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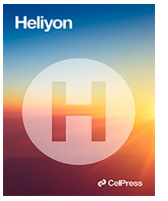

Research article

Research trends and hotspots of ferroptosis in neurodegenerative diseases from 2013 to 2023: A bibliometrics study

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ABSTRACT

Background: With the aging population, the incidence of neurodegenerative diseases increases yearly, seriously impacting human health. Various journals have published studies on the pathogenesis of ferroptosis in neurodegenerative diseases. However, bibliometric analysis in this field is still lacking. The study aims to visually analyze global research trends in this field over the past decade.

Methods: The articles and reviews regarding ferroptosis in neurodegenerative diseases were retrieved from the Web of Science on September 1, 2023. Citespace [version 6.2. R4 (64-bit)] and VOSviewer (version 1.6.18) were used to conduct the bibliometric and knowledge-map analysis.

Results: In total, 370 studies were included in the paper and ranked by their citation frequency. Many articles on ferroptosis in neurodegenerative diseases have been published in the past decade. The country, institution, author, and journal with the highest publications were China, Guangzhou Medical University, Maher, Pamela, and Free Radical Biology And Medicine, respectively. The analysis of keyword co-occurrence indicated that research frontiers were molecular mechanisms of ferroptosis in neurodegenerative diseases, especially a few key pathways that triggered ferroptosis in these diseases, including lipid peroxidation signaling, iron metabolism, and GSH/GPX4 signaling. In addition, ferroptosis inhibitors such as liproxstatins and ferrostatins had protective effects in animal models of neurodegenerative diseases. Therefore, future attention should also be focused on therapeutic drugs that target ferroptosis.

Conclusion: This study comprehensively analyzed the publications on ferroptosis in neurodegenerative diseases from a bibliometric perspective. Research on this topic is currently expanding at a rapid pace, and the China holds a leading position in this field by its scientific achievements and productivity. Moreover, the research frontiers were molecular mechanisms of ferroptosis in neurodegenerative diseases and developing targeted therapeutic drugs. In summary, our results showed an all-sided overview of the knowledge atlas and a valuable reference for the future research in this field.

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1. Introduction

Ferroptosis is an iron-dependent form of cell death, which is mainly caused by glutathione (GSH) depletion, decreased glutathione peroxidase 4 (GPX4) activity, and imbalance between intracellular ROS production and degradation [1,2]. Ferroptosis is distinct from other cell death, such as apoptosis and necrosis [3]. Ferroptosis is defined morphologically by reduced cell volume, rupture of the outer mitochondrial module, increased density of the mitochondrial membrane, and loss of mitochondrial cristae. However, the cell membrane remains intact, the nucleus size is normal, and chromatin concentration does not change [4,5]. Biochemically, during peroid of ferroptosis, the synthesis of GSH and the activity of GPX4 in cells are significantly reduced, leading to reduced lipid peroxidase metabolism [6]. Genetically speaking, ferroptosis is a biological process regulated by multiple genes, mainly involving genetic changes in iron homeostasis and lipid peroxidation metabolism [7]. Ferroptosis has a complicated and diverse mechanism. The cysteine (Cys 2)/glutamate antiporter system (system X_C^-) and GSH, lipid, iron, and mitochondrial metabolism play an essential role in ferroptosis [5]. In addition, ferroptosis can also be brought on by P53 activation and associated ion channel blockage [8–10].

Neurodegenerative diseases (NDs) are characterized by degenerative changes in neurons in specific regions of the central nervous system, including Alzheimer's disease (AD), Parkinson's disease (PD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS) and Huntington's Disease, with common pathophysiological mechanisms such as neuroinflammation and abnormal protein deposition [11]. NDs impair reasoning, emotions, skilled gestures, cognitive behavior, and memory, leading to short- and long-term disability. AD and PD are among the deadliest diseases of the 21st century [12]. The increasing annual incidence of diseases such as MS, ALS, and Huntington's Disease imposes a substantial economic burden on society and families [13]. Countries will be heavily burdened by these age-related NDs as the population mature [12].

It was reported that ferroptosis was related to oxidative stress and lipid peroxidation in neurodegenerative lesions [14]. Elevated lipid peroxidation levels were frequently seen in the brain tissue of individuals with AD, PD, MS, Huntington's disease, and motor neuron disease, even though the significance of ferroptosis in NDs is still unclear [15,16]. Ferroptosis inhibitors have protective effects on cellular or animal models of AD, PD, and HD [17]. In addition, these inhibitors have a positive therapeutic effect on ALS, suggesting that ferroptosis is closely related to the occurrence and development of NDs [17]. Therefore, it is important to investigate how ferroptosis functions in NDs and to decide where to focus future research in this area.

Mathematical and statistical methods were applied in bibliometrics to analyze the literature quantitatively [18]. A comprehensive and objective analysis through bibliometrics yields important information, including the distribution of authors, countries, institutions, etc. In this study, Citespace [version 6.2. R4 (64-bit)] and VOSviewer (version 1.6.18) were used to analyze articles about ferroptosis in NDs, and scientific knowledge maps were painted. The study aimed to explore the evolution of hotspots and trends in the research of ferroptosis in NDs, which can provide new clues and ideas for subsequent related research.

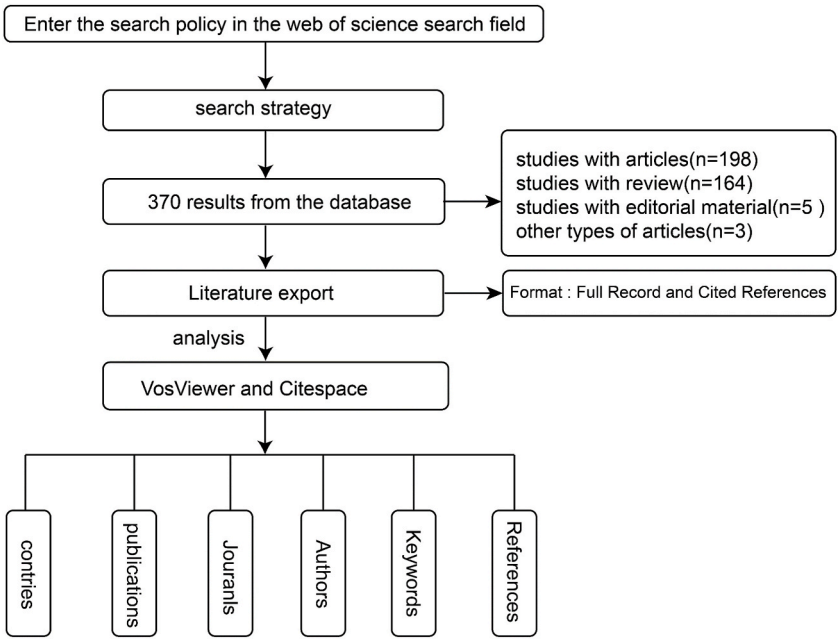

Fig. 1. Flowchart of this article.

2. Materials and methods

2.1. Data collection

The data was retrieved and downloaded from the Web of Science (WOS) database (Lanzhou University Purchase Edition) on September 1, 2023. The retrieval formula was set as follows: TS = "ferroptosis" AND TS = ("Neurodegenerative Diseases" OR "Degenerative Diseases, Neurologic" OR"Neurologic Degenerative Disease" OR "Degenerative Neurologic Diseases" OR "Degenerative Neurologic Disease" OR "Neurologic Disease, Degenerative" OR "Neurologic Diseases, Degenerative" OR "Nervous System Degenerative Diseases" OR "Neurodegenerative Disorders" OR "Neurodegenerative Disorder" OR "Neurologic Degenerative Conditions" OR "Degenerative Condition, Neurologic" OR "Degenerative Conditions, Neurologic" OR "Neurologic Degenerative Condition" OR "Neurologic Degenerative Diseases" OR "Degenerative Diseases, Nervous System" OR "Degenerative Neurologic Disorders" OR "Degenerative Neurologic Disorder" OR "Neurologic Disorder, Degenerative" OR "Neurologic Disorders, Degenerative" OR "Degenerative Diseases, Spinal Cord" OR "Degenerative Diseases, Central Nervous System"OR "Alzheimer's Disease" OR "Parkinson's Disease" OR "Multiple Sclerosis" OR "Amyotrophic Lateral Sclerosis" OR "Huntington's Disease"). All documents were published between September 1, 2013, and September 1, 2023, without any language limitation.

2.2. Data extraction

Two authors (Liu N and Yu WH) conducted the literature screening independently by examining highly cited studies in the field. The citation data for these documents were analyzed using the "Citation Reports" feature of the WOS website, including "Publications," "Citing Articles", "Times Cited", and "H-index." Literature with over 20 citations was included and ranked from highest to lowest. The retrieved papers were exported as "Full Record and Cited References" and saved in "Plain Text". The screening process was shown in Fig. 1.

2.3. Data analysis

Microsoft Office Excel 2007 was used to manage exported data and analyze annual publications. In addition, Citespace [version 6.2. R4 (64-bit)] and VOSviewer (version 1.6.18) were used to analyze the data and paint map scientific knowledge.

Chaomei Chen first created CiteSpace in 2004 with the purpose of analyzing and visualizing various kinds of scientific publications. In addition, CiteSpace is based on Java, and the WOS is the main source of software data [19]. It is a unique and influential application software in the field of information visualization analysis. Additionally, CiteSpace allows users to draw multi-dimensional, time--sharing, and dynamic visual knowledge maps, presenting the evolution process of the knowledge domain on a visual map [20]. Researchers can forecast future trends and illustrate the field's evolution and research hotspots with the use of knowledge maps [21]. VOSviewer is a literature analysis software based on Java developed by Nees Jan van Eck and Ludo Waltman in 2009. In addition, VOSviewer can handle large maps and present information in an easy-to-understand way [22].

3. Results

3.1. The annual growth trend of publication outputs

The trends in a field can be identified by counting the number of articles published each year. As the concept of "ferroptosis" was only introduced in 2013, 370 relevant studies were retrieved. As shown in Fig. 2, the annual number of publications on ferroptosis in neurodegenerative pathologies has risen. According to the analysis of the "Citation Report" function, the number of citations for each article ranged from 0 to 1739, with the average being 37.58. A total of 370 articles included 198 articles, 164 review articles, 5 editorial material, and three other types of articles. The total H-index was 57. The 370 articles were cited for a total of 13,904 times

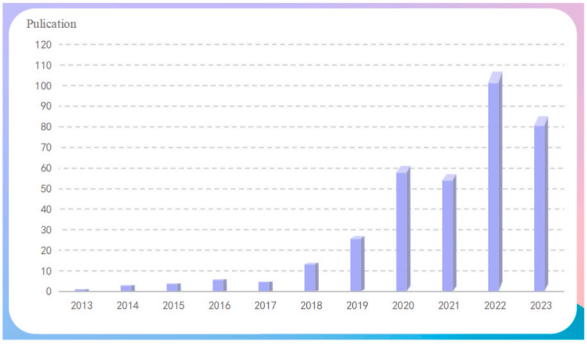

Fig. 2. Trends of yearly publications.

(12,385 excluding self-citations) at the time of analysis. These documents cited 8514 articles in their references (8198 excluding self-citations).

3.2. Journals

In total, 370 papers were published in 206 academic journals. The journals with the highest number of publications were shown in the density chart (Fig. 3A). As can be seen from Table 1, the journals with the highest number of publications were Free radical biology and Medicine (n = 13), followed by Antioxidants (n = 12), and Frontiers in neuroscience (n = 11). The Journal Citation Reports (JCR) is a measure of the quality of academic journals developed by Thomson Reuters. The JCR classifies journals into 176 different subject categories. Each subject classification is divided into Q1, Q2, Q3, and Q4 according to the journal's impact factor. Among them, the journals whose impact factors are ranked at 25 % are divided into the Q1 region, 25–50 % is the Q2 region, 50–75 % is the Q3 region, and after 75 % is the Q4 region. Among the top 10 journals, 9 were located in the Q1 JCR region, and one was located in the Q2 JCR region. In addition, Redox Biology had the highest impact factor (IF) among these journals (IF = 11.4). Among the top 10 journals, the most frequently cited journals that included the articles in these journals which were cited most frequently by other articles were Redox biology (931 times), followed by Frontiers in neuroscience (815 times) and Free Radical Biology And Medicine (603 times).

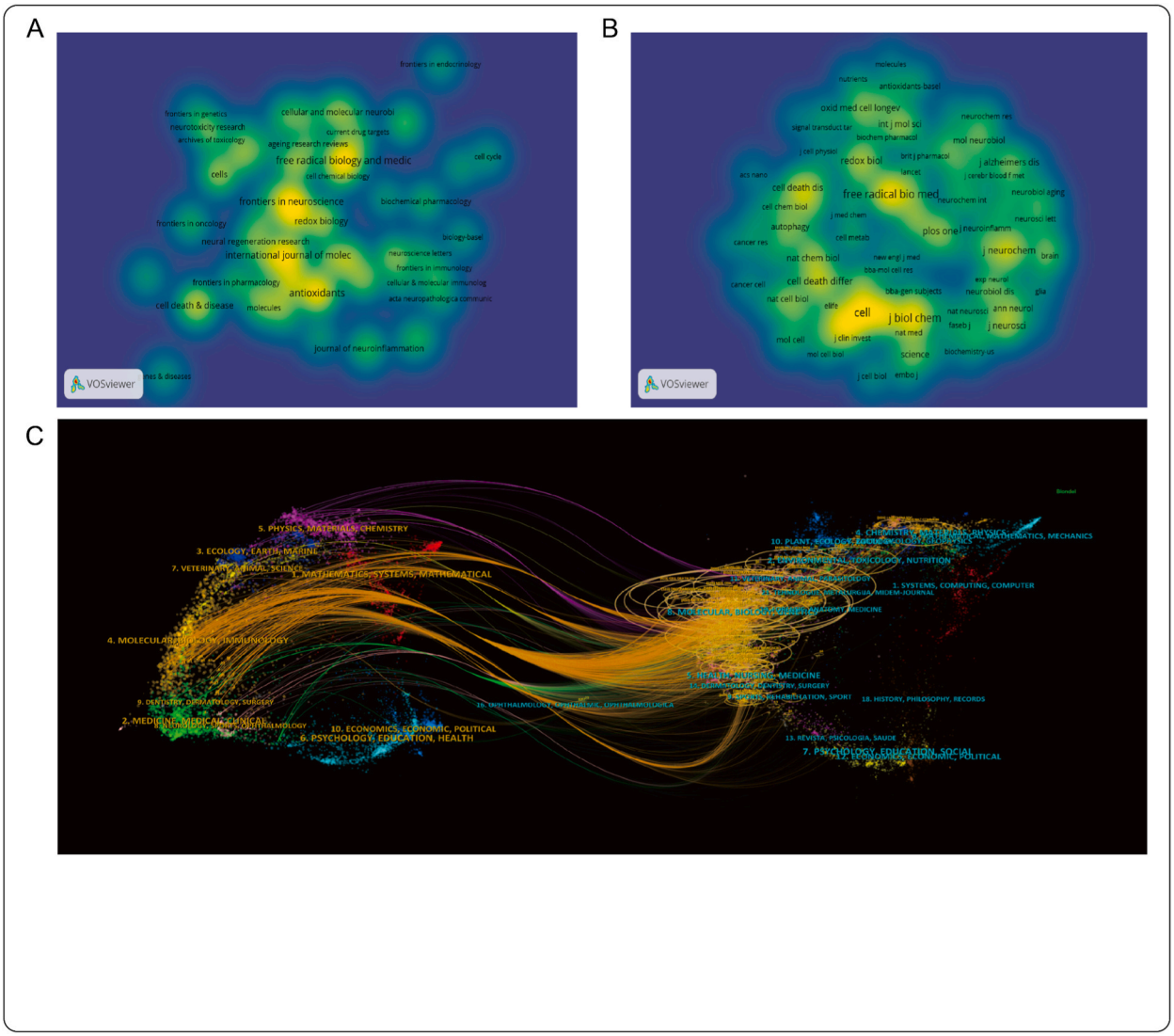

Fig. 3. Analysis of journals.(A) citation coupling analysis of most frequently cited journals, weighed by citations, visualized map.(B) Co-citation analysis of most frequently co-cited journals, weighed by citations, visualized map.(C) The dual-map overlay of jouanal. Image parameter: α : 2; Source Circle size:200; Target circle size:200 snap to centroids (< Radius): 0. The citing journal are located on the left, and the cited journld are located on the right.

Table 1
The top 10 journals, co-cited journals related to ferroptosis in neurodegenerative diseases.

Rank	Journal	Count	Citation	IF -2021	JCR -2021	Rank	Co-cited journal	Citation	IF -2021	JCR -2021
1	Free Radical Biology And Medicine	13	603	7.4	Q1	1	Cell	702	64.5	Q1
2	Antioxidants	12	90	7.0	Q1	2	Free Radical Biology And Medicine	578	7.4	Q1
3	Frontiers In Neuroscience	11	815	4.3	Q2	3	Journal Of Biological Chemistry	530	4.8	Q2
4	International Journal Of Molecular Sciences	11	274	5.6	Q2	4	Proceedings Of The National Academy Of Sciences Of The United States Of America	498	11.1	Q1
5	Molecular Neurobiology	8	385	5.1	Q2	5	Nature	448	64.8	Q1
6	Cell Death & Disease	8	192	9.2	Q1	6	Jouranl of Neurochemistry	375	4.7	Q2
7	Redox Biology	7	931	11.4	Q1	7	Cell Death & Disease	313	9.2	Q1
8	Frontiers In Cell And Developmental Biology	7	491	5.5	Q2	8	Redox Biology	297	11.4	Q1
9	Frontiers In Aging Neuroscience	6	257	4.8	Q2	9	Plos One	256	3.7	Q2
10	Scientific Reports	6	242	4.6	Q2	10	Biochemical and Biophysical Research Communications	250	3.1	Q3

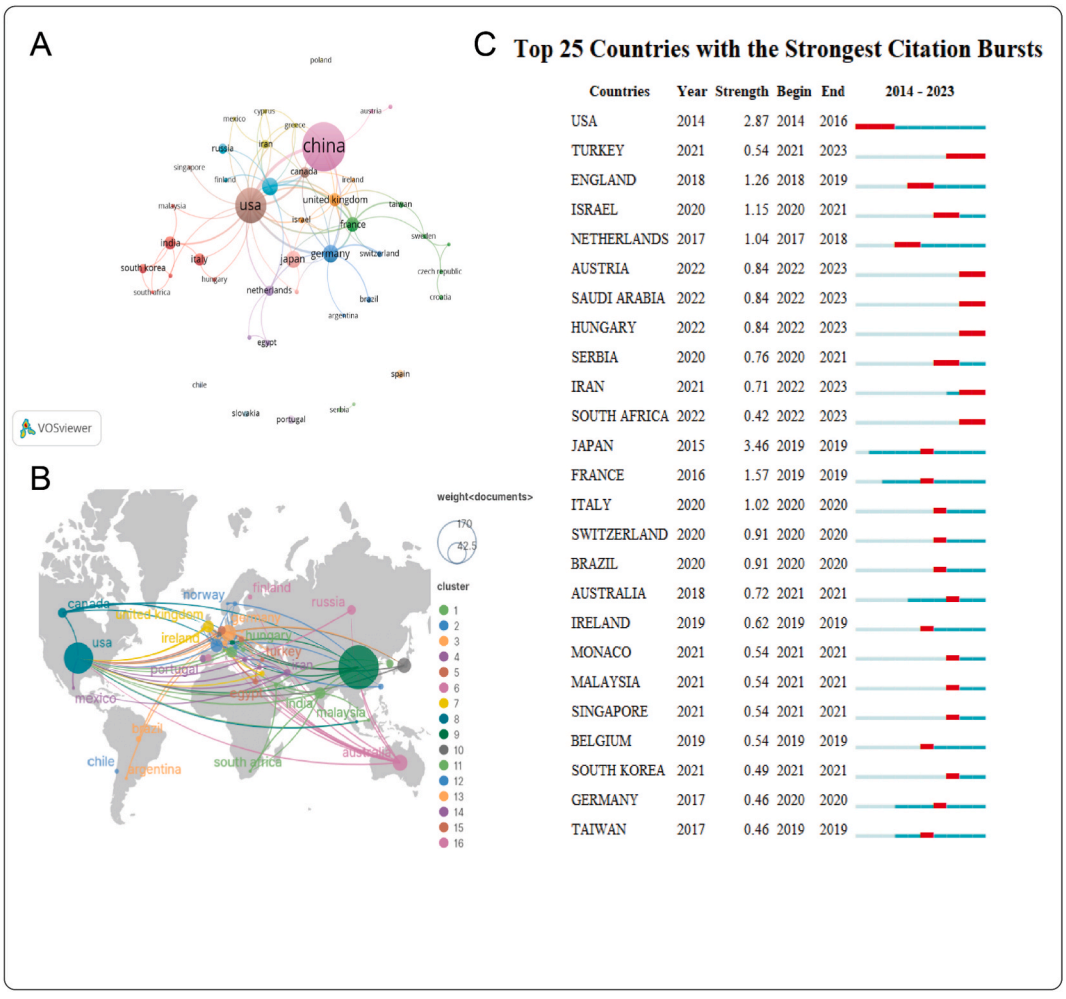

Fig. 4. Analysis of countries. (A) Co-authorship analysis highly cited countries using VOSviewer, weighted by citations, visualized map. (B)The world map. (C) Top of 20 countries with strongest citation bursts using Citespace; minimum duration:2. Red bars indicate the duration of the burst. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Co-citation analysis means that two papers (or more papers) are cited by one or more later papers at the same time, then the two papers constitute a co-citation relationship [23]. Co-citation analysis was performed on the journals (Fig. 3B). The most frequently co-cited journals were the Cell (702 times), followed by Free radical biology and medicine (578 times) and Journal of Biological Chemistry (530 times). Out of the top 10 co-cited journals, 7 were cited more than 300 times, with the Cell being cited far more often than any other journal (Table 1). The dual-map overlay of journals provided a good representation of the distribution of journals and the relationship between journals and cited journals. Fig. 3C displayed a major reference path. "System, Computing, Computer" journals were often cited in papers published in "Mathematics, System, Mathematical" journals.

3.3. Countries

Research in the field of ferroptosis in neurodegenerative pathologies was performed in 45 countries that published 370 papers (Fig. 4A). In order of citations, the China was the most cited and was the country with the most records, with 6233 total citations and 170 record counts. The second highest ranking was USA, with 5497 total citations and 88 record counts. The third highest ranking was Australia, with 1575 total citations and 23 record counts. The global distribution of these articles was shown on the world map (Fig. 4B), and the ten countries with the most citations were listed in Table 2. Citespace software can detect the strongest citation bursts, which can reflect the frequency of the detected object in a certain period, so as to detect the emerging dynamic concept and potential research direction in a certain field. The larger the value, the greater the intensity of emergence [23]. As displayed by the top 25 countries with the strongest citation bursts, the highest outbreak intensity of 3.46 was observed in the Japan, indicating that many scholars in the Japan began to study the role of ferroptosis in neurodegenerative diseases from 2019. Additionally, some scholars from USA and Turkey have joined the research in this field, demonstrating an ongoing citation intensity for three years (Fig. 4C).

3.4. Institutions

According to the VOSviewer analysis, a total of 370 articles were published by 523 institutions. After excluding institutions that were disconnected from each other, the remaining 482 organizations were used to generate the co-occurrence map (Fig. 5A). Table 3 showed the top ten most productive institutions, including four USA institutions, three Chinese institutions, one Scotland institutions, one France institutions and one Australian institutions. The findings indicated that medical institutions from the USA were more concerned about ferroptosis in the field of NDs. The institution with the most cited articles was the Guangzhou Medical University, with 2187 citations, 6 published articles, and a total link strength of 260. The second and third-ranked institutions were the University Pittsburgh and the Central South University, with citations and total link strength of 1899, 232 and 1782, 184, respectively. In terms of institutions with strongest citation bursts, the top ranking was the UDICE-French research universities, which had a prominence intensity of 2.25 (Fig. 5B). The three institutions with the longest duration of prominence were the University of California System, Qingdao University, Chinese Academy of Medical Sciences - Peking Union Medical College, and the Sun Yat Sen University, which respectively joined the field in 2020 and 2021 and were still active.

3.5. Authors

Analyzing the core authors helps to find the distribution of relevant literature. Core authors were identified by the number of published literature, the total number of citations and the H-index. In total, 2171 authors were involved in the study of ferroptosis in the field of neurodegenerative diseases, publishing 370 papers (Fig. 6A). The top ten core authors in this field from 2013 to 2023 were listed in Table 4. Pamela from the Salk Institute, David from the Universite de Lille, and Scott from the University of Melbourne were ranked in the top three authors. Pamela was the first scholar to publish 10 papers with a total of 492 citations, but How, wei from Wuhan University of Technology had the highest citation count of 1739 with only 1 published articles. Three of the top 10 scholars (Hirata, Oh-Hashi And Furuta) were from the Gifu University, Japan. Their H-index were 8, 19, and 12, respectively. The top three authors with the strongest citation bursts were Mather, Pamela from 2020 to 2020, followed by Devos, David from 2019 to 2020 and Corcia, Philippe from 2019 to 2020 (Fig. 6B).

Table 2
The top 10 countries related to ferroptosis in neurodegenerative diseases.

Rank	Country	Documents	Citations	Total link strength
1	Peoples Of China	170	6233	1101
2	USA	88	5497	848
3	Australia	23	1575	350
4	Germany	23	740	215
5	Japan	20	763	125
6	France	16	1083	326
7	England	13	623	164
8	India	12	221	92
9	Italy	11	241	107
10	Canada	9	159	89

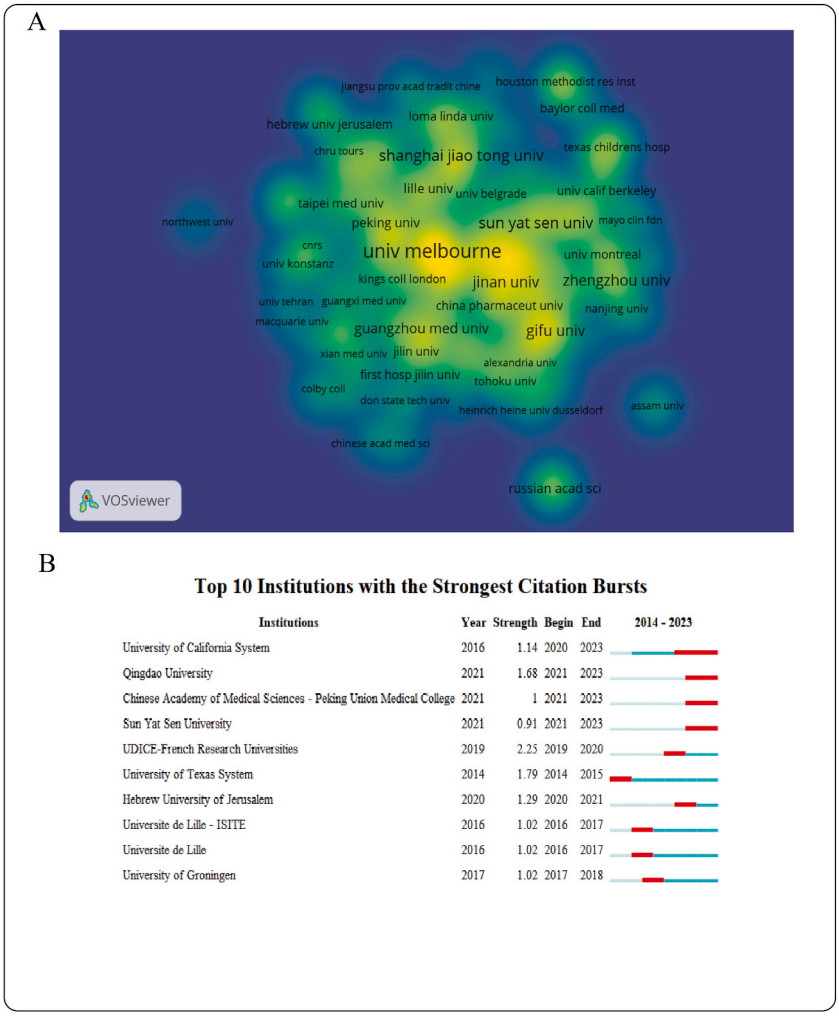

Fig. 5. The analysis of institution. A. Overlay visualization of institutions was showed using VOSviewer. B. Top 10 institutions with the strongest citation bursts by Citespace.

Table 3
The top 10 institutions related to ferroptosis in neurodegenerative diseases.

Rank	Institution	Country	Documents	Citations	Total link strength
1	Guangzhou Medical University	China	6	2187	260
2	University Pittsburgh	USA	6	1899	232
3	Central South University	China	2	1782	184
4	University Of Melbourne	Australia	20	1566	654
5	The University Of Glasgow	Scotland	2	879	12
6	South Texas Veterans Health Care System	USA	4	759	381
7	Sichuan University	China	7	539	233
8	Université De Lille	France	5	533	268
9	Salk Institute For Biological Studies	USA	11	496	230
10	South Texas Veterans Health Care System	USA	1	433	175

3.6. Keywords

Keyword co-occurrence reflects the research hotspots and directions in the field. Altogether, 1862 keywords were extracted from 370 documents with VOSviewer. Since some words, such as glutathione peroxidase 4 and GPX4, expressed the same meaning, these synonyms were combined in the analysis. Finally, 1799 keywords were obtained, and 440 met the threshold (minimum of 2 occurrences). The overlay visualization graph shows the co-occurrence relationship of keywords. A larger circle size represents a higher

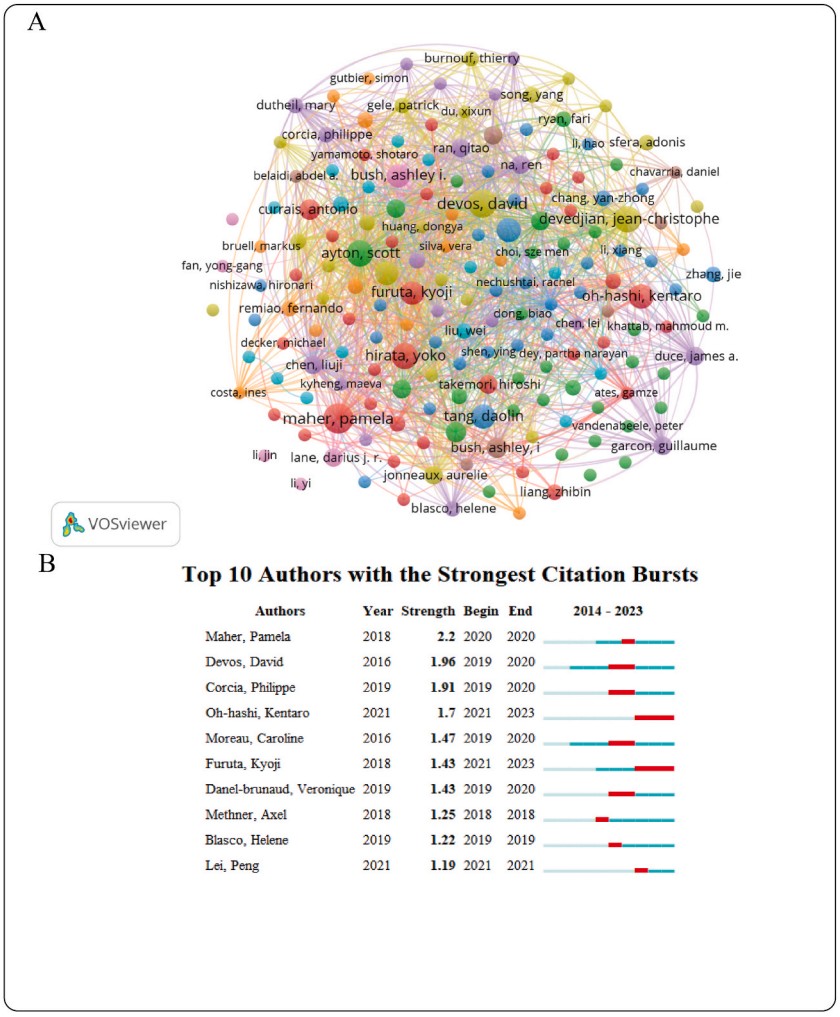

Fig. 6. The analysis of authors. A Overlay visualization of authors was showed using VOSviewer. B. Top 10 authors with the strongest citation bursts by Citespace.

Table 4
The top 10 authors related to ferroptosis in neurodegenerative diseases.

Rank	Author	Organizations	Documents	Citations	Total link strength	H-index
1	Maher, Pamela	Salk Institute	10	492	506	53
2	Devos, David	Universite De Lille	9	949	1256	113
3	Ayton, Scott	University Of Melbourne	8	449	649	58
4	Devedjian, Jean-Christophe	Universite De Lille	8	695	985	54
5	Hirata, Yoko	Gifu University	8	122	268	8
6	Kang, Rui	Beihang University	7	454	237	29
7	Oh-Hashi, Kentaro	Gifu University	7	83	244	19
8	Tang, Daolin	University Of Texas Southwestern Medical Center Dallas	7	454	237	92
9	Bush, Ashley i.	The University Of Melbourne	6	485	660	116
10	Furuta, Kyoji	Gifu University	6	60	194	12

number of keyword occurrences. As shown in Fig. 7A, ferroptosis (n = 263), oxidative stress (n = 155), cell death (n = 145), lipid peroxidation (n = 98), iron (n = 96), neurodegenerative diseases (n = 91), Parkinson's disease (n = 86), Alzheimer's disease (n = 81), Apoptosis (n = 44) and metabolism [24] were high frequency keywords (Table 5).

The network map was clustered to reflect the basic knowledge structure of the relevant research area based on the keyword co-occurrence analysis. Citespace software was used to cluster the keywords in the literature. Different color blocks represented the seven different clusters, as shown in Fig. 7B. The labels for each of the seven clusters were neurodegenerative diseases (#0), lipid

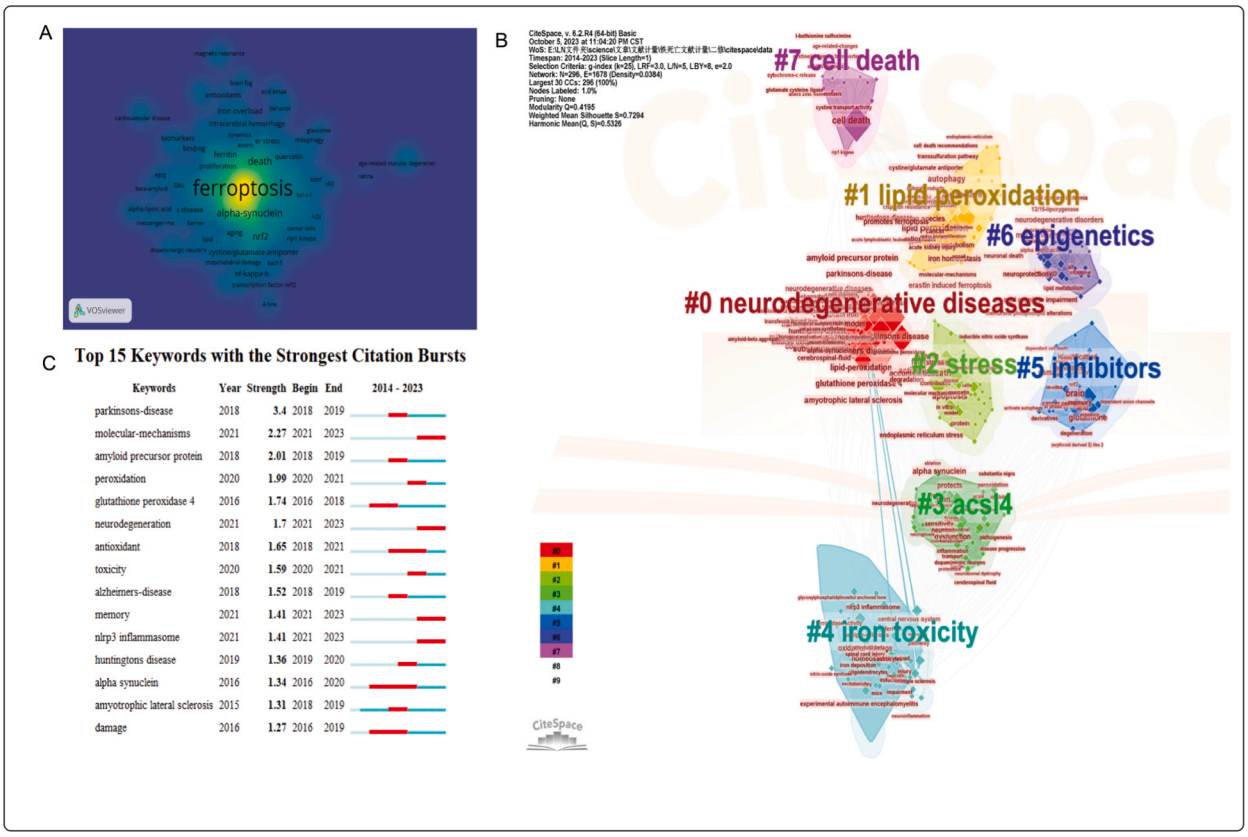

Fig. 7. The analysis of all keywords. A. The Co-occurrence analysis of all key words by VOSviewer, the weight was an occurrence. B. The cluster analysis of the keywords using Citespace. C. Top 10 keywords with the strongest ciatation bursts by Citespace.

Table 5
The top 10 keywords related to ferroptosis in neurodegenerative diseases.

Rank	Keyword	Occurrences
1	Ferroptosis	263
2	Oxidative Stress	155
3	Cell Death	145
4	Lipid Peroxidation	98
5	Iron	96
6	Neurodegenerative Diseases	91
7	Parkinson's Disease	86
8	Alzheimer's Disease	81
9	Apoptosis	44
10	Metabolism	40

peroxidation (#1), stress (#2), ASCL4(#3), iron toxicity (#4), inhibitors (#5), epigenetics (#6), cell death (#7).

Fig. 7C displayed the top 15 keywords with the strongest citation bursts. The keyword with the highest citation burst was Parkinsons-disease (3.4) from 2018 to 2019, followed by molecular (2.27) and amyloid precursor protein (2.01). The keyword with the longest duration of strongest citation bursts was alpha synuclein from 2016 to 2020. A timeline viewer for these keywords was constructed using CiteSpace. Additionally, the timeline view represented the evolution of knowledge with time, clearly showing updates in literature and mutual influence. The research focus and evolutionary trajectory of ferroptosis in neurodegenerative diseases could be visualized in Fig. 8.

3.7. Reference and Co-cited references

Based on the literature citation analysis, Table 6 listed the top 10 citations, with citations ranging from 0 to 1739. Fig. 9A showed the density map of reference. "Ferroptosis: process and function" (2016) was the most cited, reaching 1739 citations. The second highest cited paper was "Mitochondria as multifaceted regulators of cell death", published in Nature Reviews Molecular Cell Biology

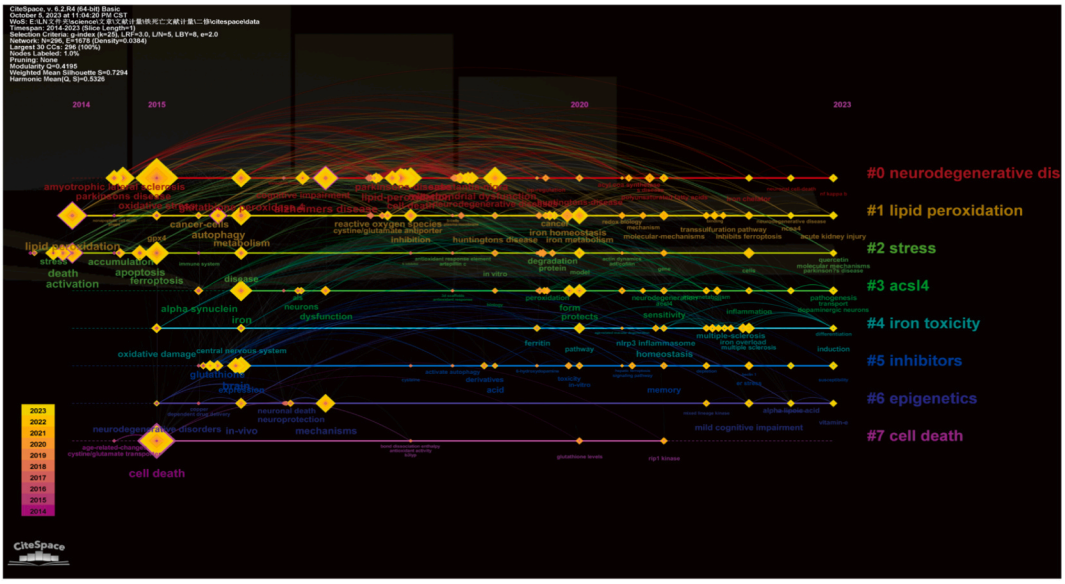

Fig. 8. The visualization map of timeline viewer.

Table 6
The top 10 references (including reviews and articles) related to ferroptosis in neurodegenerative diseases.

Rank	Title	Type of eaasy	First author	Source	Publication year	Total citations
1	Ferroptosis: process and function	Review	Xie, Y	Cell Death & Differentiation	2016	1739
2	Mitochondria as multifaceted regulators of cell death	Review	Florian J.Bock	Nature Reviews Molecular Cell Biology	2020	876
3	Ferroptosis: mechanisms and links with diseases	Review	Hong-fa Yan	Signal Transduction and Targeted Therapy	2021	311
4	Striking while the iron is hot: Iron metabolism and ferroptosis in neurodegeneration	Review	ShashankMasaldan	Free Radical Biology and Medicine	2019	254
5	Iron Metabolism in Ferroptosis	Review	Xin Chen	Frontiers in Cell and Developmental Biology	2020	248
1	Ablation of ferroptosis regulator glutathione peroxidase 4 in forebrain neurons promotes cognitive impairment and neurodegeneration	Article	William Sealy Hambright	Redox Biology	2017	433
2	Ferroptosis, a newly characterized form of cell death in Parkinson's disease that is regulated by PKC	Article	Bruce Do Van	Neurobiology of Disease	2016	392
3	Ablation of the Ferroptosis Inhibitor Glutathione Peroxidase 4 in Neurons Results in Rapid Motor Neuron Degeneration and Paralysis	Article	Liuji Chen	Journal of Biological Chemistry	2015	282
4	BID links ferroptosis to mitochondrial cell death pathways	Article	SandraNeitemeier	Redox Biology	2017	198
5	An Endoperoxide Reactivity-Based FRET Probe for Ratiometric Fluorescence Imaging of Labile Iron Pools in Living Cells	Article	Allegra T. Aron	Journal of the American Chemical Society	2016	169

(2020), with 876 citations. The third was "Ablation of ferroptosis regulator glutathione peroxidase 4 in forebrain neurons promotes cognitive impairment and neurodegeneration" (2017), reaching 433 citations.

Co-citation analysis was performed on the references of the included literature, as shown in Fig. 9B. A total of 25,447 cited references were analyzed. Table 7 demonstrated the top 10 co-cited references, published by Scott J Dixon [4], Wan Seok Yang [25], Brent R Stockwell [14], Jose Pedro Friedmann Angeli [26], Sebastian Doll [27], Bruce Do Van [16], Y Xie [28], William Sealy Hambright [29], Valerian E Kagan [30], and Wan Seok Yang [31]. These articles focused on characterizing ferroptosis, and most of them were published in the Q1 JCR region. This may be attributed to "ferroptosis" being a new concept introduced by Dixon in 2012, resulting in late research [32].

Fig. 9B showed the top 20 references with strongest citation bursts. The article published by Dixon SJ. (2012) showed the strongest bursts, with 36.89 from 2015 to 2020, and the article published by Hayano M (2016) showed the lowest. The longest duration of emergent intensity was published by Dixon SJ from 2015 to 2020.

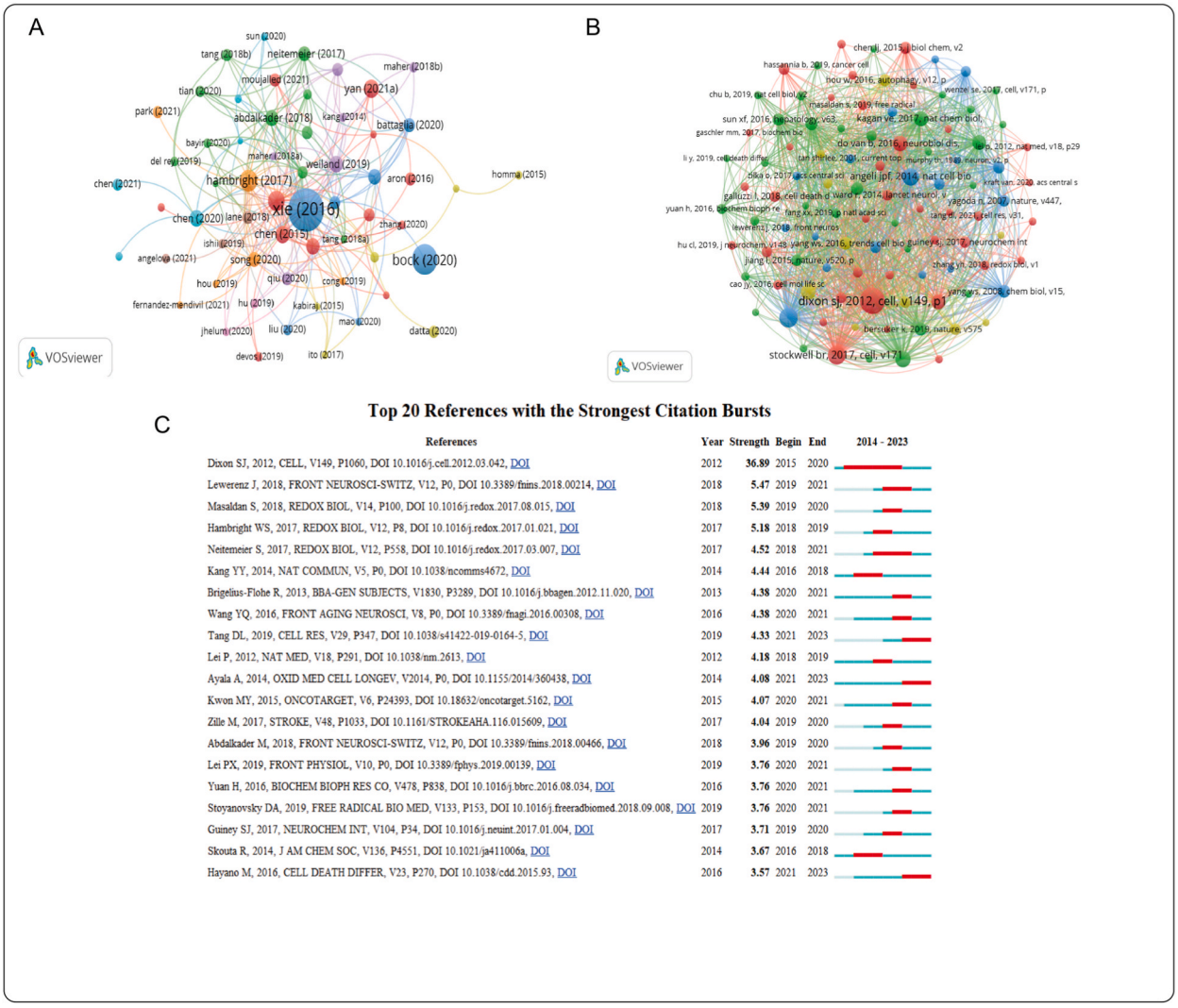

Fig. 9. The analysis of reference. A. The density map of reference, weight by citations. B. Thevdensity map of co-citaiton analysis on the refernce. C. Top 20 refernces with the strongest citation bursts by Citespace.

4. Discussion

4.1. Global research trends

This paper presented the bibliometric distribution of studies on ferroptosis in the field of NDs over the past decade. Since the concept of "ferroptosis" was proposed in 2012, the number of publications and citations in the field of neuroscience has continued to increase. Although there was still one month left until the end of 2023, the number of articles in this year has already surpassed 80 articles. These results indicated a growing number of studies on ferroptosis in NDs worldwide.

After searching by subject term on the WOS website, 370 studies including articles and reviews, were included in this paper. In terms of authoritative journals, Free radical biology and medicine (n = 13), Antioxidants (n = 12), and Frontiers in neuroscience (n = 11) had the highest number of publications. Among the top 10 journals, all of them were Q1 and Q2, indicating the high quality of research papers on ferroptosis in NDs. Redox biology had the highest number of citations (931 times). The co-citation analysis of journals revealed that the Cell (702 times) had the highest citations. 60 % of the journals were Q1. These findings indicated that research in this field is on the rise.

In terms of authoritative countries, the China published the most articles and had the most citations (n = 6233 times), followed by USA (n = 5497 times) and Australia (n = 1575 times). In terms of authoritative organization, four of the top ten institutions were from the USA. With more prestigious universities than any other country in the world, the USA was the leader in neuroscience. This was mainly because the high incidence of NDs in the USA has prompted scientists to conduct extensive research [33,34].

Table 7
The top 10 co-reference related to ferroptosis in neurodegenerative diseases.

Rank	Title	First author	Source	Publication year	Total citations
1	Ferroptosis: an iron-dependent form of nonapoptotic cell death	Scott J Dixon	Cell	2012	255
2	Regulation of ferroptotic cancer cell death by GPX4	Wan Seok Yang	Cell	2014	144
3	Ferroptosis: A regulated cell death nexus linking metabolism, redox biology, and disease	Brent R Stockwell	Cell	2017	132
4	Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice	Jose Pedro Friedmann Angeli	Nature Cell Biology	2014	112
5	ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition	Sebastian Dol	Nature Chemical Biology	2017	96
6	Ferroptosis, a newly characterized form of cell death in Parkinson's disease that is regulated by PKC	Bruce Do Van	Neurobiology of Disease	2016	91
7	Ferroptosis: process and function	Y Xie	Cell Death & Differentiation	2016	87
8	Ablation of ferroptosis regulator glutathione peroxidase 4 in forebrain neurons promotes cognitive impairment and neurodegeneration	William Sealy Hambright	Redox Biology	2017	83
9	Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis	Valerian E Kagan	Nature Chemical Biology	2017	82
10	Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis	Wan Seok Yang	Proceedings of the National Academy of Sciences	2016	81

Although the University of Melbourne was the only institution from Australia, it has published the most articles with 20. Therefore, Australian scholars were also committed to the study of neurodegeneration. Despite the extensive collaboration between countries and institutions, the research on ferroptosis in neurodegeneration diseases should focus on international collaboration with multi-center, large-sample studies in the future.

4.2. Knowledge base

Highly cited papers usually present the most representative conclusions in the field of research. In addition, original research articles and letters can represent the latest study in their field. In this study, a total of 370 papers related to ferroptosis in neurodegeneration diseases were included. From these articles, the top five most cited original articles with ferroptosis in neurodegeneration diseases were selected.

William et al. published "Ablation of ferroptosis regulator GPX4 in forebrain neurons promotes cognitive impairment and neurodegeneration" in Redox Biology [29]. This study reported that the forebrain regions of the cerebral cortex and hippocampus were prone to ferroptosis in AD patients. GPX4, a selenoprotein glutathione peroxidase, has many pleiotropic functions that reduce peroxides in esters such as myelin and cholesterol, and plays an essential role in protecting against lipid peroxides. The scientists built GPX4BIKO mice, and after 12 weeks of modeling, the GPX4BIKO mice showed significant deficits in spatial learning and memory function compared to control mice, as revealed by the Morris water maze task. Markers associated with ferroptosis, such as elevated lipid peroxides, ERK activation, and increased neuroinflammation, were observed in GPX4BIKO mice. Then, they treated GPX4BIKO mice with a ferroptosis inhibitor, liproxstatin-1, which found that the drug reduced neurodegeneration and inflammation in the GPX4BIKO mice. This study suggested lipid peroxidation occurred in neurons, which may promote cognitive impairment and hippocampal degenerative changes through ferroptosis.

Bruce Doet et al. published "Ferroptosis, a newly characterized form of cell death in Parkinson's disease that is regulated by PKC" in Neurobiology of Disease [16]. This study suggested that ferroptosis was a vital cell death pathway in dopaminergic nerves. It has been confirmed that the characteristic appearance of ferroptosis has been demonstrated in Lund human mesencephalic (LUHMES) cells stimulated by erastin. In addition, ferroptosis need the activation of mitogen-activated protein kinase (MEK) signaling but did not depend on the activation of Ras, which was mainly dependent on the specific metabolic characteristics of dopaminergic cells. In addition, in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse that was an animal model of PD, ferroptosis was also involved in the death of dopaminergic neurons. Besides, the toxicity of MPTP was inhibited by ferrostatin 1 treatment, a ferroptosis inhibitor. This study highlighted the critical role of ferroptosis in PD, which suggested that Fer-1 derivatives, iron chelators, and protein kinase C inhibitors may be strong candidates for treating PD.

Chen et al. published "Ablation of the Ferroptosis Inhibitor GPX4 in Neurons Results in Rapid Motor Neuron Degeneration and Paralysis" in Journal of Biological Chemistry [35]. The study found that GPX4, a selenoprotein glutathione peroxidase, was essential for the survival of motor neurons. In addition, motor neurons were the basis of NDs such as ALS. When they knocked GPX4 conditionally out of the neurons of adult mice, the mice progressed rapidly to paralysis and eventually death. The results of the pathological examination showed that the motor neurons were significantly degraded in the spinal cord of the paralyzed mice, but the neurons in the cerebral cortex were not. Supplementation with vitamin E, a ferroptosis inhibitor, delayed theparalysis and death of mice caused by GPX4 knockout. Although the mechanisms of motor neuron degenerative diseases were not yet understood, the research provided insight into potentialtherapeutic approaches for conditions like ALS.

Aron et al. developed FRET iron Probe 1(FIP-1), which helped to detect changes in labile iron pools within living cells with iron supplementation and/or depletion. FIP-1 provided a starting point for the study of iron signaling in living systems [36].

Neitemeieret et al. published "BID links ferroptosis to mitochondrial cell death pathways" in Redox Biology [37]. This study found

that ferroptosis and oxidative stress pathways were linked by pro-apoptotic Protein BID and subsequent mitochondrial damage. In elastin-induced neurons, they found that ferroptosis was accompanied by BID transactivation, loss of mitochondrial membrane potential, and decreased ATP levels. It was reported that oxytosis induced by the inhibition of cystine-glutamate antiporter (Xc^-) resulted in cell death. Knockout of BID by CRISPR/Cas9 approaches preserved mitochondrial integrity and function which mediated the neuroprotective effects of ferroptosis and oxidation poisoning. Moreover, BI-6c9, a BID inhibitors, inhibited ferroptosis induced by erastin. In addition, the ferrostatin-1 and liproxstatin-1 of ferroptosis inhibitors prevented cell death and mitochondrial dysfunction.

In addition, we also summarized the original studies done on several of the most classic NDs including AD, PD, MS, and ALS, which reflected the relationship with ferroptosis from specific disease processes.

Bao et al. published "Loss of ferroportin induces memory impairment by promoting ferroptosis in Alzheimer's disease" in Cell Death & Differentiation in 2021 [38]. This study reported that the loss of ferroportin in AD led to memory impairment. The authors observed typical features of ferroportin in APPswe/PS1dE9 mice (an Alzheimer's mouse model) with genetic deletion of ferroportin 1 (Fpn), which was a transmembrane iron exporting protein. The mice also exhibited AD-like hippocampal atrophy and memory deficits. The use of ferroportin inhibitors effectively reduced neuronal death and memory impairment caused by Aβ aggregation in vitro and in vivo. Moreover, restoration of Fpn ameliorated ferroptosis and memory impairment in mice. Their study demonstrated the critical role of ferroptosis caused by Fpn depletion in the progression of AD, providing promising therapeutic approaches for the disease.

Tian et al. published "FTH1 Inhibits ferroptosis through ferritinophagy in the 6-OHDA model of Parkinson's Disease" in Neurotherapeutics in 2020 [39]. The study reported that ferritin heavy chain 1 (FTH1) inhibited ferroptosis in a rat model induced by 6-hydroyxdopamine (6-OHDA) through ferritinophagy. FTH1 knockdown in PC-12 cells significantly inhibited cell viability and caused mitochondrial dysfunction. Nevertheless, ferritinophagy was hampered by FTH1 over-expression, which was a kind of selective autophagy. It down-regulated the expression of microtubule-associated protein light chain 3, ultimately inhibiting ferroptosis. In addition, the ferritinophagy inhibitors chloroquine and bafilomycin A1 inhibited ferritin degradation and ferroptosis in 6-OHDA--treated PC-12 cells. Collectively, these results indicated that FTH1 was associated with ferroptosis in the 6-OHDA rat model, providing potential pharmacological targets for PD in the future.

Hu et al. published "Reduced expression of the ferroptosis inhibitor glutathione peroxidase-4 in multiple sclerosis and experimental autoimmune encephalomyelitis" in the Journal of Neurochemistry in 2019 [40]. This study found MS patients and experimental autoimmune encephalomyelitis (EAE) model have lower expression of GPX4, an inhibitor of ferroptosis. Decreased mRNA expression of all three GPX4 isoforms (cytoplasmic, mitochondrial, and nuclear) was observed in the gray matter of MS patients and the spinal cord of EAE mice. Furthermore, abnormal mitochondrial morphology was also found in neurons, with disrupted mitochondrial outer membrane and reduced cristae, coinciding with the ferroptosis injury. This study contributed to the development of new treatments for MS.

Devos et al. published "A ferroptosis-based panel of prognostic biomarkers for Amyotrophic Lateral Sclerosis" in Scientific Reports in 2019 [24]. This study was a large phase III clinical trial (Mitotarget/TRO19622) in which the pathologic markers in 109 ALS patients were evaluated, including ferritin, hepcidin, and transferrin. The results showed that ferroptosis markers in ALS were associated with poor clinical outcomes.

Overall, these original studies explored the relationship between ferroptosis and different NDs from different aspects. Iron metabolism and lipid peroxidation pathways were considered mediators of ferroptosis. Excessive iron can produce reactive oxygen species (ROS) through the Fenton reaction, resulting in ferroptosis. In addition, nicotinamide adenine dinucleotide phosphate (NADPH)-dependent lipid peroxidation and GSH depletion were also critical for triggering ferroptosis [25]. GSH depletion leads to GPX4 inactivation, which initiated ferroptosis peroxidation through the accumulation of ROS produced by lipid peroxidation. Ferroptosis inhibitors such as liproxstatins and ferrostatins had protective effects in NDs models, including AD, PD, and MS, as well as in other forms of traumatic and hemorrhagic brain injury [14]. Therefore, the mechanism of ferroptosis in NDs should be investigated to develop targeted therapeutic drugs over the next few years.

4.3. The analysis of hotspots and emerging topics

Keywords can reflect the hotspots and directions of the research field. The most representative keywords included ferroptosis, oxidative stress, cell death, lipid peroxidation, iron, NDs, PD, AD, GPX4, apoptosis, metabolism. Through these keywords, we concluded that the current research on ferroptosis in NDs focused on the mechanism.

The co-occurrence graph of keywords showed the high-frequency keywords in this field (Fig. 7A). The cluster analysis of keywords intuitively showed the research direction and scope of this field. As shown in Fig. 7B–a total of 7 clusters were obtained. The keywords of cluster 0 were mainly about NDs. The keywords of cluster 1 concerned lipid peroxidation. The keywords of cluster 2 focused on stress. In addition, the keywords of cluster 3 were mainly about ACSL4, while the keywords of cluster 4 mainly concerned iron toxicity. Furthermore, the keywords of cluster 5 focused on inhibitors. These seven clusters represented the research focus and scope of ferroptosis in NDs to some extent. Particularly, the mechanism of ferroptosis in NDs has become one of the important research hotspots. These studies focused on a few key pathways that trigger ferroptosis, including lipid peroxidation signaling, iron metabolism, and GSH/GPX4 signaling.

Lipid peroxidation was a free radical-driven reaction that mainly affects unsaturated fatty acids in cell membranes. Its product lipid hydrogen peroxide (LOOHs) and subsequent reactive aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4HNE) increased in expression upon ferroptosis [41]. In addition, the membrane phospholipids were rich in polyunsaturated fatty acids (PUFAs) in the central nervous system, which can quickly absorb them from free fatty acids, ultimately creating an environment for lipid peroxidation. Lipid peroxidation was thought to be an early mechanism in the pathogenesis of AD. Studies have shown that the

lipid peroxidation process of ferroptosis promoted pathological Aβ accumulation within AD and that using the antioxidant CoQ10 reduced Aβ levels in the cerebral cortex and hippocampus of AD model mice [42]. This study reflected a potential link between Aβ deposition and the process of lipid peroxidation of ferroptosis. In addition, tau protein hyper phosphorylation in AD was also closely related to lipid peroxidation of ferroptosis. Up-regulation of 5′-adenosine monophosphate (AMP)-activated protein kinase (AMPK), a key regulator of ferroptosis lipid peroxidation, not only inhibited phospholipid synthesis but also inhibited phosphorylation of tau protein. The latter helped to reduce neurofibrillary tangles (NFTs) and widespread neuronal degeneration [43]. GPX4 was a glutathione peroxidase that can directly detoxify hydrogen peroxide in membrane lipids, thereby reducing damage to membrane function. In the mouse model of GPX4 knockdown, cognitive impairment and hippocampal neurodegeneration were observed. However, the treatment with an inhibitor of ferroptosis mitigated the neurodegeneration in these mice [29]. PUFAs can delay ferroptosis and reduce lipid peroxidation in brain tissue in AD mouse models (APP/PS1 transgenic mice) [44]. On the contrary, up-regulation of ApoE may accelerate intracellular PUFAs accumulation and provide a suitable environment for lipid peroxidation and ferroptosis [45]. Together, these studies suggested lipid peroxidation-mediated ferroptosis played a significant role in AD. However, the specific regulatory mechanisms need to be studied on a large scale in the future.

Another pathway regulated by ferroptosis was the iron metabolism pathway. Iron was a redox-active metal that maintained the function of normal cells in the central nervous system. By attaching to transferrin, circulating iron takes the form of ferric iron (Fe^{3+}). Fe^{3+} enters cells via the membrane protein transferrin receptor 1 (TFR1), where it finds a place in the endosome. The ferrireductase activity of STEAP3 reduces Fe^{3+} to ferrous iron (Fe^{2+}) in the endosome. Divalent metal transporter 1 (DMT1, also known as SLC11A2) is the last enzyme that facilitates the release of Fe^{2+} from the endosome into the cytoplasm's labile iron pool (LIP) [28]. LIP has high chemical reactivity and exhibits high cytotoxic potential. Fe^{2+} in the iron pool participates in the Fenton reaction to form ROS and other harmful substances, leading to the ferroptosis in cell. In conclusion, the iron accumulation cause these abnormalities [46]. It has been shown that the brain experienced neuronal death as a result of iron accumulation [47]. The scientists found PD sufferers' brains have noticeably higher iron levels. Increased iron levels in the parietal and frontal cortices were linked to a higher risk of dementia in Parkinson's disease (PD) patients, and the degree of dyskinesia changed in correlation with iron levels in the nucleus accumbens [48,49]. JOUINI N et al. [50] found that decreased activity of the plasma ceruloplasmin-transferrin system may increase cerebrospinal fluid iron levels and accelerate the neurodegenerative process in AD. These studies showed that iron overload existed in central nervous system diseases and was involved in the pathophysiologic processes of these diseases. What was more noteworthy was that iron overload can be a causative factor in neurological disorders through iron-induced neurotoxicity and neurological damage [51]. It is not clear why iron accumulates in cell [52], but excess intracellular iron generated large amounts of ROS by catalyzing the Fenton reaction, triggering oxidative stress and causing oxidative damage to DNA, proteins, and lipids [53]. In addition, iron-induced production of ROS accelerated neuronal cell death [54]. It was shown that activated microglia induced superoxide-mediated ferritin release, leading to iron-dependent lipid peroxidation and contributing to the pathologic changes characteristic of iron death. In contrast, reactive astrocytes released various antioxidant molecules, such as GSH, metallothioneins (MTs), and the nuclear factor erythroid 2-related factor 2 (Nrf2), to antagonize neuronal oxidative stress damage. Oligodendrocytes provided neurons with resistance to oxidative stress by secreting ferritin heavy chain 1 (FTH1) [39]. Inhibition of microglia-derived oxidative stress protected against 1-methyl-4-phenylpyridinium (MPP+)-induced dopaminergic neuronal damage in rats [55]. Iron deposition eventually led to intracellular ferroptosis and exacerbates cerebral neurological impairment. Ferroptosis caused by iron accumulation promoted hippocampal atrophy and memory deficits in a mouse model of AD [56].

These data suggested that ferroptosis was a feature of NDs pathology. Thus, inhibitory therapeutic measures targeting ferroptosis have gained momentum for use in the treatment of PD and represented a new therapeutic target for PD [16].

Another regulatory pathway for ferroptosis was system XC-/GSH/GPX4 signaling. System X_C^-, an anti-transporter consisting of solute carrier 3A2 (SLC3A2) and solute carrier 7A11(SLC7A11) dimers, was embedded on the surface of cell membranes which can bring cystine into cells for GSH synthesis [57]. When system X_C^- on the cell surface was too little or inactivated, the cell cannot take up enough cystine, resulting in reduced GSH synthesis. Subsequently, the activity of GPX4 decreased, which can induce the accumulation of H_2O_2 in the cells, generating excessive oxygen free radicals and causing ferroptosis [58]. β-N-methylamino-l-alanine was a non-protein amino acid that acted as an inhibitor of system X_C^-, leading to a decrease in cystine uptake, a reduction in the level of GSH, and an increase in the level of oxidative stress, which ultimately led to massive death of neuronal cells [59]. The clinically approved anticancer drug sorafenib also inhibited the function of the system X_C^-, leading to cellular ferroptosis [60].

However, the function of system X_C^- was complex. System X_C^- was involved in aberrant glutamatergic neurotransmission in the brain's striatum in a PD model [61]. System X_C^- can activate metabotropic glutamate receptor 5 (mGluR 5) by releasing large amounts of glutamate, leading to abnormal glutamatergic neurotransmission in the brain. This led to early PD symptoms and ultimately to NDs [59,62]. Furthermore, the massive loss of nigrostriatal dopaminergic neuronal cells in PD was associated with disturbed levels of GSH and glutamate, and oxidative stress within the striatum was significantly inhibited using either system X_C^- inhibitors or system X_C^- knockdown [63,64]. Thus, it was clear that while inhibiting system X_C^- helped to inhibit glutamate release, it impaired the ability of the central nervous system to fight oxidative stress. More research was required since system XC had a bidirectional regulatory role, making it specifically difficult to interfere with system XC for therapeutic purposes.

It is important to deeply analyze the mechanisms involved in ferroptosis in developing NDs. Despite the progress made so far, many important scientific questions remain to be addressed. Firstly, the molecular mechanisms of ferroptosis within NDs are still poorly studied, and there is a lack of systematic studies on ferroptosis under various conditions. Secondly, there are fewer clinical studies on the involvement of ferroptosis in NDs, and there are discrepancies between animal models and human homeostasis. It remains to be investigated whether the existing results apply to human beings. Lastly, as a newly discovered iron-dependent mode of programmed cell death, the molecular mechanisms of ferroptosis involved in various central nervous system diseases remain to be further explored.

In conclusion, a deeper understanding of the scientific significance of abnormalities in ferroptosis in central nervous system disorders can contribute to the precise treatment of various NDs.

4.4. Limitations

The study has some limitations. Only the literature in the WOS database was analyzed. However, a high number of citations did not always reflect a study's influence or impact. In addition, the number of citations may be affected by publication time. Although studies with high-impact factors published in 2023 were manually screened and included in the analysis, some may still have been omitted. In general, visual analysis of the literature can help researchers intuitively understand the research hotspots, evolution process, and trends of ferroptosis research in the field of NDs.

5. Conclusion

In conclusion, this study may help scientists identify publishing patterns and emerging trends in ferroptosis in NDs. The global studies on ferroptosis in neurodegenerative diseases have developed rapidly in the past ten years. The marked increase in annual publications indicated the growing importance of this topic. The most influential author, journal, country, and institution was Maher, Pamela from the Universite De Lille, Redox Biology, China, and Guangzhou Medical University, respectively. In the future, the research on ferroptosis in neurodegeneration diseases should focus on international collaboration with multi-center, large-sample studies. Keyword co-occurrence analysis indicated that research hotspots included developing targeted therapeutic medicines and understanding the molecular mechanisms of ferroptosis in neurodegenerative disorders. Therefore, our study examined the development pattern of research on this subject from a bibliometric perspective, and offered a thorough summary of research hotspots in this area. Besides, these findings can also help researchers to find suitable publication outlets and fostering collaborative partnerships.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Ning Liu: Writing – original draft, Data curation, Conceptualization. **Wuhan Yu:** Formal analysis, Data curation. **Mengjiao Sun:** Methodology. **Dan Zhou:** Methodology. **Jing Sun:** Supervision. **Taotao Jiang:** Software. **Wenjing Zhang:** Validation, Supervision. **Manxia Wang:** Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Wenjing Zhang reports financial support was provided by Qinghai Provincial People's Hospital. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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