which may result from the pandemic. Nevertheless, the rapid development of research in this field further confirms its potential value. At the same time, the citation volume of related papers continues to increase almost exponentially (2004–2021), which not only indicates that the field has received widespread attention, but also reflects its huge potential for future development.

Contribution of Countries/Regions

A total of 1613 articles were published. As shown in Table 1, the most significant number of publications came from China (806, 48.32%) and the US (434, 26.02%), followed by Italy (82, 4.92%), the UK (71, 4.26%), and Germany (55, 3.30%). Wherein, the largest increase in the number of publications came from China, which ranked second with 333 publications in 2021,[32] and even nearly half of the total in our statistics. Several countries, such as the US (272), China (158), the UK (112), Germany (96), and Italy (88), showed high total link strength, circled in blue in Figure 3A. This finding indicates that these countries have played an important role in the study of exosomes in CVDs. The thickness of the connection represents the closeness of the cooperation, and the connection between the two countries represents the cooperation between them. The size of a country's node represents the relative number of documents published in that country. Figure 3 shows 37 nodes and 5 clusters. It can be seen that China has the highest overall number of publications and citations. Although the United States is not the country with the highest number of publications and citations, it collaborates globally. The United States pays more attention to the global perspective and has closer ties with foreign countries.

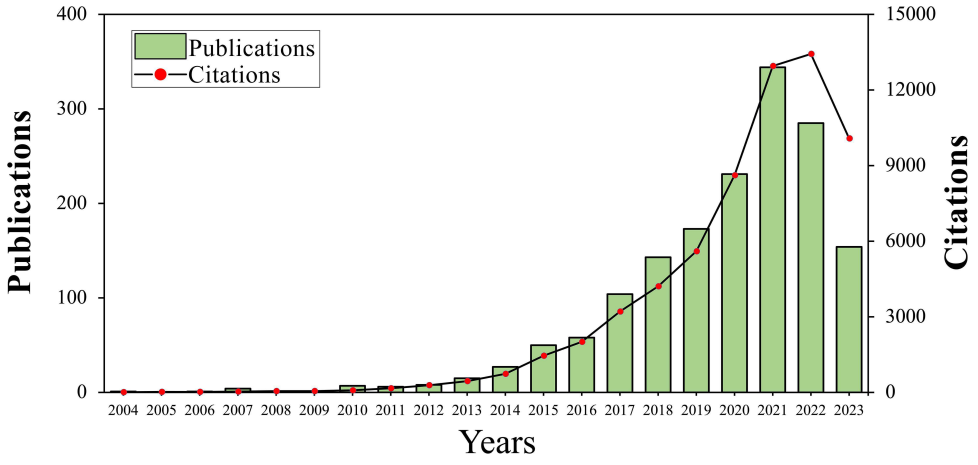

Figure 2 Trends in the growth of publications worldwide from 2004 to 2023.

Table 1 Top 10 Countries and Institutions That Contributed to Publications of Exosome in CVD

Top 10 Countries that Contributed to Publications of Exosome in CVD						
Rank	**Country**	**Document**	**Percentage (%)**	**Citation**	**Citation/ Document**	**Total Link Strength**
1	China	806	48.32	24,608	30.53	158
2	United States	434	26.02	22,804	52.54	272
3	Italy	82	4.92	3180	38.78	88
4	United Kingdom	71	4.26	4653	65.54	112
5	Germany	55	3.30	3460	62.91	96
6	Netherlands	49	2.94	5479	111.82	80
7	Spain	48	2.88	1231	25.65	44
8	Iran	43	2.58	1107	25.74	25
9	Canada	42	2.52	2811	66.93	43
10	France	38	2.28	2562	67.42	47
Top 10 institutions that contributed to publications of Exosome in CVD						
Rank	**Institution (Country)**	**Document**	**Percentage (%)**	**Citation**	**Citation/ Document**	**Total Link Strength**
1	Nanjing Medical University (China)	52	15.57	1445	27.79	51
2	Tongji University (China)	40	11.98	1261	31.53	46
3	Shanghai Jiao Tong University (China)	36	10.78	1701	47.25	30
4	Fudan University (China)	34	10.18	1441	42.38	23
5	Soochow University (China)	31	9.28	1960	63.23	23
6	Central South University (China)	30	8.98	643	21.43	3
7	Temple University (United States)	29	8.68	1448	49.93	14
8	Southern Medical University (China)	28	8.38	1101	39.32	30
9	Capital Medical University (China)	27	8.08	1040	38.52	22
9	Sun Yat-sen University (China)	27	8.08	741	27.44	19

Contribution of Institutions

A total of 1613 articles were published. According to Table 1, the most significant number of publications among institutions came from Nanjing Med Univ (52, 15.57%) and Tongji Univ (40, 11.98%), followed by Shanghai Jiao Tong Univ (36, 10.78%), Fudan Univ (34, 10.18%), and Soochow Univ (31, 9.28%). Most of the top 10 institutions came from China, which totally published 305 articles. Several institutions, such as Nanjing Med Univ (51), Tongji Univ (46) and Shanghai Jiao Tong Univ (30) showed high total link strength, colored green in Figure 3B. This finding indicates that these institutions have played an important role in the study of exosomes in CVDs. If the color is close to yellow, it means that the organization has been more active recently, while blue has been more active in the past. The thickness of the connection represents the closeness of the cooperation, and the connection between two countries represents the cooperation between them. The size of an organization's node represents the relative number of documents issued by the organization. Figure 4 shows 67 nodes and 8 clusters. There is active cooperation among institutions, including Nanjing Med Univ., Tongji Univ., and Capital Med Univ.

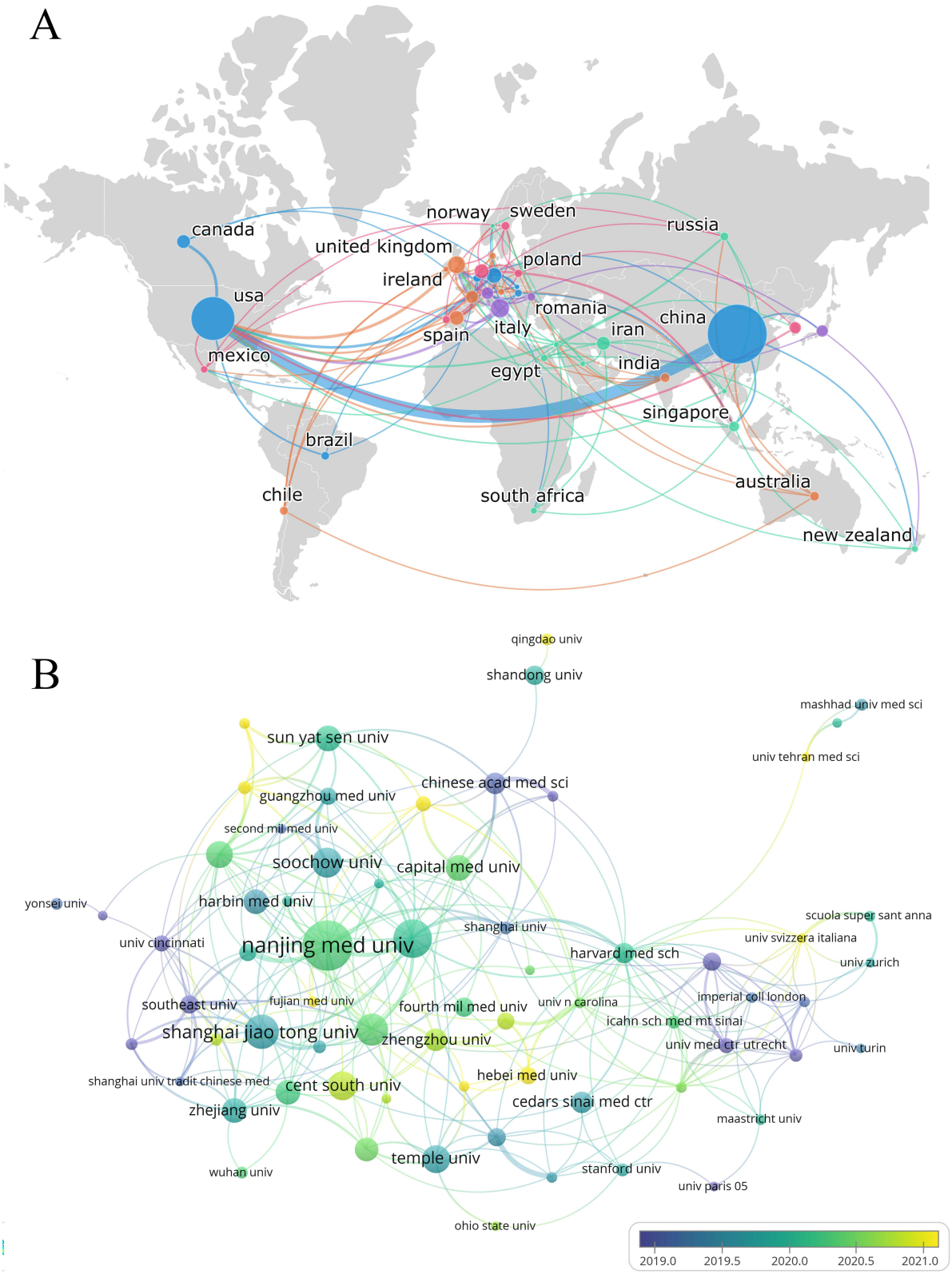

Figure 3 The top 10 active countries/regions/ institutions and cooperative relationships in this field. (**A**) The cooperative relationships of countries/regions. (**B**) The cooperative relationships of institutions.

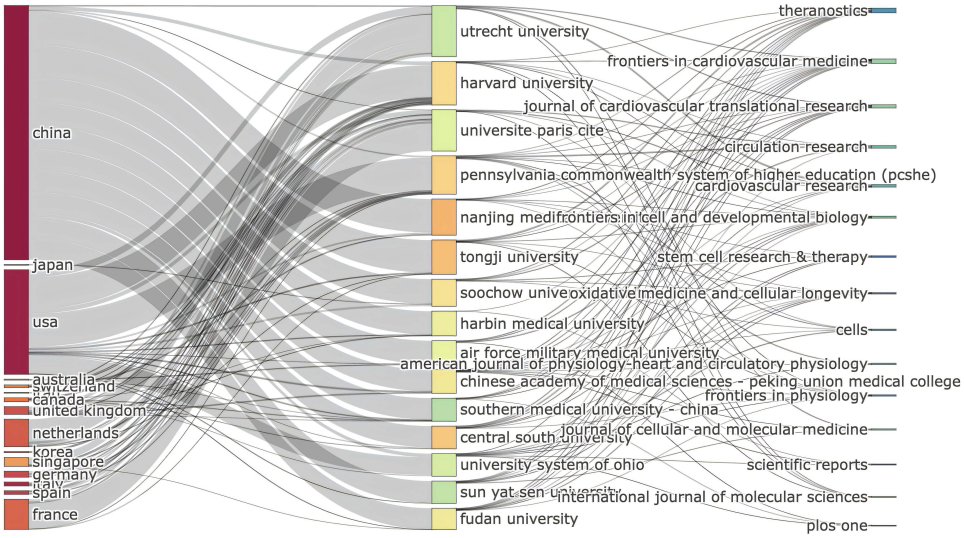

Figure 4 The relationship of the countries, institutions, and journals produced articles based on an alluvial flow map based on R for exosomes in CVDs.

Authors and Co-Cited Authors

Table 2 shows the top ten authors in extracellular vesicle research in the field of cardiovascular disease, as well as their number of publications, citations, citations/number of publications, and H-index. Marban Eduardo had the highest number of published papers (22), followed by Barile Lucio (20), Ke Cheng (19), Junbo Ge (16), and Kishore Raj (16). Marban Eduardo also had the highest citation (2206), followed by Sahoo Susmita (1940). Marban Eduardo and Barile Lucio hold the highest H-index (16). Marban Eduardo mainly focuses on heart protection[33,34] and reviewing the direction of exosome therapy.[35] Barile Lucio researched the identification and characterization of exosomes.[36] Each author has a high citation rate, suggesting that their articles have high academic value.

Table 3 shows the top 10 co-cited authors in the field of exosomes in CVDs. If two or more authors are cited simultaneously, they will create some kind of connection invisibly. The more times they are cited together, the stronger

Table 2 Top 10 Authors in the Field of Exosome in CVDs

Rank	Author	Document	Citation	Citation/ Document	H-index
1	Marban, Eduardo	22	2206	100.27	16
2	Barile, lucio	20	1596	79.80	16
3	Cheng, ke	19	1655	87.11	13
4	Ge, junbo	16	879	54.94	12
4	Kishore, raj	16	1627	101.69	11
6	Sahoo, susmita	15	1940	129.33	13
7	Davidson, Sean m.	13	1247	95.92	13
7	Tang, yaoliang	13	1033	79.46	12
7	Vassalli, Giuseppe	13	1397	107.46	13
10	Davis, Michael e.	12	681	56.75	7
10	Zhu, wei	12	1075	89.58	10

Table 3 Top 10 Co-Cited Authors in the Field of Exosome in CVDs

Rank	Author	Citations	Total Link Strength
1	Barile, I	502	21,492
2	Lai, rc	418	16,255
3	Théry, c	417	16,162
4	Sahoo, s	342	13,903
5	Wang, xh	330	14,611
6	Valadi, h	277	10,974
7	Ibrahim, age	273	12,256
8	Bang, c	246	10,369
9	Jansen, f	243	12,507
10	Zhang, y	235	8891

the connection between them, which is co-cited author. The most frequently co-cited authors were Barile, L (502 citations, TLS: 21492), Lai Rc (418 citations, TLS: 16255) and Thery C (417 citations, TLS: 16162).

Journal and Co-Cited Journals

According to Table 4, It can be seen that the total citations of these journals vary from 22 to 59. Among them, the journal with the highest number of articles is "International Journal of Molecular Sciences", which has 59 articles. We can observe the citation/ document of each article. This index can reflect the influence and quality of journals. It can be seen from the data that each article in "Journal of Cellular and Molecular Medicine" has been cited 43.13 times on average, which is the most frequently cited of all journals. We can also focus on the total link strength of journals. This index can reflect the citation relationship and network influence between journal articles. It can be seen from the data that the total link strength of "Circulation Research" is the highest, reaching 1057. We can also focus on the impact factor (IF2022) and H-index (H-index) of journals. These two indicators are also important indicators to evaluate the influence of journals. According to the data, the impact factor of "Circulation Research" is the highest, reaching 20.1, while the journal with the highest H-index is "Circulation Research", reaching 24.

The purpose of co-citation analysis is to measure the degree of relationship between articles. According to Table 4, the most frequently co-cited journals were Circulation Research (5506 citations, TLS: 473,799), followed by Circulation (3104 citations, TLS: 318,897), PLOS ONE (2463 citations, TLS: 235,082). In the past decade, the impact factors of the top ten cited journals have shown an upward trend.

Figure 4 shows that China has the most influence among the 15 institutions, followed by the United States. Among the top six major institutions, Nanjing Medical University and Tongji University mainly focus on domestic research fields, while Utrecht University, Harvard University, Université Paris Cité, and Pennsylvania Commonwealth System of Higher Education are more involved in international cooperation.

When turning to the collaborations between institutions and journals, Theranostics is at the top of the list based on the density of the lines, followed by Frontiers in Cardiovascular Medicine, Journal of Cardiovascular Translational Research, Circulation Research, Cardiovascular Research, Frontiers in Cell and Development Biology.

References and Co-Cited References

We listed the top 10 frequently cited references related to research on exosomes in cardiovascular medicine in Table 5, including 8 original research and 2 reviews. The article with the highest citation (1583) is "Exosome secreted by MSC

Table 4 Top 10 Journals and Co-Cited Journals by Papers of Exosome in CVD

Rank	Journal	Document	Total Citation	Citation/ Document	Total Link Strength	IF 2022	H-Index	Rank	Co-cited Journal	Citations	Total Link Strength
1	International Journal of Molecular Sciences	59	1174	19.90	668	5.6	18	1	Circulation Research	5506	473,799
2	Frontiers in Cardiovascular Medicine	56	643	11.48	732	3.6	16	2	Circulation	3604	318,897
3	Journal of Cardiovascular Translational Research	35	635	18.14	589	3.4	15	3	PLoS One	2463	235,082
4	Frontiers in Cell and Developmental Biology	32	515	16.09	479	5.5	14	4	Cardiovascular Research	2371	225,251
5	Journal of Cellular and Molecular Medicine	30	1294	43.13	418	5.3	18	5	Journal of Extracellular Vesicles	1816	190,840
6	Circulation Research	28	5113	182.61	1057	20.1	24	6	Journal of the American College of Cardiology	1712	158,215
7	Cardiovascular Research	24	2973	123.88	818	10.8	21	7	Scientific Reports (UK)	1610	168,196
8	Theranostics	23	1782	77.48	481	12.4	19	8	Journal of Molecular and Cellular Cardiology	1572	151,096
8	American Journal of Physiology-Heart and Circulatory Physiology	23	897	39.00	460	4.8	13	9	Proceedings of the National Academy of Sciences of the United States of America	1547	151,993
10	Frontiers in Physiology	22	563	25.59	414	4.0	14	10	Nature	1398	135,171
10	Cells	22	403	18.32	410	6.0	10				

Table 5 The Top 10 References and Co-Cited References Based on the Number of Citations

Top 10 References Based on the Number of Citations							
Rank	**Citations**	**Title**	**First Author**	**Document Type**	**Year**	**Journal**	**IF (2022)**
1	1583	Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury	Lai, Ruenn Chai	Article	2010	STEM CELL RESEARCH	1.2
2	804	Mesenchymal stem cell-derived exosomes increase ATP levels, decrease oxidative stress and activate PI3K/Akt pathway to enhance myocardial viability and prevent adverse remodeling after myocardial ischemia/reperfusion injury	Arslan, Fatih	Article	2013	STEM CELL RESEARCH	1.2
2	804	Circulating MicroRNAs Novel Biomarkers and Extracellular Communicators in Cardiovascular Disease?	Creemers, Esther E.	Review	2012	CIRCULATION RESEARCH	20.1
4	721	Cardiac fibroblast-derived microRNA passenger strand-enriched exosomes mediate cardiomyocyte hypertrophy	Bang, Claudia	Article	2014	JOURNAL OF CLINICAL INVESTIGATION	15.9
5	597	Exosomes as Critical Agents of Cardiac Regeneration Triggered by Cell Therapy	Ibrahim, Ahmed Gamal-Eldin	Article	2014	STEM CELL REPORTS	5.9
6	595	Exosomes Mediate the Cytoprotective Action of Mesenchymal Stromal Cells on Hypoxia-Induced Pulmonary Hypertension	Lee, Changjin	Article	2012	CIRCULATION	37.8
7	590	Characterization of the proteins released from activated platelets leads to localization of novel platelet proteins in human atherosclerotic lesions	Coppinger, JA	Article	2004	BLOOD	20.3
8	520	Embryonic Stem Cell-Derived Exosomes Promote Endogenous Repair Mechanisms and Enhance Cardiac Function Following Myocardial Infarction	Khan, Mohsin	Article	2015	CIRCULATION RESEARCH	20.1
9	517	Extracellular vesicles from human cardiac progenitor cells inhibit cardiomyocyte apoptosis and improve cardiac function after myocardial infarction	Barile, Lucio	Article	2014	CARDIOVASCULAR RESEARCH	10.8
10	486	Exosomes: Vehicles of Intercellular Signaling, Biomarkers, and Vectors of Cell Therapy	Kourembanas, Stella	Review	2015	ANNUAL REVIEW OF PHYSIOLOGY	18.2

(*Continued*)

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Table 5 (Continued).

Top 10 References Based on the Number of Citations							
Rank	**Citations**	**Title**	**First Author**	**Document Type**	**Year**	**Journal**	**IF (2022)**
1	277	Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells	Hadi Valadi	Article	2007	Nature cell biology	21.3
2	276	Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury	Ruenn Chai Lai	Article	2010	Stem Cell Research	1.2
3	253	Exosomes as Critical Agents of Cardiac Regeneration Triggered by Cell Therapy	Ahmed Gamal-Eldin Ibrahim	Article	2014	Stem Cell Reports	5.9
4	224	Extracellular vesicles from human cardiac progenitor cells inhibit cardiomyocyte apoptosis and improve cardiac function after myocardial infarction	L. Barile	Article	2014	Cardiovascular Research	10.9
5	216	Cardiac fibroblast–derived microRNA passenger strand-enriched exosomes mediate cardiomyocyte hypertrophy	Claudia Bang;	Article	2014	Journal of Clinical Investigation	15.9
6	211	Embryonic Stem Cell–Derived Exosomes Promote Endogenous Repair Mechanisms and Enhance Cardiac Function Following Myocardial Infarction	Mohsin Khan;	Article	2015	Circulation research	20.1
7	209	Mesenchymal stem cell-derived exosomes increase ATP levels, decrease oxidative stress and activate PI3K/Akt pathway to enhance myocardial viability and prevent adverse remodeling after myocardial ischemia/reperfusion injury	Fatih Arslan	Article	2013	Stem Cell Research	1.2
8	186	Exosomes secreted by cardiosphere-derived cells reduce scarring, attenuate adverse remodelling, and improve function in acute and chronic porcine myocardial infarction	Romain Gallet	Article	2017	European heart journal	39.3
9	176	Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines	Clotilde Théry	Article	2018	Journal of Extracellular Vesicles	16.0
10	161	Plasma Exosomes Protect the Myocardium From Ischemia-Reperfusion Injury	Jose M. Vicencio	Article	2015	Journal of the American College of Cardiology	24.4

https://doi.org/10.2147/VHRM.S473520 DovePress

reduces myocardial ischemia/reperfusion injury" written by Lai, Ruenn Chaiet al published in STEM CELL RESEARCH in 2010.[37] The article titled "Exosomes Mediate the Cytoprotective Action of Mesenchymal Stromal Cells on Hypoxia-Induced Pulmonary Hypertension" written by Lee, Changjin et al in 2012 published in CIRCULATION with the highest IF (37.8).[38] All the articles came from different writers.

Co-citation is when two or more papers are cited by one or more papers at the same time.[39] All the co-cited references had over 150 citations, and the references listed top 3 were all cited over 250 times (Table 5). The article "Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells" written by Hadi Valadi et al in 2007 ranks first,[40] followed by the article "Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury" authored by Ruenn Chai Lai et al in 2010.[37] All of the articles in the list were original research. There are currently no articles published after 2020 in the list.

Burst detection can be used for events that occur abnormally frequently or suddenly over a period of time.[41] Significant changes in citations within a specific period of time were detected through co-citation burst detection. This is a method of discovering a decrease or increase in specific co-citation studies. Citation-based clustering analysis revealed different research hotspots of exosomes in cardiovascular diseases.

The graph spectrum of the highest cited references and the references with the strongest citation burst is shown in Figure 5 based on CiteSpace. In Figure 5A, the larger the node is, the higher the frequency of the document is. In fact, the higher the number of citations is. For a layer of different colors and thicknesses of a point, the color represents the time of publication. The closer it is to blue purple, the earlier it is quoted, and the closer it is to yellow, the more recent it is quoted. The thickness represents the number of citations in that time period (year), and the thicker it is, the more the number of citations. The top five references are "Ibrahim AGE (2014)", "Khan M (2015)", "Xiao J (2016)", "Yu B (2015)" and "Gallet R (2017)". An article published by Kalluri et al in SCIENCE in 2020 had the highest burst strength (44.66). The important information in Figure 5B reflects or prompts is: there are 13 clusters, showing the top 8 clusters. The top 7 clusters were "pregnancy" (cluster #0), "extracellular vesicles" (cluster #1), "cell-derived microparticles" (cluster #2), "myocardial infarction" (cluster #3), "nanomedicine" (cluster #4), "telocytes" (cluster #5), "laterality" (cluster #6) and "osteoarthritis" (cluster #7), Among these, 3 clusters, "extracellular vesicles" (cluster #1), "cell-derived microparticles" (cluster #2) and "myocardial infarction" (cluster #3) had the highest number of published papers in recent years. These fields to some extent indicate the research centers in the cross field of exosomes and cardiovascular.

Figure 6 shows the top 25 references with the strongest citation burst. These references are distributed in a specific time period and can reflect the hotspots at that time. The first citation outbreak occurred between 2011 and 2015, and the latest citation outbreak references have been recorded since 2021. The largest explosive force came from Kalluri et al (Strength = 44.66), Théry et al (Strength = 41.84) and lbrahim et al (Strength = 40.23). In addition, Kalluri et al (2020), Huang et al (2020), and Mathieu et al (2019) have received more attention in recent years.

Keyword Analysis

Keyword is the essence of research topics. Table 6 lists the top 20 high-frequency keywords. The most common keywords were "exosome" (1242 times; TLS:10,257). A comprehensive analysis of keyword clustering was conducted using CiteSpace and VOSviewer software. The analysis results are shown in Figure 7A. The most frequently occurring keyword and highest centrality are "extracellular vesicles" (Fre = 570), followed by "exosome" (Fre = 440) and "myocardial infarction" (Fre = 316). Figure 7B reveals that the most significant cluster was "mechanisms" (#0), followed by "cardiovascular" (#1), "mesenchymal stem cells" (#2), "extracellular vesicles" (#3), "myocardial infarction" (#4), "endothelial cells" (#5), "cardiomyocyte apoptosis" (#6), "urine exosomes" (#7), "heart failure" (#8). Figure 7C shows the timeline analysis of the keyword cluster of exosomes in CVD based on CiteSpace software.

By analyzing emerging keywords, we can find the significant occurrence of specific terms within a specific time interval. These valuable pieces of information provide insights into the sustained development of the research field and become important indicators for depicting the latest trends in academic pursuits. The top 25 keywords that exhibit the strongest citation bursts are presented in Figure 8. These keywords were distributed in a specific time period and can reflect the hot spots at that time. Over a decade, the longest outbreak period is proteomic analysis, which lasts from 2004

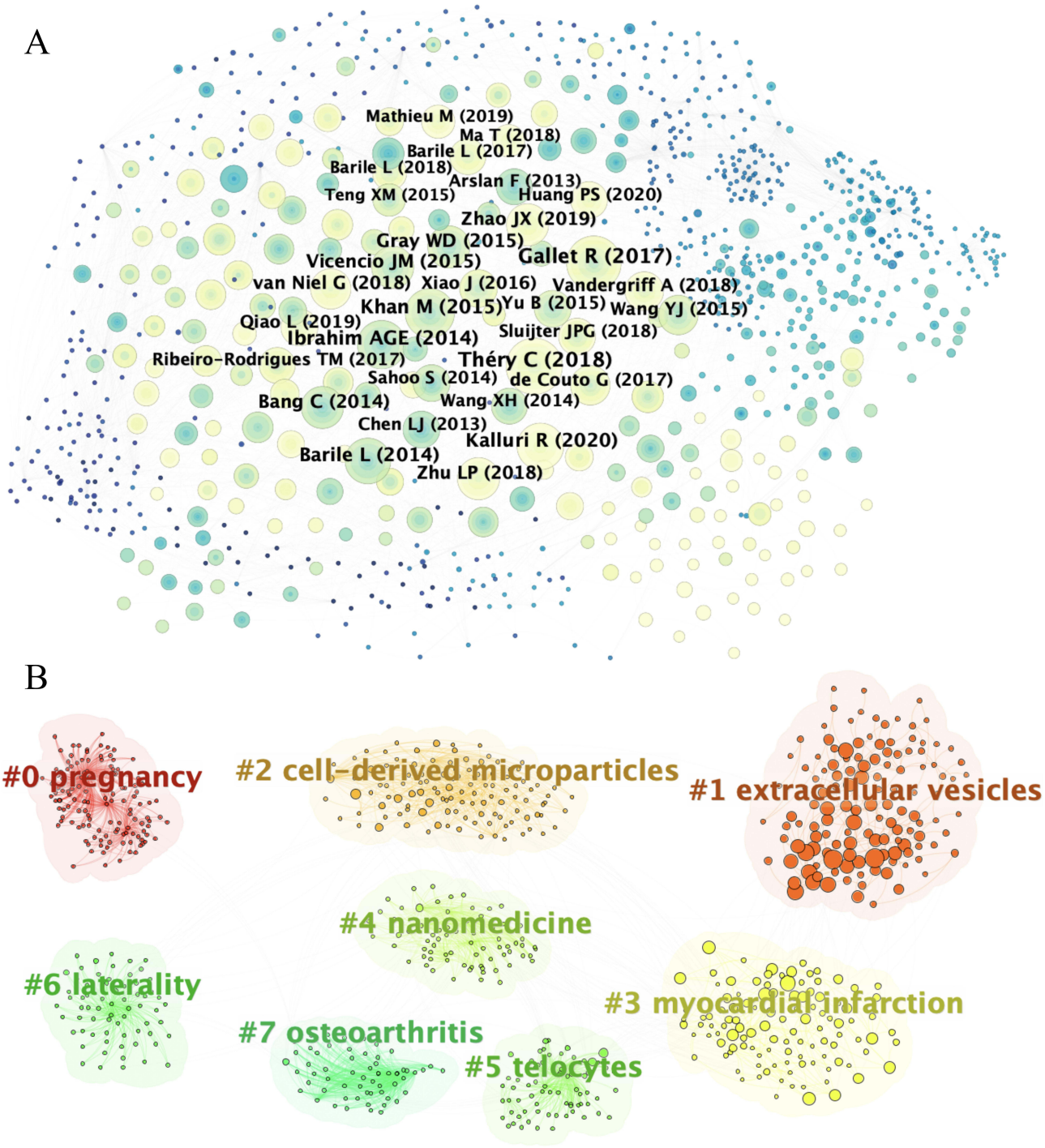

Figure 5 Analysis of Co-cited references. (**A**) the co-cited references network graph in WOSCC. (**B**) Keyword cluster map of co-cited references network.

to 2017. In contrast, the highest burst intensities associated with exosomes in cardiovascular disease came from circulating microRNAs (intensity = 9.36), cardiac progenitor cells (intensity = 8.63), mediated transfer (intensity = 7.5) and membrane vesicles (intensity = 7.09). In addition, fibrosis (2015), as well as atrial fibrillation (2010) and inhibition (2013) were found to be the most concern at present.

Figure 9 shows the association and connection between the top 20 co-cited references, authors and keywords (only 19) in the application of exosomes in cardiovascular aspects, which are presented in the form of an alluvial flow diagram.

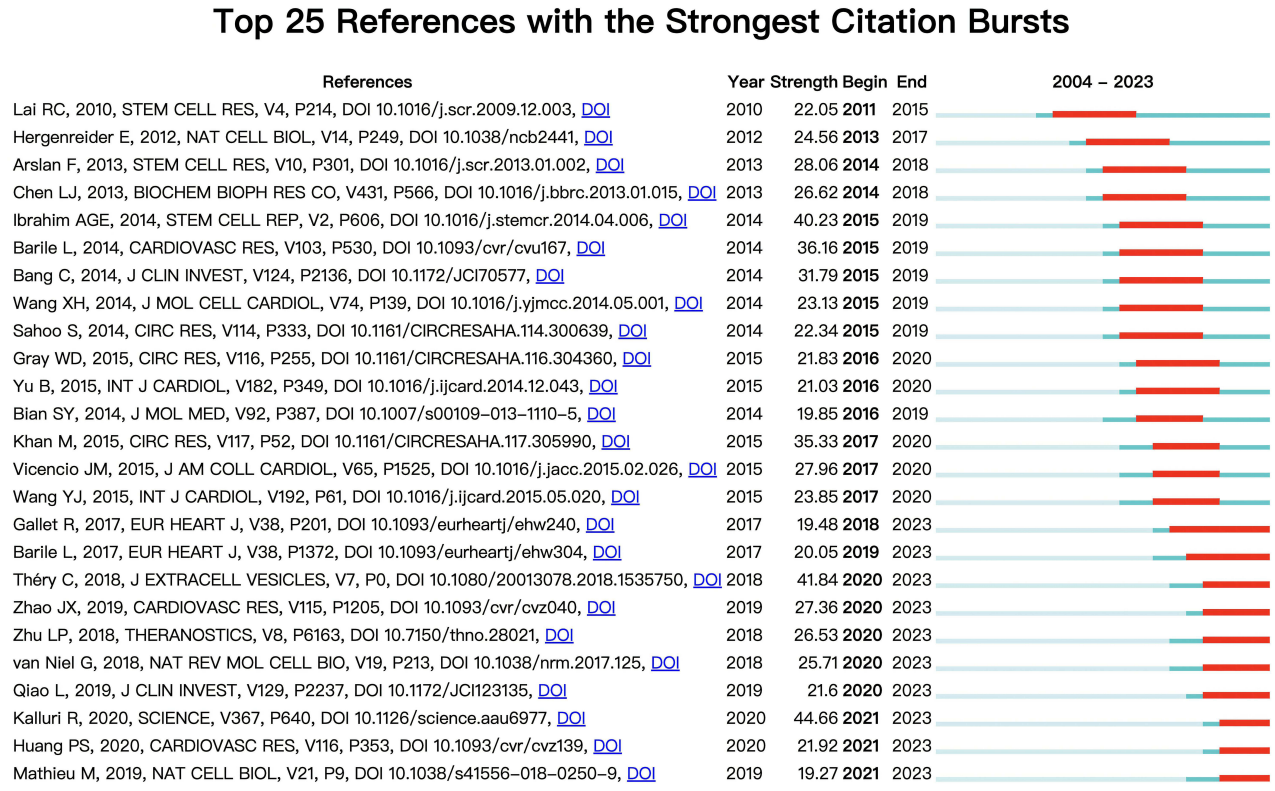

Figure 6 Analysis of references. The top 25 references with the strongest citation bursts. The blue line represents the time from its first appearance to 2023; the redline represents the burst time.

Obviously, the top 20 most frequently co-cited references are more closely related to the study of exosomes, and the related fields of cardiovascular are also reflected.

Discussion

General Information

The number of annual publications can reflect the development of a specific field.[42] From 2020 to 2021, the number of publications increased from 231 to 344, with a rate of 70%. Citations increased from 8617 to 12952 which was an even more significant increase. This showed that researchers have realized the importance of exosomes and started to carry out extensive research on them. At the same time, these early studies have been widely recognized and cited. Between 2021 and 2022, the number of articles published in this research direction decreased to 285, but the number of citations increased to 13431. This shows that there may be some bottlenecks in the research of exosomes, or it is due to the global epidemic, but it is still a research hotspot. After 2022, publications and citations have declined significantly, which indicates that the research in this field may become mature, and may also be affected by external factors, such as the global epidemic, changes in the research environment, allocation of funds, changes in research direction, etc.

The results of the country analysis showed that China has far more documents than other countries, and citation ranks first. However, it can be clearly seen that China's citation/document is not very leading. The Netherlands is in the leading position in citation/document. It can be seen that its papers are of high quality and are cited more. In terms of total connection strength, the United States is more advanced, which shows that the United States pays more attention to global cooperation. In addition, Italy, Britain, Germany, the Netherlands and other countries have also made significant contributions to the development of this field, and the publications of scholars from these countries can also be concerned. The institution analysis also indicated that Nanjing Medical University ranked first with 52 articles, Tongji University ranked second with 40 articles, and Shanghai Jiao Tong University ranked third with 36 articles. The overall article quality of Soochow University is high for citation ranks first. The top 10 institutions that have made great

Table 6 Top 20 Frequency Keywords Related to Exosome in CVDs

Ranking	Keyword	Occurrences	Total Link Strength	Ranking	Keyword	Occurrences	Total Link Strength
1	Exosome	1242	10,257	11	microRNA	160	1515
2	Extracellular vesicles	570	5299	12	Microvesicles	156	1574
3	Angiogenesis	221	2058	13	Therapy	154	1351
4	Expression	220	1861	14	Atherosclerosis	147	1309
5	Myocardial-infarction	205	1961	15	Cells	143	1164
6	Heart	204	1856	16	Mesenchymal stem-cells	137	1291
7	Myocardial infarction	203	1804	17	Heart-failure	132	1214
8	microRNAs	197	1775	18	Endothelial-cells	131	1301
9	Inflammation	189	1662	19	Mechanisms	128	1119
10	Apoptosis	168	1472	19	Repair	128	1118

contributions to the development of exosomes in cardiovascular diseases are all in China. This may be due to the large population, high prevalence of cardiovascular disease and heavy treatment burden.[43–46]

The journal analysis results show that the journal with the highest number of publications is "International Journal of Molecular Sciences", and each article of "Journal of Cellular and Molecular Medicine" has been cited 43.13 times on average, which is the highest number of citations among all journals, while "Circulation Research" has the highest total link strength, impact factors and H-index. These three journals are particularly important (especially Circulation Research), and they have high influence and links in the academic community. Therefore, when studying this field, it is recommended to pay more attention to the literature of these journals. Marban, Eduardo has the highest number of publications and the most citations. Marban, Eduardo and Barile, Lucio both hold the highest H-Index. Secondly, we can observe that Susmita Sahoo, the sixth-ranked author, has 129.33 citations/articles, which is the highest in the top ten. This shows that her research results have a high influence on the academic community. Their articles should be read through when studying the field. Barile, L and Lai Rc have a high number of co-citations for their articles, reflecting the research direction and the interdisciplinary development of academia. It is worth pointing out that cluster analysis shows that a large part of the published papers are from China. Academic research is both domestic and international cooperation. In order to make a breakthrough, cooperation at home and abroad is necessary.

Analysis of Key Literature

The hot research directions can be obtained by analyzing the contents of highly cited and highly cited literature. We listed the top 10 frequently cited references related to research on exosomes in cardiovascular medicine in Table 5, including 8 original research and 2 reviews. The article with the highest citation (1583) is "Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury" written by Lai, Ruenn Chai et al published in STEM CELL RESEARCH in 2010.[37] It tells us that MSCs can secrete exosomes to mediate their cardioprotective paracrine effects, expanding the vision of cell-cell mediation of tissue injury and repair, and opening up ideas for the development of tissue repair biologics. The article titled "Exosomes Mediate the Cytoprotective Action of Mesenchymal Stromal Cells on Hypoxia-Induced Pulmonary Hypertension" written by Lee, Changjin et al in 2012 published in CIRCULATION with the highest IF.[38] This study confirms that MEX can pleiotropically protect the lung and inhibit pulmonary hypertension by inhibiting hyperproliferative pathways, including hypoxia-induced STAT3-mediated signaling. It proves that exosomes play a direct and crucial role in regulating pulmonary arterial hypertension and provides an essential basis for future research.

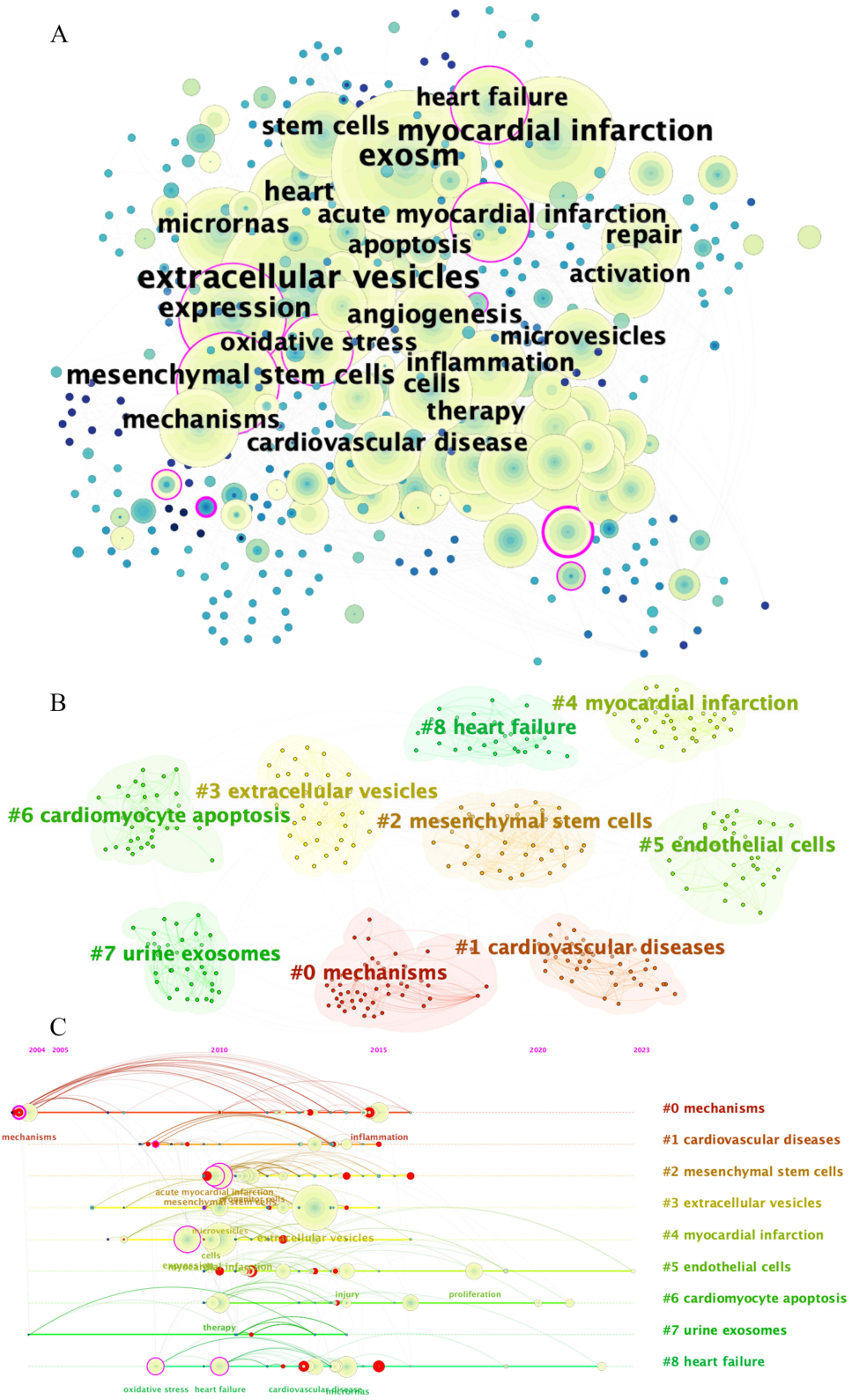

Figure 7 Analysis of keywords. (**A**)co-occurrence network visualization map of keywords. (**B**) The clustering map of keywords in the field of exosomes in CVDs from 2013 to 2023. (**C**) Timeline view of keywords in publications on exosomes in CVDs.

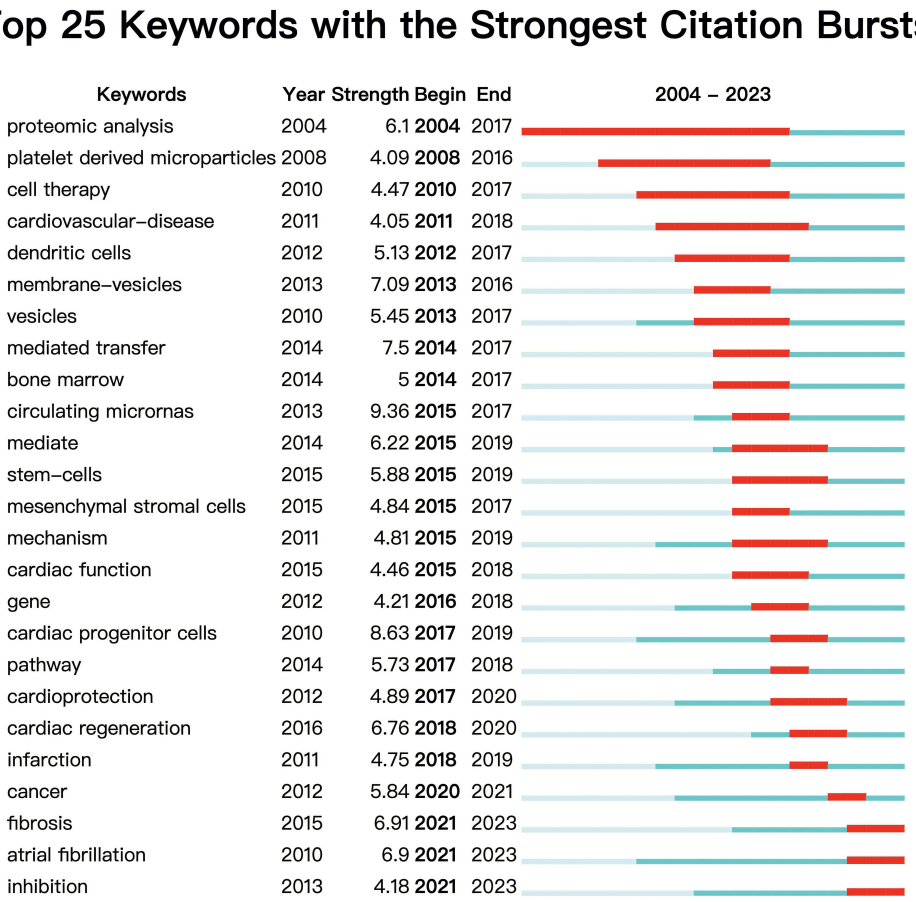

Figure 8 The top 25 keywords with the strongest citation bursts. The red segment of the blue line represents the burst references. (**B**) Cluster diagrams of references.

All the co-cited references had over 150 citations, and the references listed top 3 were all cited over 250 times (Table 5). The article "Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells" written by Hadi Valadi et al in 2007 ranks first,[40] followed by the article "Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury" authored by Ruenn Chai Lai et al in 2010.[37] All of the articles in the list were original research. There are currently no articles published after 2020 in the list.

Burst detection can be used for events that occur abnormally frequently or suddenly over a period of time.[41] Significant changes in citations within a specific period of time were detected through co-citation burst detection. This is a method of discovering a decrease or increase in specific co-citation studies. Citation-based clustering analysis revealed different research hotspots of exosomes in cardiovascular diseases.

The graph spectrum of the highest cited references and the references with the strongest citation burst is shown in Figure 5 based on CiteSpace. In Figure 5A, an article published by Kalluri et al in SCIENCE in 2020 had the highest burst strength. Figure 5B shows the clustering and time distribution of the citations. Among these, "extracellular vesicles", "cell-derived microparticles" and "myocardial infarction" had the highest number of published papers in recent years. The above literature and the top-ranked highly cited and highly cited articles cover important research achievements of exosomes in cardiac regeneration, myocardial ischemia-reperfusion injury, myocardial hypertrophy and other aspects, and are published in different journals with high impact factors. They are widely cited in the field of exosome research and have an important impact on the research of cardiovascular disease and cell therapy.

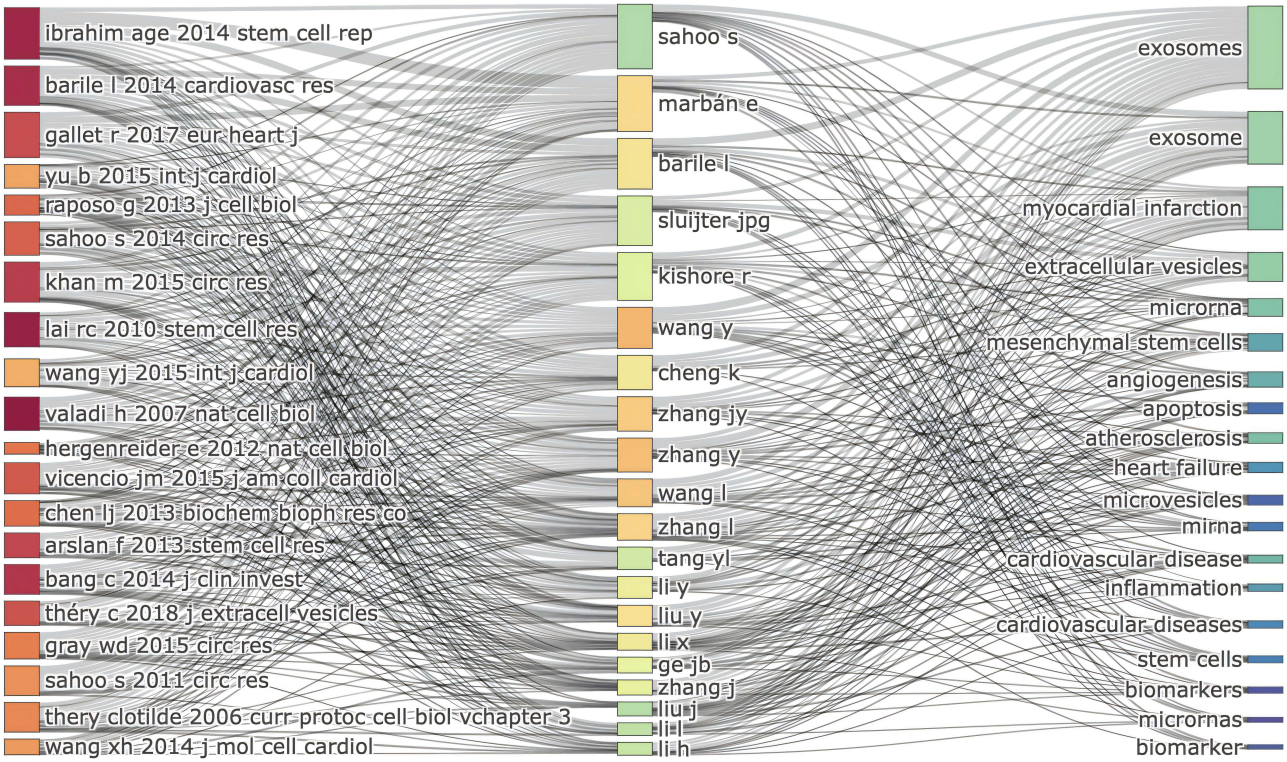

Figure 9 The relationship of the top 20 co-cited reference, author and keyword evolutions based on an alluvial flow map based on R for exosomes in CVDs.

Research Hotspots and Trends

Keyword is the essence of research topics. A comprehensive analysis of keyword clustering was conducted using CiteSpace and VOSviewer software. Table 6 lists the top 20 high-frequency keywords. The current hotspots and future trends in the study of exosomes in CVDs were searched by keyword frequency and total link strength. It is possible to realize the allocation and growth of distinct research hotspots in this field.

The most common keywords were “exosome”, followed by “extracellular vesicles” and “angiogenesis”. The analysis results are shown in Figure 6. Keyword clusters can be divided into two main areas, corresponding to different applications of exosomes in CVD. One group focuses on the use of exosomes as biomarkers, the detection and diagnosis of cardiovascular diseases, and how it achieves its goals. Another group focused on the mechanism and function of exosomes in cardiovascular disease, including “oxidative stress”, “heart failure”, etc.

By analyzing emerging keywords, we can reveal the significant occurrence of specific terms within a specific time interval. These valuable pieces of information provide insights into the sustained development of the research field and become important indicators for depicting the latest trends in academic pursuits. The top 25 keywords that exhibit the strongest citation bursts are presented in Figure 7. The top 25 keywords that exhibit the strongest citation bursts were presented. Over the span of a decade, “circulating microRNAs” ranked first with the highest burst strength followed by “cardiac progenitor cells” and “membrane-vesicles”. We can tell that from 2004 to 2018, the research hotspots mainly focus on what mechanisms and pathways extracellular vesicles affect cardiovascular disease. Thus, we see the citation bursts of such keywords as “mediated transfer”, “mechanism” and “pathway”. Then, the emerging keywords of “cardioprotection”, “cardiac regeneration”, “cancer” and “inhibition” suggest that the focus of the research has shifted to the specific role of extracellular vesicles in specific diseases. It is also worth noting that “fibrosis”, “atrial fibrillation” and “inhibition” have shown the most obvious outbreak in recent years, which indicates that they will continue to be hot topics for future research.

In Figure 8, based on the alluvial flow diagram or three field diagrams, the association and connection between the top 20 commonly cited references, authors, and keywords in exosomes in CVD are presented. The top 20 most commonly

cited references were found to be more closely related to extracellular vesicle research and represent various types of CVD.

Mechanisms of Exosomes in CVDs

Exosomes are a type of extracellular vesicle (EVs). More and more evidence showed that EVs can transmit bioactive molecules to participate in cell-cell communication, so the research on EVs began to develop.[47,48] With the continuous in-depth research on EVs, they can be roughly divided into three types [exosomes (30–100 nm), microparticles (0.1–1 μm), and apoptotic bodies (1–5 μm)] based on their size, biological mechanisms, and surface markers.[49–51] Exosomes have the characteristics of carrying and transferring DNA, RNA, miRNA and protein as well as promoting cell-cell communication, which play an important role in vivo.[52–54] Research has shown that exosomes carrying miRNA can mediate the protective effects of exercise on diabetic myocardial injury.[55] In addition, exosome-mediated signal transduction is involved in the progress of cardiovascular diseases, such as myocardial infarction, myocardial ischemia and atherosclerosis.[56–60]

Exosomes Involved in Apoptosis in CVDs

Apoptosis is the autonomous and orderly death of cells controlled by genes.[61] In CVDs, it is related to heart failure (HF),[62,63] myocardial infarction (MI)[64,65] and reperfusion injury,[66,67] etc. It was found that there is a relationship between exosomes and myocardial cell apoptosis. Gupta et al found that the release of heat shock protein (HSP) 60 was associated with exosomes,[68] which can bind selectively to the cardiac myocyte and induce apoptosis.[69–71] Yu et al indicated that the Circ-cacng2/mir-197-3p/caspase3 axis is an important pathway for MM-exosomes to inhibit cardiomyocyte viability and promote apoptosis.[72] Huang pointed out that exosome-mediated miR-328-3p transfer can promote myocardial cell apoptosis by activating Caspase-3 signaling.[73]

On the contrary, some authors have shown that miR-144, miR-126, etc. inhibited the process of cell apoptosis through exosomes.[74–77] Wen et al found that exosomes derived from MSC are capable of inhibiting cell apoptosis damage under hypoxic conditions by delivering miR-144 to cells, which targets the PTEN/AKT pathway.[78] Wang et al discovered that exosomes derived miR-126 cab attenuate apoptosis from ischemia and reperfusion injury by targeting ERRFI1.[79] The above studies indicate that exosomes indirectly protect or promote cell apoptosis.

Exosomes Involved in Angiogenesis in CVDs

In recent years, attempts have been made to improve CVD by promoting angiogenesis since the limited blood supply is closely related to heart failure.[80–83] Exosomes were found to promote angiogenesis. Sun et al found that HIF-1α Overexpressed exosomes rescued the abilities of HUVECs damaged by hypoxia, thereby promoting angiogenesis.[59] Xiao indicated that MSC-exosomes are necessary for vascular endothelial cells (VECs) to induce angiogenic activity.[84–86] Zhang et al revealed that Plasma exosomes play an angiogenic role in ECs through the FGFR2 signaling pathway under the regulation of CD44.[87] Wang et al showed that ADSC-exosomes can repair MI-induced cardiac injury through the miRNA-205 signaling pathway, which indicates that DSC exosomes containing miRNA-205 have good prospects in MI.[88]

Exosomes Involved in Inflammation in CVDs

Low-degree chronic inflammation will increase the risk of atherosclerosis and insulin resistance, which is the main mechanism for the development of CVD.[89–91] Exosomes also play an important role in it.[92–94] Gao et al demonstrated that Mature dendritic cell (DC) - derived exosomes in membrane TNF-α mediated by NF-κB pathway increase endothelial inflammation and atherosclerosis.[79] Tang et al indicated that the CDS region of PPARα mRNA directly binds to mir-27b-3p of exosomes to downregulate PPARα, thus leading to inflammation and atherosclerosis.[95]

By contrast, more research pointed to the alleviating effect of exosomes on inflammation. Laura et al showed that exosomes produced by naive bone marrow-derived macrophages (BMDM-exosome) contain anti-inflammatory microRNA-99a/146b/378a, suppressing inflammation by targeting NF-κB and TNF-α signaling.[96] Yao found that high-level expression of MiR-25-3p in P-exosomes can reduce ADAM10 expression to inhibit ox LDL-induced inflammation and lipid deposition.[97] The above research demonstrates the impact of exosomes on inflammation. Most of the focus is on

NF-κB pathway. Inflammation in CVDs is closely related to atherosclerosis, pending further research on the treatment of atherosclerosis in the direction of exosomes.

Therapeutic Role of Exosomes in CVDs

The basic function of exosomes is to deliver cargo intracellularly, which can be used as an attractive drug delivery agent.[98–100] At the same time, stem cell-derived exosomes have cardioprotective effects and have great prospects in the treatment of CVD.[101–103] Most importantly, exosomes derived from microRNAs (miRNAs) are important biomarkers in cardiovascular diseases, and they are expected to be put into clinical risk assessment after further research.[104–106]

Exosomes as a Potential Biomarker in CVDs

Some studies have shown that exosomes can be used as an important biomarker in cardiovascular disease.[105,106] Exosomes have different sources and quantities under different pathological conditions, and have great potential for disease-specific biomarkers.[107,108] Silvia-Palacios reported that Ischemia promotes an increase in exosome release in patients with myocardial infarction. After acute MI and reperfusion, a high content of mir-223-3p (a miRNA targeting inflammatory molecules) was found in patients' exosomes.[109] In adipose tissue (AT), Xie et al found that exosomes released from adipose tissue at different locations and under stress have different atherosclerosis-promoting effects.[110] In patients with heart failure, elevated levels of miR-217 in cardiac tissue are associated with poorer left ventricular ejection fraction.[111,112] Allison et al listed exosomal miRNAs of specific interest in CVD, highlighting the exosomal miRNAs with high clinical relevance, including MiR-19b (significantly increased in patients with unstable angina),[113] MiR-130a (overexpression leads to atherosclerosis),[114] MiR-10b (elevated levels are seen in patients with atherosclerotic plaques, but have myocardial protection against apoptosis in hypoxic environments),[115,116] MiR-33 (increased collagen deposition in myocardial infarction and promotes cardiac fibrosis through the p38 MAPK signaling pathway),[117] MiR-186-5p (levels decreased within 72 hours of the onset of acute myocardial infarction).[118,119] Ji et al indicated recently that foam cell-derived exosomes can be used as circulating biomarkers for detecting atherosclerosis in vitro after fluorescence labeling.[120]

Exosomes as Therapeutic Agents in CVDs

Researchers have found that exosomes not only play an important role in the prognosis and diagnosis of CVD, but can also be used for treatment.[121–123] Research has found that exosomes can regulate oxidative stress (OS) in CADs, and miRNAs play an important role in this process.[123–125] It can reduce OS-induced cell apoptosis by regulating OS. Arslan et al indicated that a single intravenous injection of extracellular vesicles (5mm) before reperfusion can reduce the infarct area of mice by about 45%.[126] Exosomes from various cell sources have potential therapeutic effects on CVD. Exosomes derived from hematopoietic stem cells (HSCs) provide support for repairing heart tissue by differentiating into cardiomyocytes.[127,128] Exosomes derived from cardiospheres (CDCs) seem to be able to convert inert dermal fibroblasts into cells with therapeutic activity, which may reduce scar size and improve cardiac function in chronic myocardial infarction models.[129] Exosomes derived from mesenchymal stem cells (MSCs) help reduce the infarct size of mouse heart tissue.[37] Multiple methods were developed to enhance exosome activities,[130,131] but its long-lasting efficacy and safety remain to be studied. The potential impact of targeted modifications on the structural integrity of exosomes remains uncertain.[132] The current research focuses on optimizing the route of dosing,[133] preparing formulations with excellent in vivo stability,[134] improving target specificity,[135,136] and designing exosomes without changing their biophysical and biochemical properties.

Exosomes can transport and deliver proteins and nucleic acids intracellularly, which contributes to their potential as drug delivery agents for CVD.[137] Cardiomyocyte-specific peptides exist on the surface of exosomes isolated from CDCs expressing lamb 2B and can lead to increased uptake by cardiomyocytes.[138] Mir-199b-5p exists in exosomes isolated from HIPSC ECs and promotes angiogenesis.[139] Exosomes have the high efficiency and specificity of targeted delivery of cargo, and will not cause immune response. They have the prospect of being used as natural drug delivery vehicles, which is worthy of further exploration and is expected to be applied in clinics. As a drug delivery vehicle, its current

defect is that there is no standardized large-scale method to produce exosomes, and its loading capacity and targeting ability need to be enhanced at the same time.[133,140]

Limitation

This study has some limitations. First, because our research was limited to the scientific web, we did not search other academic databases and may have missed some influential articles. However, due to the limitation of bibliometric software, it is difficult to combine and analyze various databases. Secondly, only articles published in English enter the scope of this study. Therefore, relevant studies in other languages were not included. However, because English is widely used in academia, we believe that the most important studies have been included in our analysis. Third, this study includes articles and reviews, and there may be a certain bias in using the number of citations to reflect the academic impact of articles. Fourthly, although a variety of commonly used software is used for bibliometric analysis, there are differences and biases in the operation mode and analysis results of different software. Therefore, the results of different software were summarized to improve the reliability of this paper.

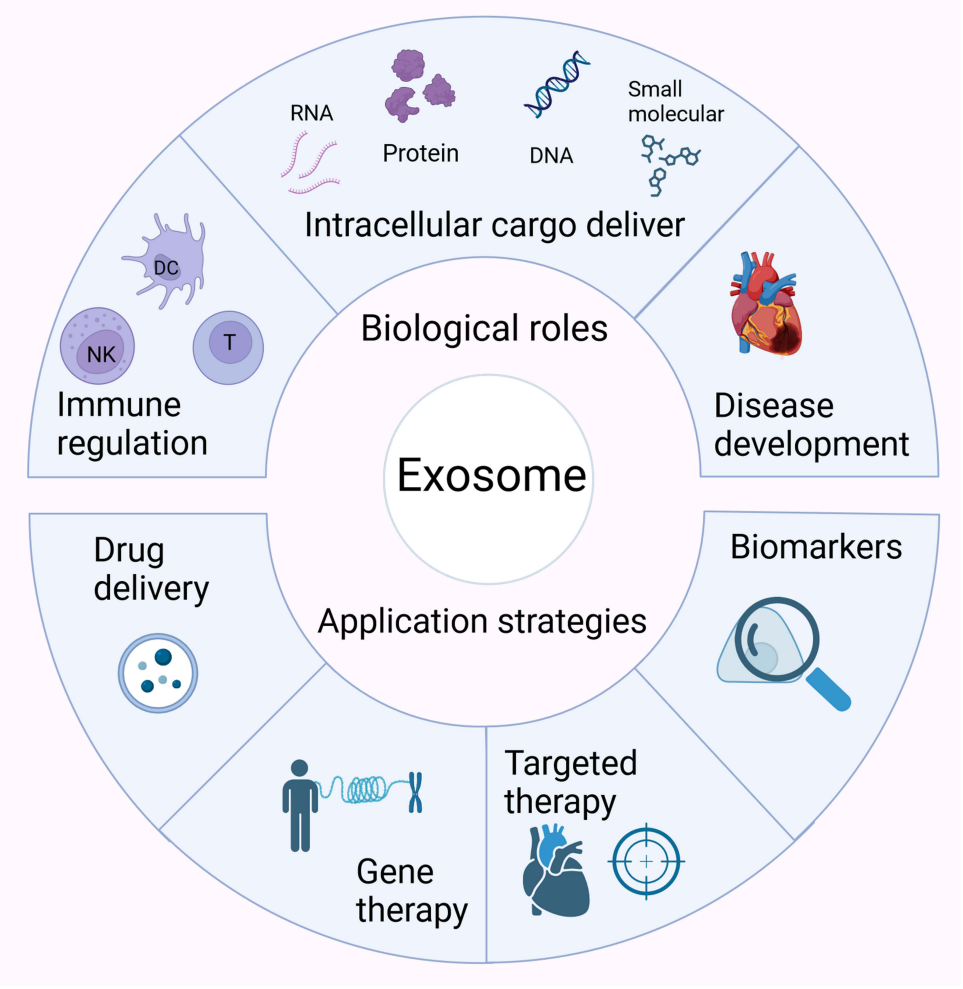

Figure 10 Different biological roles and application strategies that exosomes tend to play in CVDs have been annotated in the figure. Exosomes can mediate intercellular communication through the cargo they carry, such as nucleic acids, proteins, small molecules, and so on. In addition, exosomes can also regulate the immune system and play a role in disease progression. Exosomes can also serve as biomarkers for disease diagnosis, and engineered exosomes can be a valuable tool for gene therapy and targeted drug delivery.

Conclusion

In conclusion, the number of annual publications on the use of exosomes in CVDs has continued to rise basically over the past decade except for the possible impact of the epidemic. China, as a pioneer country in the field, has contributed to the development of exosomes in CVDs greatly. Among the institutions, Nanjing Med University ranks first in the number of publications, citations, and total link strength. By analyzing journals found that International Journal of Molecular Sciences has the highest number of publications while Circulation Research had the highest number of citations, indicating their importance in the field. The author analysis identified Marban Eduardo had the highest number of published papers. The most frequently co-cited authors were Barile, L. While focusing on basic research, the most common keywords were "exosome". Current research on exosomes in CVDs focuses on exosomes, extracellular vesicles and angiogenesis. These will be hot topics for future research. This study comprehensively introduces the research status of cardiovascular disease exosomes by analyzing and summarizing cutting-edge and popular directions by drawing visual graphics. It provides a foundation and new frontiers for future research on exosomes in CVD, enabling readers to obtain useful information quickly and effectively in this field (Figure 10). These findings are expected to help scholars grasp the research direction, further study exosomes in cardiovascular disease, and lay a theoretical foundation for the clinical application of cardiovascular disease in the future.

Data Sharing Statement

The data in this study is accessible in the public domain and not of a confidential nature.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interest in this work.

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