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ORIGINAL RESEARCH

Research Hotspots and Frontier Trends of Autophagy in Diabetic Cardiomyopathy From 2014 to 2024: A Bibliometric Analysis

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Objective: In recent years, the investigation of autophagy mechanisms has gained prominence as a key focus for understanding the pathogenesis and therapeutic potential of diabetic cardiomyopathy. This study aims to present an overview of the current state, major research areas, and emerging trends in autophagy related to diabetic cardiomyopathy through bibliometric analysis, offering a scientific foundation for future research.

Methods: The Web of Science Core Collection served as the data source for this study, from which full-text publications were extracted. Using CiteSpace 6.3.R1, VOSviewer v1.6.18, and R-Bibliometrix, the analysis evaluated research output across dimensions such as subjects, countries, institutions, journals, authors, and co-cited references, generating a comprehensive visual map.

Results: A total of 367 publications met the inclusion criteria. Between 2014 and 2024, the volume of articles demonstrated a consistent upward trajectory. Research on autophagy in diabetic cardiomyopathy predominantly spans the disciplines of biology and medicine. China and the Fourth Military Medical University emerged as leading contributors among 41 countries and 505 institutions. Sun Dongdong was identified as the most prolific author, while Jia GH was the most frequently cited. Key journals in this field include Biochimica et Biophysica Acta - Molecular Basis of Disease and Frontiers in Cardiovascular Medicine, while Circulation Research recorded the highest number of co-citations. The most cited reference was an experimental study by Xie ZL. Current research focuses on autophagy, diabetic cardiomyopathy, oxidative stress, and their underlying mechanisms.

Conclusion: Research on the role of autophagy in diabetic cardiomyopathy has reached a stable phase of development. Future investigations should prioritize mechanistic studies and emphasize the clinical application of novel pharmacological interventions, thereby advancing therapeutic strategies and contributing to improved human health outcomes.

Keywords: diabetic cardiomyopathy, autophagy, mechanism, bibliometric analysis

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia.[1] By 2045, an estimated 700 million people will be living with DM.[2,3] The disease is associated with numerous severe complications, including cardiovascular disease, kidney disease, neuropathy, and retinopathy.[4–7] Among these, diabetic cardiomyopathy (DCM) is one of the most significant and detrimental condition, profoundly impacting the diabetic population.[8] Despite stringent blood glucose control, the prevalence of DCM remains high.[9] This condition is marked by pathological structural and functional abnormalities in the heart, which may progress to heart failure and contribute to mortality in approximately 12% of diabetes patients.[10] These outcomes pose a severe threat to public health and impose a substantial societal burden.[11,12] In recent years, studies on autophagy mechanisms have suggested that dysregulated autophagy may play

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a critical role in the development of DCM. However, the precise relationship between autophagy levels and DCM pathogenesis remains controversial, underscoring the need for further investigation.

Autophagy is a fundamental cellular process that mediates the degradation and recycling of intracellular components through lysosomal pathways.[13,14] It plays a pivotal protective role against various diseases.[15–18] In a hyperglycemic environment, elevated production of free radicals leads to increased oxidative stress, impaired mitochondrial function, organelle damage, apoptosis, and fibrosis in cardiomyocytes, thereby heightening susceptibility to cardiomyopathy.[19] Autophagy contributes to cellular homeostasis by facilitating the clearance and recycling of cytoplasmic aggregates and damaged components, processes particularly crucial in cardiac tissue.[19] Evidence suggests that enhancing autophagy in myocardial cells can alleviate DCM.[20,21] However, excessive autophagy may accelerate myocardial cell death, exacerbating the disease.[22,23] While animal and cell studies have advanced understanding in this area, clinical research remains limited. Expanding such research is critical to deepen insights into the interplay between autophagy and DCM and to inform future clinical strategies.

Bibliometric analysis, which employs mathematical and statistical tools, has become a valuable approach for mapping and interpreting scientific literature. Tools such as VOSviewer v.1.6.18, CiteSpace 6.3.R1, and R-bibliometrix are widely used in this field. Applying these methodologies, the present research has identified key trends and gaps in the literature on autophagy in DCM, offering valuable insights and references for future investigations.

Materials and Methods

Database

The Web of Science Core Collection (WOSCC) database is widely recognized for its precision in categorizing diverse types of literature, making it a preferred resource for bibliometric analyses. Accordingly, this study conducted a comprehensive search of the WOSCC database.

Search Strategy

On September 15, 2024, for articles on autophagy in DCM published between 2014 and 2024. The search strategy was defined as follows: TS=(“diabetic cardiomyopathy“ OR ”diabetes cardiomyopathy”) AND (Autophagy OR Autophage). The selection criteria for literature included in this study are as follows: (1) Articles with topic containing the words ‘diabetic cardiomyopathy’ and ‘autophagy’ or related terms; (2) English literature published from January 1, 2014, to September 15, 2024. The exclusion criteria were as follows: (1) Documents with incomplete information; (2) Repeatedly published literature; (3) newspaper articles, conference articles, achievement reports, and other non-paper-format documents.

Data Collection

The analysis of publication trends was conducted using GraphPad Prism 10.2.0, with additional insights derived from CiteSpace 6.3.R1, VOSviewer v.1.6.18, and R-Bibliometric. Each tool offered distinct capabilities: VOSviewer v.1.6.18 excelled in processing and visualizing large-scale datasets, while CiteSpace 6.3.R1 specialized in identifying temporal dynamics and research frontiers. R-Bibliometric provided advanced statistical analyses and facilitated the creation of scientific maps. The comprehensive screening and analytical workflow is depicted in Figure 1.

Results

General Analysis of Publications

The chronological analysis of publication years revealed significant insights into the evolution of this research field. In the initial three years, annual publication counts remained below 20; however, a marked growth trend emerged starting in 2017 (Figure 2A). Despite a slight decline in 2019, the annual total remained above 20, with a research peak observed in 2022. Existing studies highlight the dual role of autophagy in DCM, demonstrating both protective effects and its potential to induce myocardial injury.[24] This complexity underscores the need for further exploration of autophagy’s

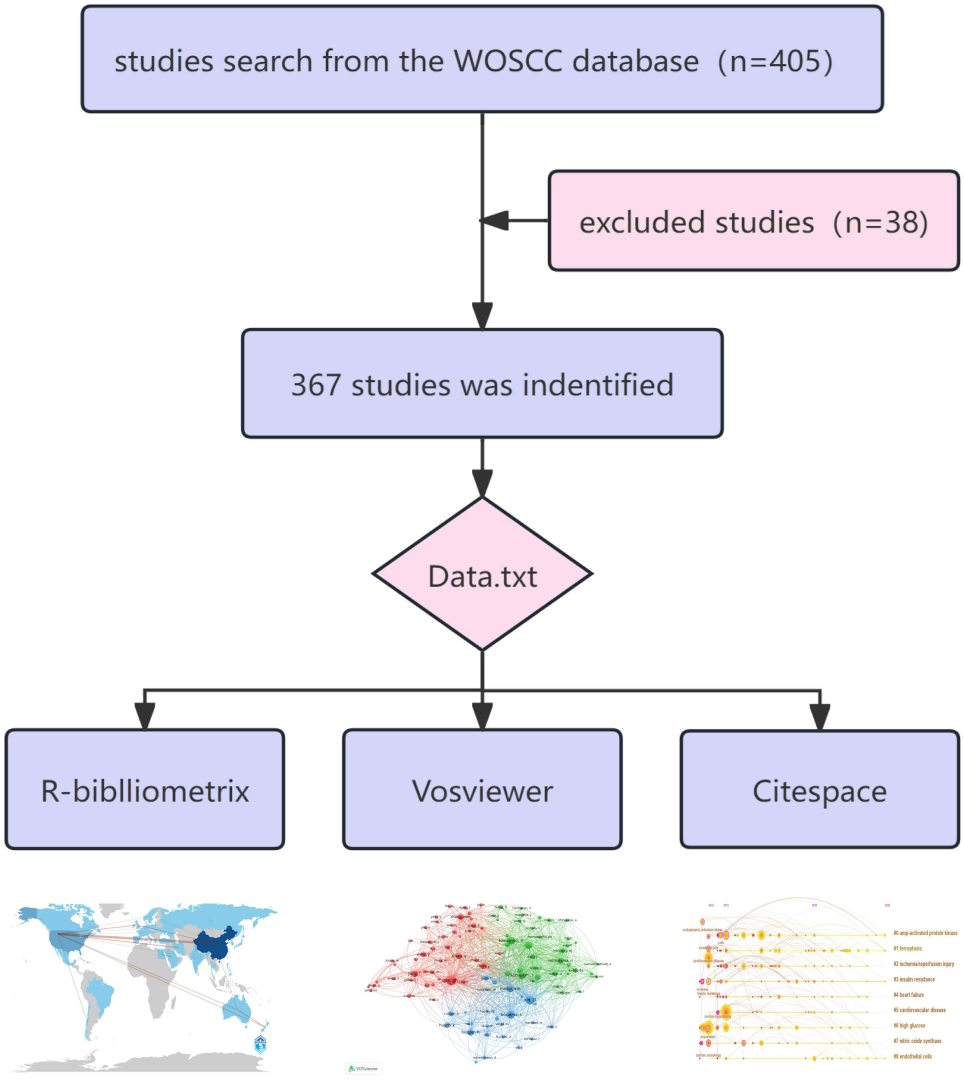

Figure 1 Flowchart of the literature search process.

mechanisms under varying pathological conditions. Although the annual publication volume has yet to exceed 60, the steady upward trajectory suggests continued growth and increasing research interest.

The analysis of research hotspots identified ten distinct thematic clusters within the collected literature. These clusters demonstrate the interdisciplinary nature of the field, encompassing contributions from cell biology, cardiovascular systems, molecular biochemistry, and pharmacology (see Figure 2B). Notably, recent studies reveal promising therapeutic mechanisms. For instance, transient receptor potential melastatin 2 (TRPM2) knockdown has been shown to reduce cardiomyocyte apoptosis and promote autophagy in DCM models by modulating the mitogen-activated protein kinase kinase(MEK)/extracellular regulated protein kinases(ERK) and Mammalian target of rapamycin complex 1(mTORC1) signaling pathways.[25] Similarly, mitochondrial aldehyde dehydrogenase has been implicated in regulating key processes such as protein kinase B(Akt) and glycogen synthase kinase-3β(GSK3β) activation, parkin-mediated mitochondrial autophagy, and overall mitochondrial function.[26] As a foundational discipline, cell biology maintains a central role in biological sciences, offering critical insights into life processes that have profound applications in medical research and practice.

Countries and Institutions

From 2014 to 2024, research on autophagy in DCM was conducted across 41 countries and regions. The top contributors, in terms of publication count, include China, the United States, India, Egypt, and Australia (Table 1).

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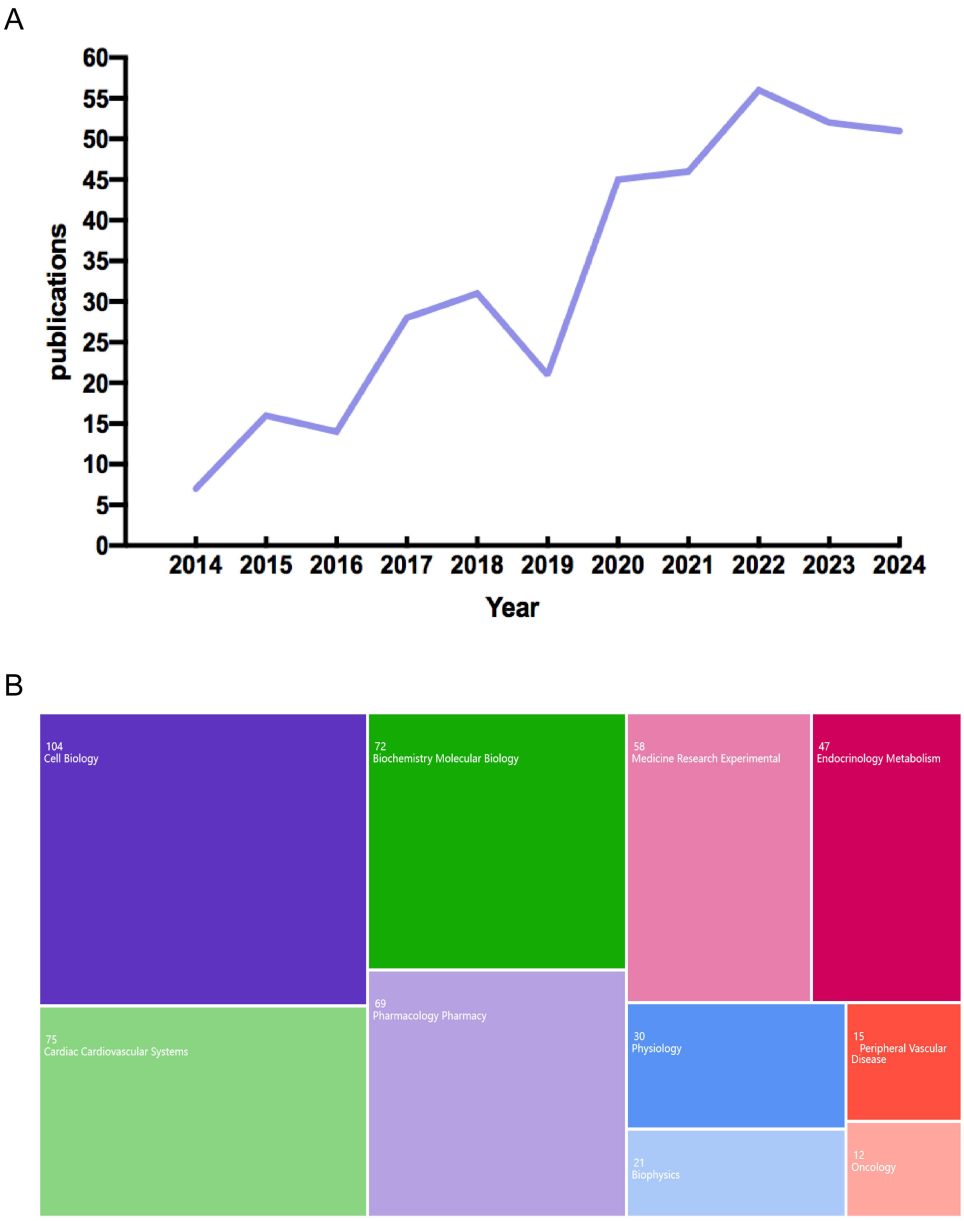

Figure 2 (**A**) Trends in annual publications for studies of autophagy in DCM. (**B**) Tree map of the top 10 subject categories.

China leads with 69.48% of the total publications but ranks sixth in the citation-to-publication ratio, averaging 28.02 citations per paper. In contrast, the United States achieves the highest citation-to-publication ratio, averaging 62.15 citations, reflecting the publication of high-quality, influential studies. Figure 3A visualizes the international cooperation network, highlighting robust collaborations between China, the United States, and other nations such as England and South Korea. Among the top 10 institutions by publication count, nine are based in China, while one is located in the United States (Table 2). A total of 505 organizations have contributed to studies on autophagy in DCM. Among these, the Fourth Military Medical University leads with 20 publications and 1117 citations, achieving an impressive average of 55.85 citations per article. Harbin Medical University ranks second with 14 papers garnering 586 citations (41.86 citations per article), followed by Shandong University with 12 papers and 454 citations (37.83 citations per article). Notably, the University of Wyoming achieves the highest citations per publication (CP) with 63.88, underscoring the exceptional quality of its fewer yet highly impactful studies. Collaborative networks reveal that the University of Wyoming has partnered with institutions such as the Fourth

Table 1 Top 10 Countries by Publication Productivity

RANK	Countries	Publications	Percentage (%)	Citations	Citation/Publication
1	China	255	69.48	7144	28.02
2	USA	78	21.25	4848	62.15
3	India	13	3.54	357	27.46
4	Egypt	12	3.27	211	17.58
5	Australia	9	2.45	372	41.33
6	Saudi Arabia	8	2.18	80	10
7	England	7	1.91	212	30.29
8	New Zealand	6	1.63	319	53.17
9	Japan	6	1.63	308	51.33
10	Canada	6	1.63	108	18

Military Medical University, Fudan University, Shanghai University, and Mashhad University of Medical Sciences, with a particularly strong relationship with Fudan University (Figure 3B). While the Fourth Military Medical University has engaged in some international collaborations, its partnerships are predominantly domestic, involving institutions such as Lanzhou University and Shaanxi Province People's Hospital. Geographic analysis of autophagy-related DCM research indicates significantly lower participation from Africa compared to other continents (Figure 3C). Among the top 10 contributing countries, Australia demonstrates the highest level of international collaboration, partnering with nations such as China, the United States, Switzerland, and New Zealand (Figure 3D). International cooperation remains critical for advancing research, fostering innovation, and enabling scientific progress in this field.

China's growing prominence in DCM research is linked to the rising prevalence of DM over the past two decades.[27] In 2015, the national cost of DM in China was approximately $51 billion, have surged to $165.3 billion by 2021.[28] Given its large population, diabetes research is imperative to improving public health and reducing healthcare costs. Traditional Chinese Medicine (TCM) has shown promising clinical outcomes in treating DM and its complications, particularly through autophagy enhancement.[29–31] However, while progress has been made, Chinese herbal compounds and extracts remain underexplored. Future research should prioritize elucidating their mechanisms of action and optimizing extraction techniques using modern methodologies to expand their clinical applications. In contrast, Africa has the highest global prevalence of undiagnosed DM cases, with 59.7% of the world's undiagnosed population concentrated in sub-Saharan Africa.[32,33] Despite this urgent need, research efforts in Africa are hindered by limited medical resources, inadequate infrastructure, brain drain, and restricted international collaboration. To address these challenges, countries with advanced research capabilities must foster collaborative exchanges with African institutions. Such cross-institutional and transnational partnerships can drive innovation, improve efficiency, and enhance scientific advancement, creating a shared pathway for global progress in healthcare and research.

Journals

Table 3 lists the ten journals with the highest publication counts in this field. *Biochimica et Biophysica Acta -Molecular Basis of Disease* and *Frontiers in Cardiovascular Medicine* lead with 14 articles each, followed by *Frontiers in Pharmacology* and *Oxidative Medicine and Cellular Longevity* (dropped), which have 11 articles each. The *Journal of Cellular and Molecular Medicine* ranks next with 8 articles. Figure 4A highlights the leading journals in this area, with many focusing on medicine, such as *Frontiers in Cardiovascular Medicine* and the *American Journal of Physiology - Heart and Circulatory Physiology*. Others, like *Biochimica et Biophysica Acta - Molecular Basis of Disease* and *Frontiers in Cell and Developmental Biology*, emphasize biological sciences. However, a high number of publications does not necessarily reflect a journal's academic influence. Journal impact is better measured through co-citation frequency, which gauges a journal's role within the scientific community. Table 4 identifies the most-cited journals, with *Circulation Research* leading with 1017 citations, followed by *Autophagy* (756 citations) and *Circulation* (734 citations). As illustrated in Figure 4B, the most frequently cited journals are predominantly focused on biology and

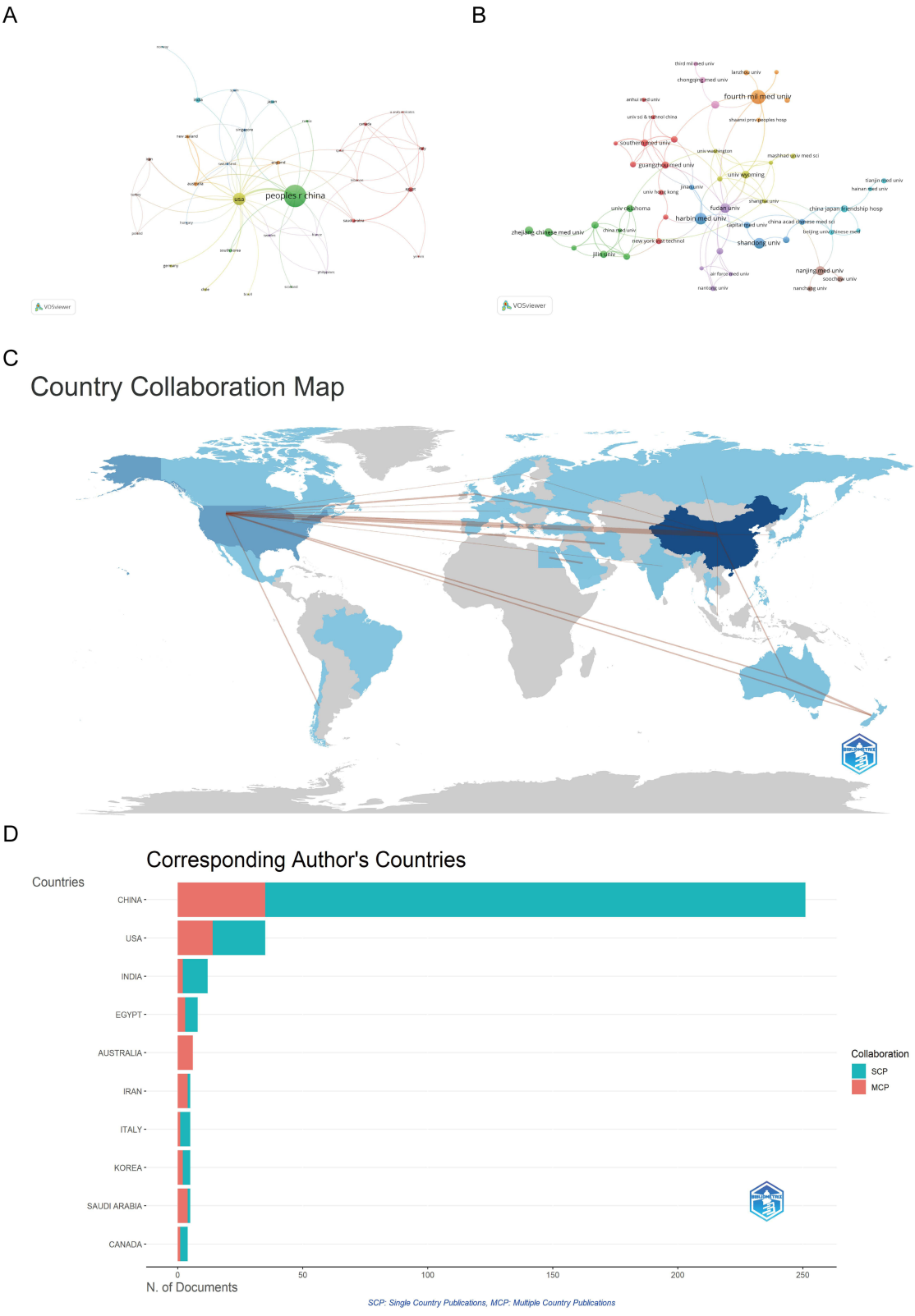

Figure 3 (**A**) Map of countries (or regions) cooperation networks. (**B**) Map of organizations' cooperation networks. (**C**) Country collaboration map. (**D**) Corresponding author's countries.

Table 2 Top 10 Organizations by Publication Productivity

RANK	Organizations	Publications	Citations	Citation/ Publication
1	Fourth Military Medical University	20	1117	55.85
2	Harbin Medical University	14	586	41.86
3	Shandong University	12	454	37.83
4	Fudan University	11	568	51.64
5	Nanjing Medical University	10	255	25.50
6	Zhejiang Chinese Medical University	9	125	13.89
7	University of Wyoming	8	511	63.88
8	Huazhong University Science & Technology	8	245	30.63
9	Zhejiang University	8	202	25.25
10	Wenzhou Medical University	7	219	31.29

Table 3 Top 10 Journals by Publication Productivity

RANK	Journals	Publications	Percentage (%)
1	Biochimica et Biophysica Acta-molecular Basis of Disease	14	3.81
2	Frontiers in Cardiovascular Medicine	14	3.81
3	Oxidative Medicine and Cellular Longevity	11	3.0
4	Frontiers in Pharmacology	11	3.0
5	Journal of Cellular and Molecular Medicine	8	2.18
6	Biomedicine & Pharmacotherapy	7	1.91
7	American Journal of Physiology-heart and Circulatory Physiology	6	1.63
8	Frontiers in Cell and Developmental Biology	6	1.63
9	Biochemical and Biophysical Research Communications	6	1.63
10	Frontiers in Endocrinology	6	1.63

medicine, with the majority classified within the Science Citation Index (SCI) Q1 or Q2 categories. Figure 4C demonstrates the temporal distribution of articles published in these journals, revealing a marked increase in publications across most journals in 2022. This surge reflects a growing emphasis on the intersection of autophagy and DCM within these publications. The subject distribution of academic research is further detailed through the superimposed dual map (Figure 4D), which highlights knowledge flow in autophagy-DCM studies. This diagram reveals that articles published in journals specializing in molecular biology, immunology, and clinical medicine are predominantly cited by studies in molecular biology and genetics journals. This citation pattern underscores the interdependence of these fields, with definitions and advancements in clinical medicine frequently influencing molecular biology and genetics research.

The journal *Biochimica et Biophysica Acta - Molecular Basis of Disease* provides a platform for exploring the molecular mechanisms underlying various diseases. Research published in this journal not only elucidates disease complexities but also lays the groundwork for personalized medicine and targeted therapies. Similarly, *Frontiers in Cardiovascular Medicine*, published by Frontiers Media S.A., covers diverse aspects of cardiovascular medicine, encouraging innovative investigations into treatment methodologies and mechanisms. High-impact journals such as *Circulation Research*, recognized as a leading publication in the medical field, significantly influence academic discourse. With a 2023 impact factor of 16.5 and SCI Q1 classification, *Circulation Research* exemplifies excellence in disseminating research across medicine, biology, and pharmacology. The synergistic relationship between biology and medicine has been further strengthened by advancements in biotechnology, including genomics, proteomics, and bioinformatics. These disciplines play a pivotal role in elucidating molecular disease mechanisms and enabling precise therapeutic approaches. Interdisciplinary research effectively integrates diverse knowledge and technologies, addressing complex challenges with innovative solutions. As vehicles for emerging trends and hot topics, academic journals must balance specialization and

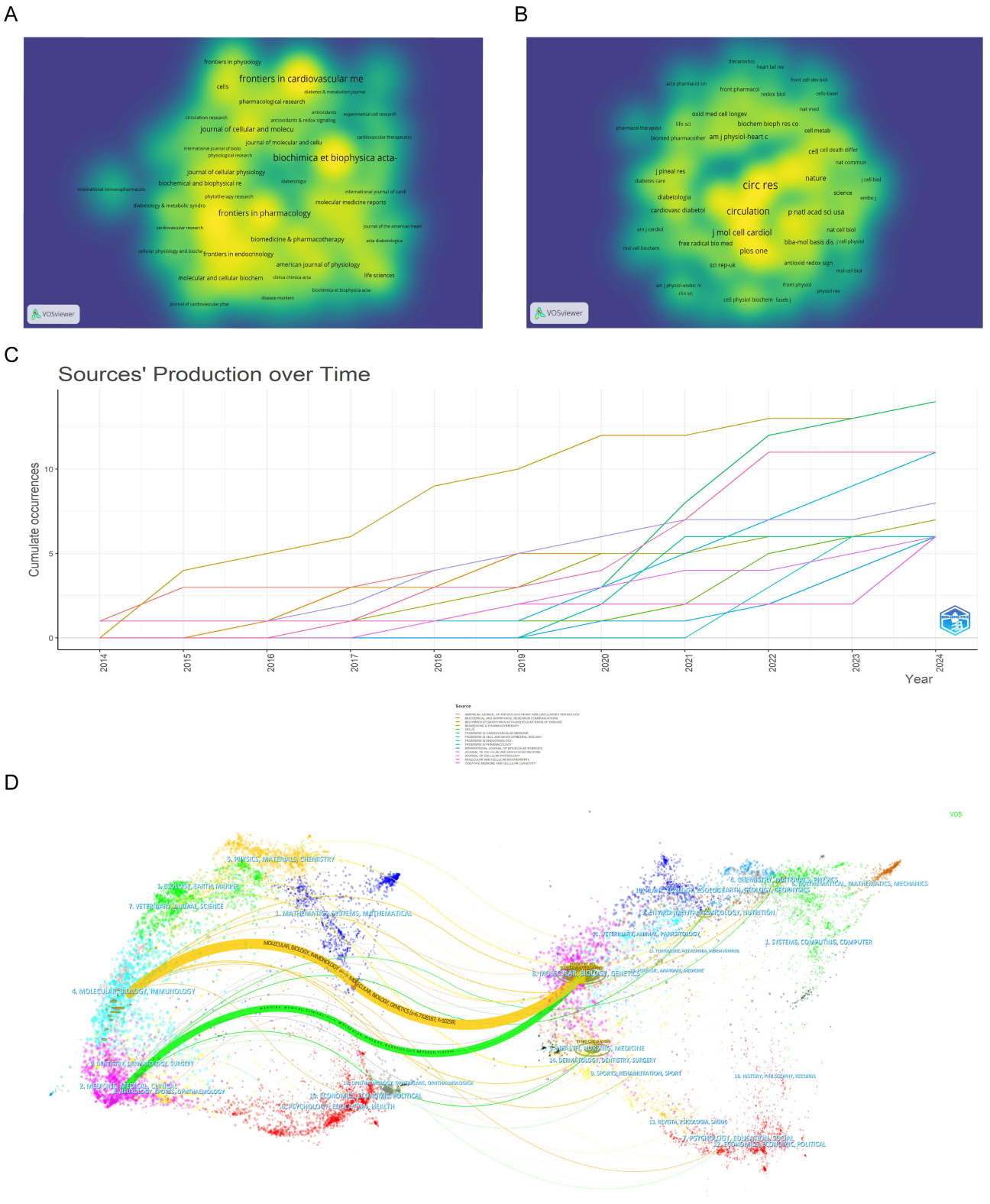

Figure 4 (**A**) Density map of journal publications. (**B**) Density map of journal co-citation analysis. (**C**) Sources' production over time. (**D**) Dual map of journals (The color track indicates the citation connections, with the cited journals positioned on the left and the citing journals on the right).

Table 4 Co-Citation Table of Journals

RANK	Journals	Co-Citation	Quartile in category
1	Circulation Research	1017	Q1
2	Autophagy	756	Q1
3	Circulation	734	Q1
4	Diabetes	729	Q1
5	Journal Of Biological Chemistry	641	Q2
6	Journal of Molecular and Cellular Cardiology	599	Q1
7	PLoS One	458	Q1
8	Nature	434	Q1
9	Cardiovasc Research	409	Q1
10	Proceedings of the National Academy of Sciences of the United States of America	406	Q1

innovation with a commitment to maintaining academic integrity. Recent years have seen the SCI delist journals for violations of academic ethics, such as data fabrication, citation manipulation, and other systemic issues. Strengthening the framework for scientific integrity and standardizing academic practices is essential for the long-term credibility and sustainability of scholarly publishing.

Authors

Table 5 highlights the ten most cited authors and the ten with the highest publication counts. Highly cited authors include Jia GH (166 citations), Xie ZL (115 citations), and Kanamori H (110 citations). Collectively, the 10 authors with the most publications have contributed 82 papers, accounting for 22.34% of all publications in this field. Sun Dongdong leads with 12 articles, followed by Wang Haichang with 11 and Lin Jie with 10. The co-citation diagram in Figure 5A identifies authors with the highest citation frequency, with 23 authors cited over 50 times, demonstrating significant scholarly impact. The collaborative network diagram (Figure 5B) reveals stable cooperative sub-networks among core research teams. This collaboration is reflected in the low centrality scores of most authors, with only three—Ren Jun, Zhang Mingming, and Zhang Yingmei—achieving a centrality score of 0.01, while others scored below 0.01. Figures 5C and D provide additional insights: most authors' publications were concentrated between 2017 and 2019, and the primary research topics include autophagy, oxidative stress, DCM, apoptosis, and associated mechanisms.

A review by the author Jia GH, published in *Circulation Research*, ranks among the top 10 most-cited references.[34] This review offers contemporary insights into the factors inducing DCM and explores mechanism-based strategies for its prevention and treatment, making a significant contribution to the field. Sun Dongdong, the most prolific author in this domain, highlights the potential of chitosan in modifying the surface properties of nanostructures to enhance their performance in drug delivery, release, biocompatibility, and related applications.[35] Collaborative research across

Table 5 Co-Citation Table and Author's Publications

RANK	Co-cited Authors	Citation	RANK	Authors	Publications
1	Jia, gh	166	1	Sun, Dongdong	12
2	Xie, zl	115	2	Wang, Haichang	11
3	Kanamori, h	110	3	Lin, Jie	10
4	Boudina, s	102	4	Zhang, Mingming	9
5	Sciarretta, s	101	5	Ren, Jun	9
6	Kobayashi, s	92	6	Zhang, Yingmei	7
7	Yang, f	87	7	Hu, Jianqiang	6
8	Chen, y	79	8	Li, Congye	6
9	Mellor, km	77	9	Wang, Shanjie	6
10	Zhang, mm	76	10	Cheng, Zheng	6

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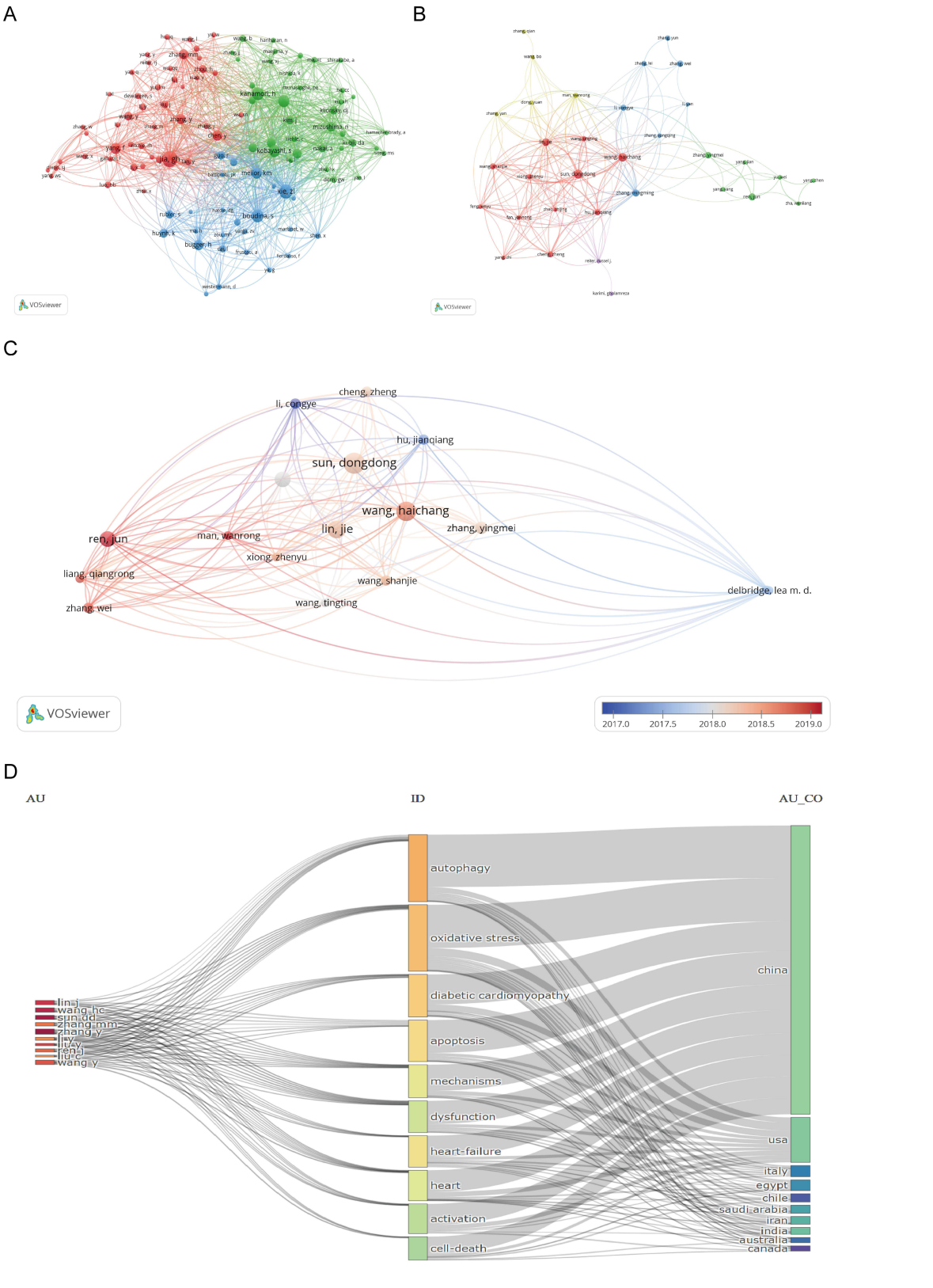

Figure 5 (**A**) Authors' co-citation visualization map. (**B**) Authors' cooperation network. (**C**) Authors' timeline map. (**D**) Sankey diagram (authors-keywords-countries).

institutions and teams has long-term benefits for advancing research and development. Thus, scholars are encouraged to actively participate in technology exchange and cooperative learning. In 2016, Japanese scientist Yoshinori Ohsumi was awarded the Nobel Prize in Physiology or Medicine for elucidating the molecular mechanisms of autophagy, which spurred a surge in global interest in this field over the following three years.[36,37] However, research emphases vary across countries. For instance, China prioritizes the interplay between autophagy and oxidative stress, whereas the United States focuses more on oxidative stress and its relationship with DCM. These distinctions reflect differing national research paradigms and underscore opportunities for collaboration and integration to advance the global understanding of these mechanisms.

Co-Cited References

As summarized in Table 6, the top 10 most-cited publications include contributions from the journal *Diabetes*, which appears prominently with two articles in the top 10 list. Figure 6A highlights frequently cited works, with recent documents from 2022 coexisting alongside influential texts from as early as 1972. Notably, most highly cited articles were published between 2010 and 2020 (Figure 6B).

Diabetes, a journal of the American Diabetes Association, has significantly influenced diabetes-related research by consistently publishing high-quality articles. One notable study, *Improvement of Cardiac Functions by Chronic Metformin Treatment Is Associated With Enhanced Cardiac Autophagy in Diabetic OVE26 Mice* by Xie ZL, demonstrates that chronic activation of AMP-activated protein kinase (AMPK) by metformin can mitigate cardiomyopathy by upregulating autophagy in diabetic OVE26 mice.[38] This finding suggests AMPK stimulation as a promising therapeutic strategy for DCM. Another key article, *Dissociation* of Bcl-2–Beclin 1 Complex by Activated AMPK Enhances Cardiac Autophagy and Protection Against Cardiomyocyte Apoptosis in *Diabetes* by He CY, reveals that AMPK activation facilitates the dissociation of the B-cell lymphoma-2 (Bcl-2) and beclin-1 complex. This dissociation restores autophagy and protects against cardiac cell apoptosis, presenting a crucial mechanism for DCM prevention.[39] Collectively, these two studies provide foundational insights into the role of autophagy in DCM and the therapeutic potential of AMPK activation. A closer analysis of these studies' references shows a blend of recent and pre-2000 publications, demonstrating the enduring relevance of older research. Modern technologies applied to these historical findings enable the

Table 6 Co-Citation Table of Literature

RANK	Title	Journal	Author(s)	Total Citations
1	Improvement of Cardiac Functions by Chronic Metformin Treatment Is Associated With Enhanced Cardiac Autophagy in Diabetic OVE26 Mice	*DIABETES*	Xie ZL	87
2	Diabetic Cardiomyopathy	*CIRCULATION RESEARCH*	Jia GH	83
3	Autophagic adaptations in diabetic cardiomyopathy differ between type 1 and type 2 diabetes	*AUTOPHAGY*	Kanamori H	68
4	Diminished Autophagy Limits Cardiac Injury in Mouse Models of Type 1 Diabetes	*JOURNAL OF BIOLOGICAL CHEMISTRY*	Xu XM	65
5	Dissociation of Bcl-2–Beclin1 Complex by Activated AMPK Enhances Cardiac Autophagy and Protects Against Cardiomyocyte Apoptosis in Diabetes	*DIABETES*	He CY	58
6	New type of cardiomyopathy associated with diabetic glomerulosclerosis	*AMERICAN JOURNAL OF CARDIOLOGY*	Rubler S	54
7	Autophagy and mitophagy in diabetic cardiomyopathy	*BIOCHIMICA ET BIOPHYSICA ACTA-MOLECULAR BASIS OF DISEASE*	Kobayashi S	48
8	Diabetic Cardiomyopathy Revisited	*CIRCULATION*	Boudina S	47
9	The role of autophagy in cardiomyocytes in the basal state and in response to hemodynamic stress	*NATURE MEDICINE*	Nakai A	45
10	Molecular mechanisms of diabetic cardiomyopathy	*DIABETOLOGIA*	Bugger H	41

Figure 6 (**A**) Literature co-citation network. (**B**) Top 10 co-citated literature.

extraction of new insights, ensuring their continued contribution to contemporary research. This cross-era citation practice exemplifies the continuity of academic knowledge and underscores the principles of scientific progress.

Keywords

By analyzing keywords, researchers can quickly assess the current state and developmental trajectory of this field. As shown in Table 7, the keyword "autophagy" is the most frequently occurring, with 256 mentions, followed by "diabetic cardiomyopathy" (248 mentions) and "oxidative stress" (139 mentions). Keyword co-occurrence highlights key research focuses, including modes of cell death, pathological changes in diseases, and the mechanisms underlying these processes (Figure 7A). Keyword clustering further identifies research hotspots and trends. Figure 7B reveals that primary research

Table 7 Table Showing High-Frequency Keywords

RANK	Keyword	Counts
1	Autophagy	256
2	Diabetic cardiomyopathy	248
3	Oxidative stress	139
4	Apoptosis	119
5	Heart	70
6	Mechanisms	63
7	Heart failure	63
8	Dysfunction	55
9	Activation	53
10	Cell death	48

topics include AMPK, ferroptosis, ischemia/reperfusion injury, insulin resistance, and heart failure. In 2024, leading research directions emphasize AMPK, ferroptosis, insulin resistance, and endocrine cells (Figure 7C). The keyword burst diagram illustrates the timing and evolution of keyword trends, with ”cardiac autophagy” showing the strongest burst intensity (Figure 8), underscoring its pivotal role in research. Additionally, ”cardiac hypertrophy” demonstrates the

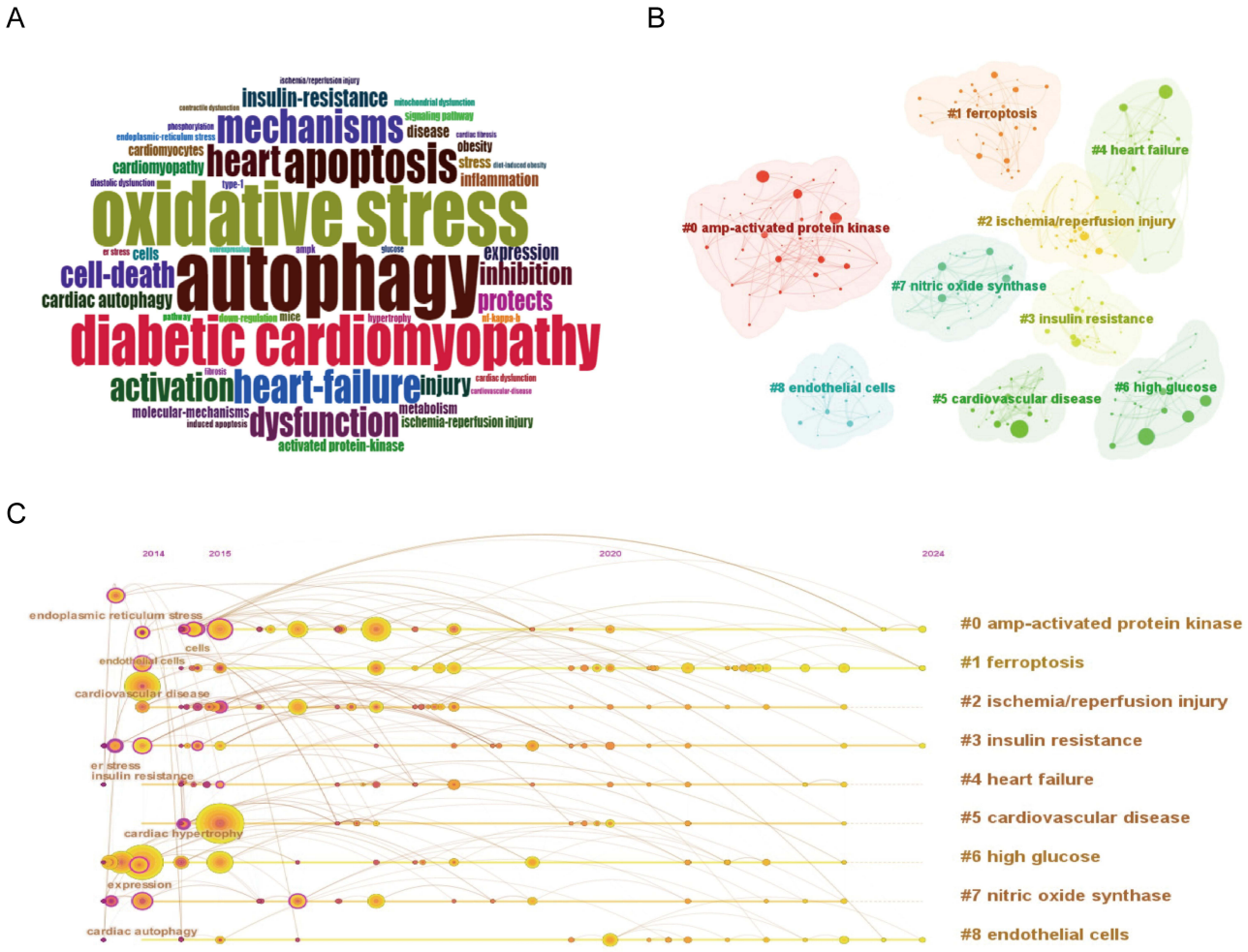

Figure 7 (**A**) Word cloud of keywords from the included studies. (**B**) Keywords clustering network diagram. (**C**) Timeline cluster graph of keywords.

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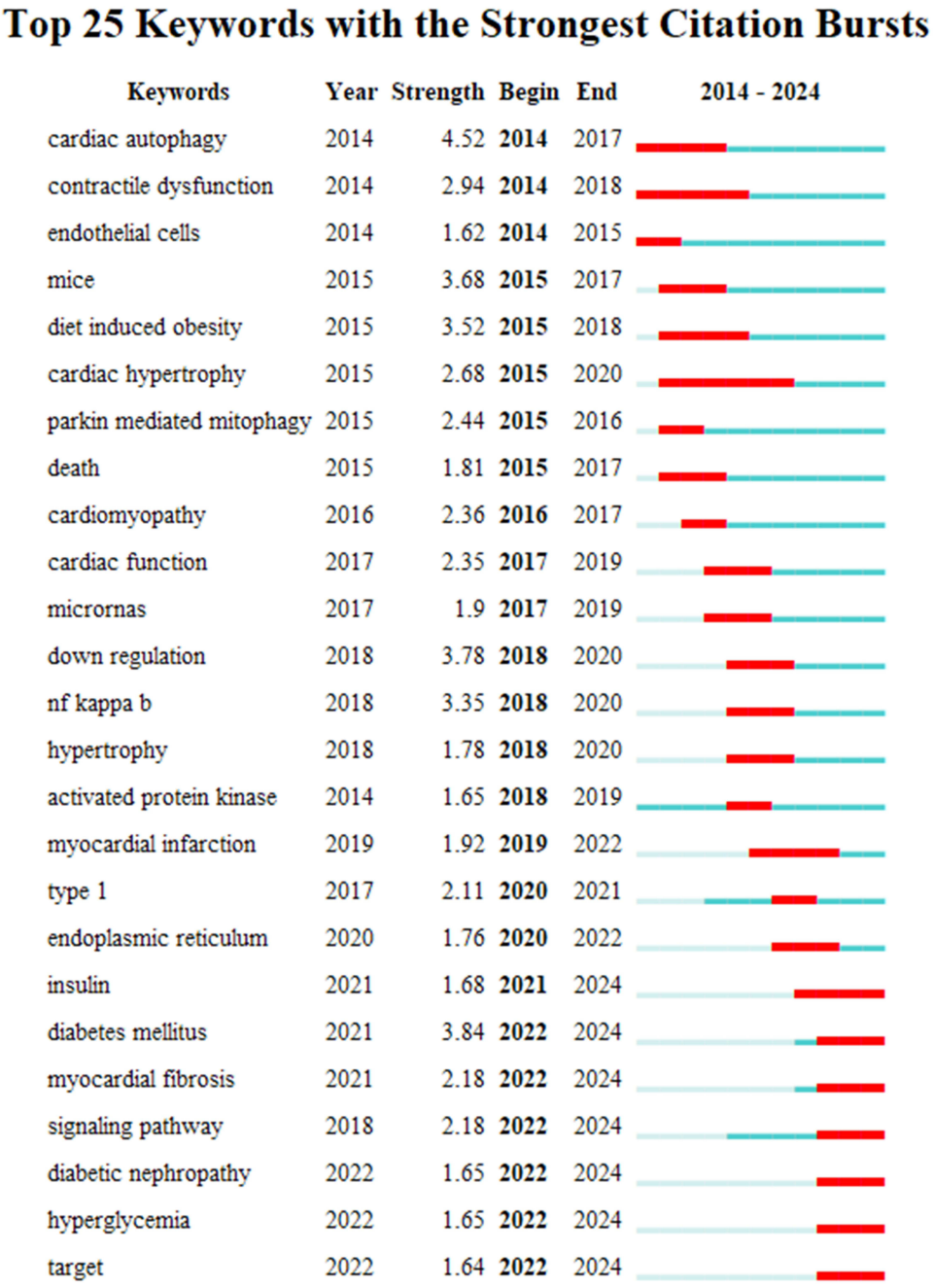

Figure 8 Top 25 keywords with the strongest citation bursts. Red lines indicate that the years when the keyword was used frequently. Green lines indicate the years when the keyword was not used frequently during 2014–2024.

longest burst duration, reflecting its sustained relevance. Over the past three years, emerging keywords—such as DM, myocardial fibrosis, signaling pathway, target, diabetic nephropathy, and hyperglycemia—highlight current research priorities and suggest potential future directions.

In DCM, oxidative stress contributes to pathogenesis by increasing reactive oxygen species (ROS) production and impairing antioxidant defenses.[40,41] Conversely, autophagy mitigates oxidative stress and enhances myocardial function by clearing damaged organelles and cellular debris.[42,43] Thus, regulating autophagy presents a promising therapeutic strategy for DCM. Regarding cell death mechanisms, autophagy and apoptosis are critical and intricately linked.[44] Autophagy can reduce apoptosis by removing damaged cellular components, whereas impaired or inhibited autophagy may exacerbate apoptosis.[45,46] This bidirectional relationship underscores their mutual regulatory role within cells. From

a signaling pathway perspective, AMPK remains a central focus in the study of diabetes and its complications. AMPK activation inhibits ferroptosis, improves insulin resistance, and maintains cellular energy balance by regulating fatty acid metabolism and the antioxidant system. These effects collectively reduce myocardial injury and improve cardiac function.[47,48] These findings offer promising avenues for developing novel therapeutic strategies to treat DCM.

Discussion

General Information

A detailed examination of bibliometric data reveals a significant growth in research on autophagy and DCM, likely driven by rising DCM incidence and mortality rates, as well as increasing interest in autophagy's role in disease mechanisms. Countries in Asia, North America, and Oceania have conducted numerous studies, demonstrating a strong trend toward international collaboration. Such transnational cooperation is essential for advancing global medical research and addressing shared health challenges.

A notable contribution to this field comes from Sun Dongdong of the Fourth Military Medical University, in collaboration with the First Hospital of Lanzhou University. Their study revealed that transforming growth factor-β1 (TGF-β1)-containing exosomes from cardiovascular endothelial cells mediate cardiac fibroblast activation under high-glucose conditions.[49] This research highlights the importance of partnerships, as the team collaborates with prominent domestic institutions such as Fudan University and Huazhong University of Science and Technology, as well as international organizations such as the University of Wyoming. Expanding such collaborative efforts will foster innovation and enable more effective solutions to the challenges posed by DCM and other diseases.

Among the co-cited journals, *Circulation Research* stands out as the most frequently cited, reflecting its pivotal role in disseminating research on this topic. Notably, Jia GH's 2018 publication has garnered significant attention for its high citation count, establishing the author as a leading contributor in the field. Extensive research on autophagy in DCM has been conducted globally, yielding important findings. For instance, UCF101, a selective protease inhibitor, has been shown to ameliorate structural and functional cardiac alterations associated with diabetes by regulating AMPK-mediated mitochondrial autophagy.[50] Additionally, studies have demonstrated that inhibiting glycosphingolipids in myocardial cells enhances Sirtuin3 protein expression, scavenges intracellular ROS, and restores mitochondrial autophagy homeostasis, thereby mitigating myocardial hypertrophy.[51] Despite these advances, most research remains foundational, underscoring the need for further clinical investigations.

Hot Topics and Frontiers

Keyword analysis reveals that research on the mechanisms underlying autophagy in DCM continues to be a prominent focus. Burst analyses of keywords over the past three years highlight topics such as diabetes, hyperglycemia, cardiac fibrosis, associated complications, signaling pathways, and therapeutic targets. Notably, significant progress has been made in understanding autophagy in diabetic neuropathy.[52–54] By contrast, the interplay between DCM and autophagy remains a relatively underexplored yet promising area of study. Investigating the pathogenesis and therapeutic strategies targeting autophagy in DCM offers valuable insights for drug development and clinical applications.

Mechanism Research

Mechanism of Autophagy

Autophagy is a cellular process that transports abnormal components—such as unfolded proteins, aging-related damaged organelles, and accumulated harmful substances—to lysosomes or vacuoles for digestion, degradation, and recycling.[55,56] This mechanism not only provides energy but also maintains cellular homeostasis, functioning as a self-protective strategy for cells.[57] Autophagy is classified into three main types based on the pathways involved in binding degradation products to lysosomes: conventional autophagy, selective autophagy, and molecular-partner-mediated autophagy.[58,59] Although baseline autophagy levels are generally low, the process is activated under stress or adverse conditions to maintain homeostasis.[60] The primary steps in autophagy include initiation, formation and extension of phagocytic vesicles, autophagosome maturation, autophagy-lysosome system assembly, and substrate degradation.[61,62]

This pathway plays a critical role in biological processes, offering theoretical foundations and potential targets for disease treatment.

Mechanism of Autophagy in DCM

DCM, a chronic microvascular complication of the myocardium resulting from prolonged diabetes, is closely linked to autophagy dysfunction.[63] Under normal conditions, autophagy mitigates oxidative stress, inflammation, and apoptosis in myocardial tissue by clearing damaged mitochondria, the endoplasmic reticulum, free fatty acids, and ROS.[64–67] This protective process is crucial for preventing and treating DCM.[68] Conversely, autophagy inhibition compromises these clearance mechanisms, leading to the accumulation of harmful substances that exacerbate DCM progression.[69] Excessive autophagy activation, however, can degrade normal organelles and proteins, impairing cellular function and further aggravating DCM.[70,71] Emerging evidence suggests that the impact of autophagy dysregulation in DCM depends on the type, stage, and severity of the disease.[72,73] Therefore, targeted modulation of autophagy presents a promising therapeutic approach for managing myocardial injury in DCM.

In hyperglycemia, metabolic disorders elevate oxidative stress and inflammatory responses, collectively contributing to tissue damage.[74] This process involves increased levels of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which further accelerate disease progression.[75] Diabetes affects multiple organs and systems, with recent research highlighting the impact of diabetic neuropathy on reparative capabilities and immune responses.[76,77] Autophagy plays a pivotal role in regulating immunity and cellular repair, suggesting mechanistic links between DCM and diabetic polyneuropathy. Studies have shown that mitochondrial function in diabetic patients is impaired, characterized by reduced adenosine triphosphate (ATP) production, heightened oxidative stress, and abnormal mitochondrial morphology.[78,79] Observations in a DCM mouse model revealed mitochondrial swelling and autophagy, while upregulation of mitochondrial autophagy has been associated with diabetic neuropathic pain (DNP).[80] For example, dimethyloxalylglycine, a hypoxia-inducible factor-1 agonist, has been shown to enhance mitochondrial function and alleviate pain.[81] The intersection of autophagy in DCM and DNP suggests novel therapeutic approaches, with advancements in neurobiological and genetic strategies for DNP offering potential insights for DCM treatment.

Pathways and Major Proteins

The primary signaling pathways regulating autophagy are categorized as mTOR-dependent and mTOR-independent.[82] The mTOR-dependent pathways include the AMPK pathway, the phosphoinositide 3-kinase (PI3K)/Akt pathway, and the mitogen-activated protein kinase (MAPK) pathway.[83] In contrast, mTOR-independent pathways involve beclin-1 and p53 signaling.[84,85] DCM, as a multifaceted condition, engages a wide array of signaling pathways,[86–88] many of which are implicated in its pathogenesis. Modulating autophagy-related pathways could yield therapeutic insights for managing DCM.

AMPK

The AMPK signaling pathway is central to regulating cellular processes. When activated, AMPK promotes autophagy, thereby maintaining cellular homeostasis and energy balance.[89] It exerts anti-inflammatory, anti-apoptotic, and autophagy-enhancing effects by modulating myocardial energy metabolism.[90] Neuregulin-4 activates autophagy through the AMPK/mTOR pathway, alleviating DCM.[91] However, inhibition of autophagy or compromise of the AMPK/mTOR pathway diminishes these beneficial effects. Additionally, studies show that metformin enhances the survival of random-pattern skin flaps by promoting angiogenesis and inhibiting apoptosis and oxidative stress.[92] These effects are attributed to the increased autophagy mediated by the activation of the AMPK-mTOR-TFEB signaling pathway. This regulation mitigates ischemia-reperfusion injury, improves heart failure, reduces cardiac remodeling, and addresses vascular endothelial dysfunction.[93,94] However, caution is warranted with AMPK activators; for instance, while MK-8722, an AMPK agonist, improved diabetes outcomes in animal models, it also induced cardiac hypertrophy.[95] These findings underscore the need to balance benefits and risks when targeting AMPK for therapeutic purposes.

PI3K/Akt

The PI3K/Akt signaling pathway is integral to DCM pathogenesis, influencing blood glucose regulation, lipid metabolism, endothelial cell protection, inflammation reduction, cardiac function improvement, fibrosis resistance, and myocardial apoptosis modulation.[96–98] Studies in hyperglycemia-treated H9C2 cells have shown that microRNA-494 regulates cardiovascular apoptosis and autophagy via the PI3K/Akt/mTOR pathway.[99] Dysregulation of this pathway can lead to complications such as prolonged QT intervals, attributed to increased persistent sodium currents from PI3K pathway dysfunction.[100] This highlights the significance of regulating the PI3K/Akt signaling pathway in the diabetic heart to maintain normal cardiac electrophysiological characteristics. The dysregulation of the PI3K/AKT signaling pathway in DCM can have detrimental effects. Such dysregulation exacerbates myocardial apoptosis and fibrosis, compromising the protective effects of ischemic preconditioning in diabetic hearts.[101] Thus, targeting the PI3K/Akt signaling pathway offers a promising avenue for addressing diabetic cardiac complications.

MAPK

The MAPK family includes numerous members, with the p38 MAPK signaling pathway playing a pivotal role in the progression of DCM.[102–104] Activation of p38 MAPK is associated with insulin resistance, endothelial dysfunction, and accelerated atherosclerosis—key contributors to the advancement of type 2 diabetes mellitus (T2DM).[105–107] Additionally, research has demonstrated that ivabradine can improve cardiac function in streptozotocin-induced DCM by inhibiting c-Jun N-terminal kinase (JNK) and p38 MAPK-mediated inflammation and apoptosis.[104] The p38 MAPK pathway is activated by oxidative stress and is involved in cell differentiation, survival, and apoptosis.[108] These findings suggest that targeting this pathway through the inhibition of JNK and p38 MAPK activities could serve as an effective strategy for preventing and treating DCM.

Beclin-1

Beclin-1 is integral to initiating autophagic lysosome formation through phosphorylation.[109] In mouse models of DCM, beclin-1 expression is inversely correlated with myocardial fibrosis and positively correlated with myocardial cell apoptosis.[110] Studies have shown that beclin-1 haploinsufficiency alleviates high-fat diet-induced myocardial injury by suppressing alternative mitophagy.[111] Furthermore, downregulation of lncRNA MEG3 has been shown to inhibit the mTOR signaling pathway, restore beclin-1 expression, and correct autophagy abnormalities in myocardial cells.[112] Other studies reveal that hyperglycemia elevates beclin-1 expression, while inhibiting this protein mitigates nerve axon damage.[113] These findings indicate that fluctuations in beclin-1 levels are closely linked to the onset and progression of DCM, highlighting its potential as a therapeutic target.

p53

The p53 signaling pathway is critical for regulating cell cycle progression, DNA damage response, and apoptosis.[114,115] Evidence suggests that pifithrin-α, a p53 inhibitor, prevents cardiomyocyte apoptosis in high-glucose environments.[116] Other studies report that the acetylation of p53 is significantly elevated in diabetic mouse heart tissue, and suppressing this modification enhances cardiac function.[117] Additionally, astragaloside IV has been shown to protect the sciatic nerve in diabetic rats by reducing p53 activity and apoptosis.[118] These findings underscore the importance of modulating p53 activity in addressing DCM-related complications. Therapeutic strategies could involve targeting p53-associated pathways or utilizing natural compounds and pharmacological agents to mitigate its effects on cell death and tissue damage.

Rapeutic Method

SGLT2 Inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a novel class of oral antidiabetic agents that not only improve glycemic control but also offer significant cardiovascular protection.[119] Hyperglycemia drives the accumulation of advanced glycation end products and oxidative stress, leading to myocardial extracellular matrix synthesis, deposition, and eventual fibrosis.[120] Inflammatory cells infiltrate myocardial tissue in DCM, releasing factors that activate nod-like receptor pyrin domain-containing 3 (NLRP3) inflammasomes. This activation increases the expression of downstream

cytokines such as interleukin-1β (IL-1β) and interleukin-18 (IL-18), which, in turn, promote macrophage infiltration and exacerbate myocardial fibrosis.[121,122] Subclinical myocardial dysfunction, secondary to fibrosis, can be noninvasively detected using speckle tracking echocardiography, with reduced myocardial strain parameters correlating with greater fibrosis.[123,124] Although SGLT2 inhibitors have shown promise in reducing fibrosis and inflammation, as well as enhancing systolic function, further studies are needed to assess their impact on myocardial strain parameters. For example, dapagliflozin has been shown to improve DCM by modulating the Akt/mTOR signaling pathway, while empagliflozin ameliorates sunitinib-induced cardiac dysfunction via AMPK–mTOR-mediated autophagy regulation.[125,126] These findings reinforce the cardioprotective potential of SGLT2 inhibitors in DCM management. Studies indicate that canagliflozin offers protection against DCM by reducing fibrosis, preserving myocardial integrity, and enhancing mitochondrial function.[127] This class of inhibitors has been clinically used for over a decade, providing multiple benefits such as reduced cardiovascular and renal risks, weight loss, lower blood pressure, protection of islet β-cell function, and improved insulin sensitivity.[128] However, their use is associated with notable drawbacks, including an increased risk of urogenital infections, potential hypoglycemia, ketoacidosis, and the possibility of fractures and lower limb amputations.[129] To maximize therapeutic outcomes, future research should prioritize elucidating the precise mechanisms of SGLT2 inhibitors, optimizing their design, and addressing these limitations. A global, collaborative effort among researchers is essential to develop safer and more effective treatments for diabetes.

Traditional Chinese Medicine Formula

As a cornerstone of traditional Chinese culture, TCM has received significant government support in China, fostering remarkable progress in research. Recent advancements highlight TCM's role in regulating autophagy to manage DM and its complications. For instance, the Yunpi-Huoxue-Sanjie formula has been shown to mitigate DCM by promoting autophagy, while the Shengjie Tongyu decoction regulates cardiovascular autophagy by modulating the ROS-PI3K/Akt/mTOR axis through LncRNA H19.[130,131] Additionally, the Chinese herbal medicine Fufang Zhenzhu Tiaozhi improves DCM by correcting abnormal lipid metabolism and mitochondrial dynamics in diabetic mouse models.[132] The bidirectional regulatory functions of TCM offer unique advantages in managing chronic diseases, coupled with minimal side effects. However, challenges persist, including inconsistent quality control, limited dosage forms, and suboptimal routes of administration. Addressing these issues requires standardized cultivation and harvesting of medicinal herbs, improved processing techniques, advanced formulation technologies, and expanded internationalization efforts to elevate TCM's global presence.

Native Compounds

Natural compounds, derived from animals, plants, marine organisms, insects, and microorganisms, hold immense potential in medicine and food sciences, particularly in drug development. Extensive research has revealed their therapeutic potential in managing DCM. Curcumin protects against DCM by inducing autophagy and reducing apoptosis, while berberine improves cardiac function by altering myocardial lipidomic profiles in DCM models.[133,134] Urolithin A, identified as a mitochondrial autophagy inducer, has demonstrated efficacy in both in vivo and in vitro models of DCM.[135] Fructus Zanthoxyli extract enhances glycolipid metabolism in T2DM through the activation of the AMPK/PI3K/Akt pathway, and Lindera lactone mitigates myocardial hypertrophy and inflammation by inhibiting the MAPK/ATF6 signaling pathway.[136,137] Despite their diverse biological and pharmacological activities, challenges such as complex compositions, low extraction yields, and limited solubility hinder their broader application. Advancements in modern technologies, including structural transformation, chemical synthesis, and biotransformation, are vital to overcoming these obstacles and expanding the utility of natural compounds in medical science.

Strengths and Limitations

Existing bibliometric studies address diverse topics, including ferroptosis and other cell death mechanisms associated with diabetic complications, as well as autophagy in cardiovascular diseases, thus encompassing a wide range of research areas.[138–141] This study specifically focuses on the relationship between autophagy and diabetes, analyzing relevant literature, summarizing key findings, and identifying research hotspots. Its goal is to provide valuable insights and guide

future research in this domain. However, several limitations must be acknowledged. First, the pathogenesis of DCM involves multiple forms of cell death, with autophagy being only one aspect. Second, the analysis is confined to data from the WOSCC, potentially limiting the scope and robustness of conclusions. Third, only English-language publications were considered, which may exclude important findings from other languages. Fourth, the search outcomes are influenced by the selected keywords, introducing a degree of subjectivity. Finally, delays in the publication of some cited studies could lead to inaccuracies in evaluating citation rates. Additionally, the study's timeframe, spanning from 2014 to 2024, restricts the evaluation of trends over a longer duration. Future research should prioritize extensive, large-scale, multicenter studies to validate and expand upon these findings.

Conclusion

This study employs bibliometric methods to analyze English-language literature on autophagy in DCM from 2014 to 2024, using the WOSCC database. Through visual analysis, it identifies key research hotspots and trends, demonstrating sustained growth in research activity. Investigations into autophagy have expanded beyond its biological functions to explore its therapeutic potential. Previous studies have established a strong link between autophagy and DCM, suggesting that this field will continue to evolve. Advancing research into pathogenesis, therapeutic mechanisms, and clinical applications is essential for the development of novel treatments. Traditional medicine also represents an underexplored area, where ancient prescriptions could be optimized and innovated using modern analytical techniques. With ongoing advancements in science and technology, coupled with sustained research efforts, effective autophagy-based strategies for addressing DCM and its complications could significantly enhance global health outcomes.

Abbreviation

DM, Diabetes mellitus; DCM, Diabetic cardiomyopathy; WOSCC, Web of Science core collection; MEK, Mitogen-activated protein kinase kinase; ERK, Extracellular regulated protein kinases; mTORC1, Mammalian target of rapamycin complex 1; Akt, Protein kinase B; GSK3β, Glycogen synthase kinase-3β; CP, Per publication; TCM, Traditional Chinese medicine; SCI, Science citation index; AMPK, AMP-activated protein kinase; Bcl-2, B-cell lymphoma-2; ROS, Reactive oxygen species; TGF-β1, Transforming growth factor-β1; TNF-α, Tumor necrosis factor-alpha; IL-6, Interleukin-6; ATP, Adenosine triphosphate; DNP, Diabetic neuropathic pain; PI3K, Phosphoinositide 3-kinase; MAPK, Mitogen-activated protein kinase; T2DM, Type 2 diabetes mellitus; JNK, C-Jun N-terminal kinase; SGLT2, Sodium-glucose co-transporter 2; NLRP3, NOD-like receptor family pyrin domain containing 3; IL-1β, Interleukin-1β; IL-18, Interleukin-18.

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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: the Journal of Multidisciplinary Healthcare; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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