

Mapping the Research of Ferroptosis in Parkinson's Disease from 2013 to 2023: A Scientometric Review

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Methods: Related studies on PD and ferroptosis were searched in Web of Science Core Collection (WOSCC) from inception to 2023. VOSviewer, CiteSpace, RStudio, and Scimago Graphica were employed as bibliometric analysis tools to generate network maps about the collaborations between authors, countries, and institutions and to visualize the co-occurrence and trends of co-cited references and keywords.

Results: A total of 160 original articles and reviews related to PD and ferroptosis were retrieved, produced by from 958 authors from 162 institutions. Devos David was the most prolific author, with 9 articles. China and the University of Melbourne had leading positions in publication volume with 84 and 12 publications, respectively. Current hot topics focus on excavating potential new targets for treating PD based on ferroptosis by gaining insight into specific molecular mechanisms, including iron metabolism disorders, lipid peroxidation, and imbalanced antioxidant regulation. Clinical studies aimed at treating PD by targeting ferroptosis remain in their preliminary stages.

Conclusion: A continued increase was shown in the literature within the related field over the past decade. The current study suggested active collaborations among authors, countries, and institutions. Research into the pathogenesis and treatment of PD based on ferroptosis has remained a prominent topic in the field in recent years, indicating that ferroptosis-targeted therapy is a potential approach to halting the progression of PD.

Keywords: Parkinson's disease, ferroptosis, bibliometric analysis, iron accumulation, alpha-synuclein, mitochondrial dysfunction, oxidative stress, lipid peroxidation

Introduction

Parkinson's disease (PD) is the second most common central neurodegenerative disorder globally,¹ with the fastest-growing prevalence and disability rate.² By 2040, more than 12 million PD patients are predicted worldwide.³ Cardinal motor symptoms, including bradykinesia, rigidity, and tremor, are of crucial importance in the accurate diagnosis of PD, and non-motor manifestations such as constipation, depression, anosmia, cognitive decline, and sleep disorders are prominent during the disease course.⁴ The etiology and pathogenesis of PD remain unclear, while compelling evidence suggests that complex interactions between genetic, environmental, and age factors determine the risk and progression of PD,⁵ and various mechanisms, such as oxidative stress (OS), neuroinflammation, and mitochondrial dysfunction, are intimately involved in pathophysiological development. The gradual degeneration of dopaminergic neurons in the substantia nigra (SN), along with abnormally aggregated α -synuclein (α -syn) forming Lewy bodies, are the pathological hallmarks of PD.⁶ Although the current dopamine-

based pharmacological therapies can alleviate motor symptoms in early-stage patients, there is a lack of effective neuroprotective treatment methods to prevent PD from progressively deteriorating. Therefore, investigating the underlying mechanisms of PD to explore novel targets and develop the next generation of therapies is urgently needed.

Ferroptosis, a newly proposed cell death pathway characterized by iron-dependent reactive oxygen species (ROS) accumulation and lipid peroxidation of polyunsaturated fatty acids (PUFAs) present in plasma membranes, has been found to be a key player in the pathomechanism of PD and has gained the spotlight.⁷ Recent studies have increasingly indicated that the principal features or triggering factors of ferroptosis, including iron ion imbalance, reduced glutathione levels, lipid peroxidation, DJ-1 depletion, and coenzyme Q10 (CoQ 10) decline, are consistent with the pathological features observed in PD,^{8–14} suggesting a strong link between ferroptosis and the development of PD. Moreover, ferroptosis is a novel potential therapeutic target for PD, as ferroptosis inhibitors or iron chelators considerably attenuate the death of dopaminergic neurons and impede PD progression. Thus, studies into the aetiopathogenesis and therapeutic strategy of PD based on ferroptosis have attracted widespread attention, with its extensive research potential and value.

The past decade has witnessed a consistent rise in the amount of related research in this field. However, bibliometric analysis and visualization methodologies have rarely been used in this study area. CiteSpace, a Java-based information data processing tool that can analyze and visualize trends and patterns of related literature through metrics, co-occurrence analysis, and clustering analysis, is one of the most widely deployed bibliometric software in various research fields.¹⁵ Therefore, in this study, we conducted a comprehensive analysis of relevant literature accessed from the WOSCC database mainly based on CiteSpace software, aiming to explore the current status, hot topics and potential trends of ferroptosis in PD mechanism research.

Materials and Methods

Data Sources and Search Strategy

The original literature data were extracted from the WOSCC database, with the time span for retrieval extending from extending from the database's inception to May 23, 2023. The search query employed was TS=(Parkinson or Parkinson's disease) AND TS=(Ferroptosis). The recorded contents comprised the quantity of papers and citations, H-index, publication year, countries/regions, affiliations, authors, journals, cited references, and keywords. A total of 167 articles were retrieved. After deduplication, screening, and reading, 160 articles were ultimately selected based on the pre-determined inclusion and exclusion criteria (Figure 1).

Inclusion Criteria

- (1) Literature related to ferroptosis and Parkinson's disease;
- (2) Published in English;
- (3) The types of literature included clinical trial studies, in vitro experimental studies, in vivo experimental studies, public database analysis studies, reviews, etc. ;
- (4) Complete bibliographic information (including title, country, authors, keywords, source).

Exclusion Criteria

- (1) Duplicated publications;
- (2) Publications unrelated to the themes.

Data Conversion and Standardization

After completing the screening process, the literature was exported in both Refworks and plain text formats. All special symbols were removed, and keywords were standardized. For example, "Parkinsons disease" was merged into "Parkinson's disease", and "Parkinson's-disease" was confirmed as "Parkinson's disease". Format conversion of the retrieved literature was performed using the Data Import/Export feature in CiteSpace software.

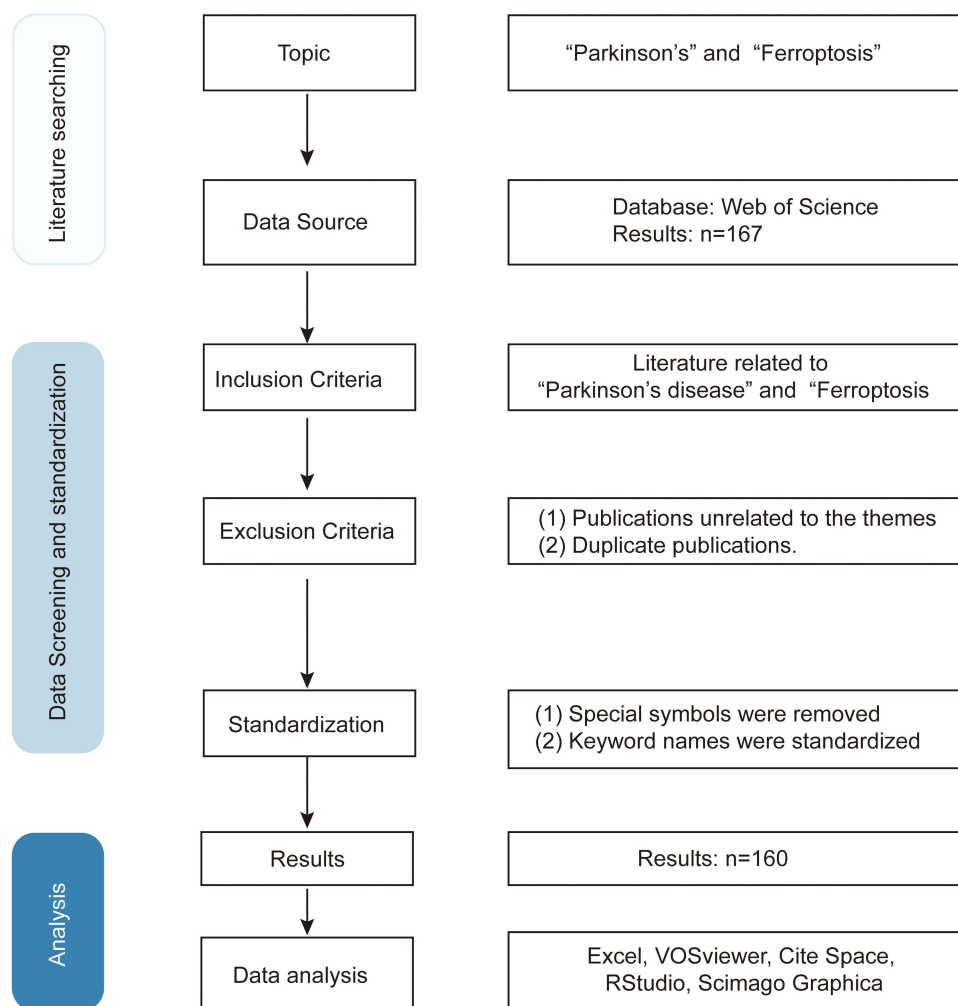


Figure 1 Detailed process for literature screening.

Analysis Tools and Methods

CiteSpace (Version 6.1. R3), VOSviewer (Version 1.6.18), and RStudio software (Version R-4.2.2) were employed as the main visualized analysis tools for statistical computing and graphics. R, a highly extensible language or environment capable of automating statistical computing and graphics, served to visually present journal literature, countries, cited authors, and keyword clouds. VOSviewer software assisted in constructing maps of core authors and keywords. Moreover, CiteSpace software is mainly adopted for analyzing keywords, research institutes and cited literature. Keyword integration was conducted, and synonyms were merged. Software-based keyword categorization or classification relies on mainstream bibliometric algorithms. The size of nodes in the graph depicts the frequency of occurrence, while the connecting lines represent co-occurrence relationships, and centrality is a metric for assessing node significance in the visual network. LLR algorithm analysis, a clustering label extraction algorithm provided by CiteSpace, was implemented for keyword clustering, where the silhouette average silhouette value (S value) and modularity (Q value) indicate the efficiency of clustering. Generally, an S value above 0.5 suggests reasonable clustering, and a Q value above 0.3 represents a significant clustering structure. In the visual analysis of authors, the evaluation was performed based on Price's law formula ($M_p=0.749*\sqrt{N_{pmax}}$, N_{pmax} = the maximum number of papers published by the most productive authors), in which core authors have more than M_p publications.

Results

Analysis of Literature by Year of Publication and Journal Source

The analysis of the volume of publications concerning ferroptosis in the PD domain demonstrated an overall upward trend, despite the initial low base number (Figure 2A). The first article appeared in 2013, and the highest peak of publications occurred in 2022, with 40 articles. The publication trend is divided into two phases: from 2013 to 2018 as the initial phase, with an annual publication volume consistently below 10 articles; from 2018 to the present as the stable growth phase, where the trend shows a steady increase, indicating growing interest from scholars in this field.

The articles were published in a total of 105 journals, among which *Free Radical Biology and Medicine* had the most frequent publications, with 13 articles, as displayed in Figure 2B. Based on Bradford's law, the following 12 journals were identified as core journals in this field: *Free Radical Biol. Med.*, *Oxid. Med. Cell. Longevity*, *Antioxidants*, *Mol. Neurobiol.*, *Neuroscience*, *Ageing Res. Rev.*, *Cells*, *Front. Cell. Neurosci.*, *Front. Pharmacol.*, *Neurobiol. Dis.*, *Acta Pharmacol. Sin.*, and *Antioxid. Redox Signaling* (Figure 2C). *J Biol Chem*, with 479 citations, held the topmost position in the field of Parkinson's disease and ferroptosis research (Figure 2D). Furthermore, the publication volume for *Free Radical Biol. Med.* and *Oxid. Med. Cell. Longevity* experienced noticeable growth after 2018 and 2021, respectively (Figure 2E).

The dual-map overlay of journals illustrated the citation relationships between citing and cited journals, with the left side representing the cluster of citing journals and the right side representing the cluster of cited journals. The orange path in Figure 2F depicts that journals from the domains of Molecular Biology and Genetics possess the highest likelihood of being cited by journals in the fields of Molecular Biology and Immunology.

Country/Regional Contributions to Global Publications

Figure 3A shows the literature from 35 countries that have published studies related to ferroptosis and PD. Typically, this sort of information is depicted by maps or bubble charts. The top ten countries in terms of the number of publications were China (84 articles), USA (27 articles), Australia (16 articles), France (12 articles), England (11 articles), India (8 articles), Germany (7 articles), Japan (7 articles), Sweden (5 articles), and Italy (4 articles). The country with the most citations was USA (3546 articles), followed by China and Australia (Figure 3B). In Figure 3C and D, which illustrate the collaborative relationships among various countries in the research on ferroptosis and PD, the thickness of the connecting line between any two countries is directly proportional to the extent of their cooperation in the respective research field. Based on this, we can infer that China had a closer working relationship with other countries, especially in cross-continental collaborations. Single Country Publications (SCP) in Figure 3E indicates that all the authors of an article come from the same country, while Multiple Country Publications (MCP) indicates that the article's authors are from multiple countries. It is inferred that both China and Australia boast the largest number of co-authors from foreign nations within this field, while internal collaborations in China still accounted for a larger proportion.

In summary, this result reveals the global cooperation patterns and trends related to ferroptosis and PD. Such information could aid researchers in ascertaining which countries wield greater influence in this field, as well as which nations collaborate more frequently. Furthermore, it could assist researchers in identifying appropriate collaboration partners and gaining insight into the worldwide research landscape.

Author and Affiliations Analysis

According to the visualization chart of 160 screened publications, a total of 958 authors performed related studies. The top 10 authors ranked by the output of publications are displayed in Figure 4A, and their annual publication variations are displayed in Figure 4B. The highest quantity of publications (9 articles) belongs to Devos, David from Université Lille Nord de France. The author with the most cited documents was Bush AI from the University of Melbourne, with 152 articles, as shown in Figure 4C. $M_p = 1.98$ was determined based on Price's law formula. Accordingly, authors with ≥ 2 publications were designated core authors, and there existed 84 core authors in total. In the co-authors network (Figure 4E), nodes stand for authors, whose publication count is indicated by node size. The number of connecting lines illustrates the degree of cooperation between authors, and different colours denote various cooperation groups. The

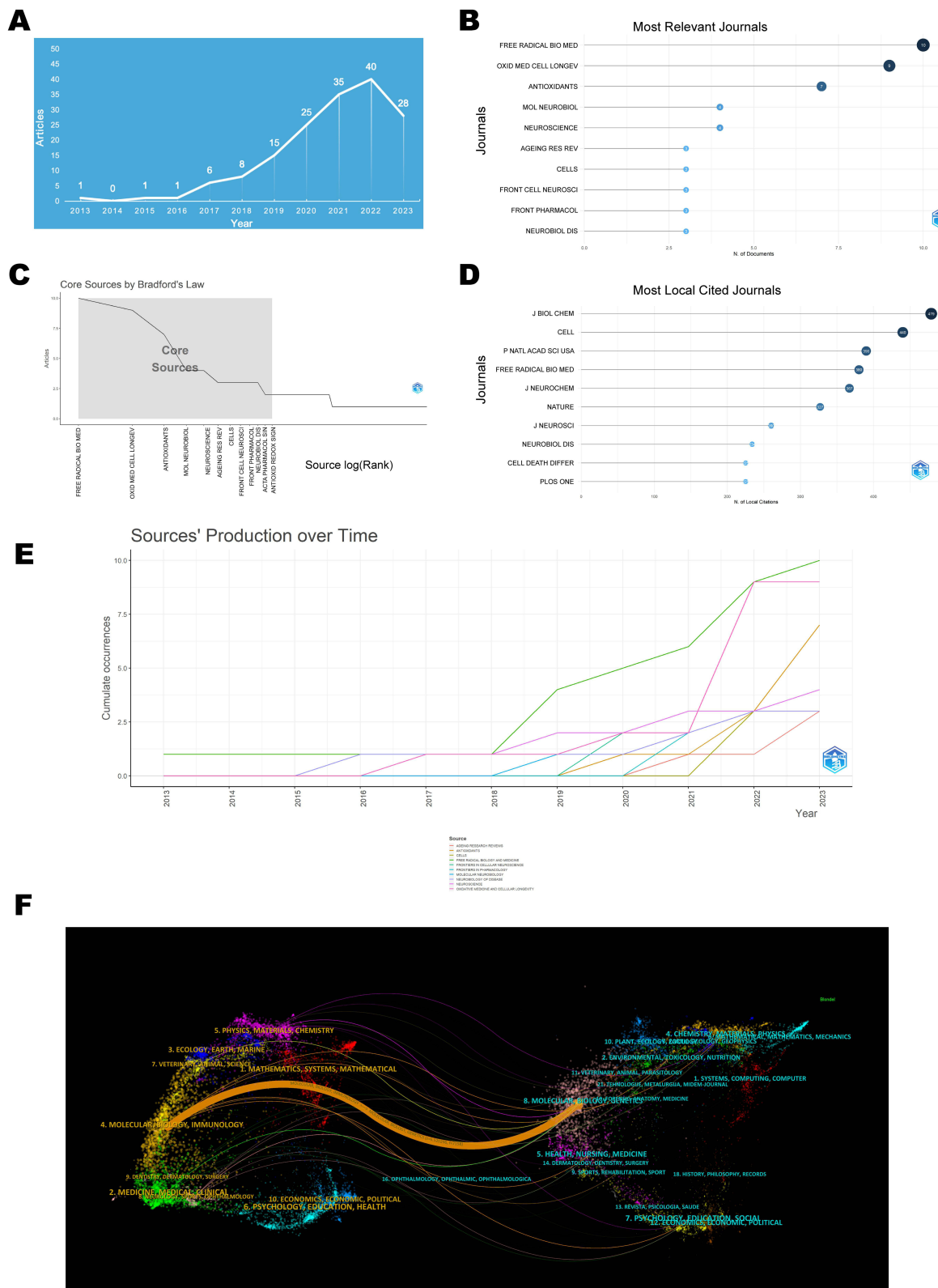


Figure 2 Visualization map of publication volume and journal sources. (A) Distribution of annual publication volume. (B) Top 10 journals by publication volume. (C) Core journals based on Bradford's law. (D) Top 10 Most Cited Journals. (E) Annual Publication Trends of the Top 10 Journals. (F) Dual-Map Overlay of Journals.

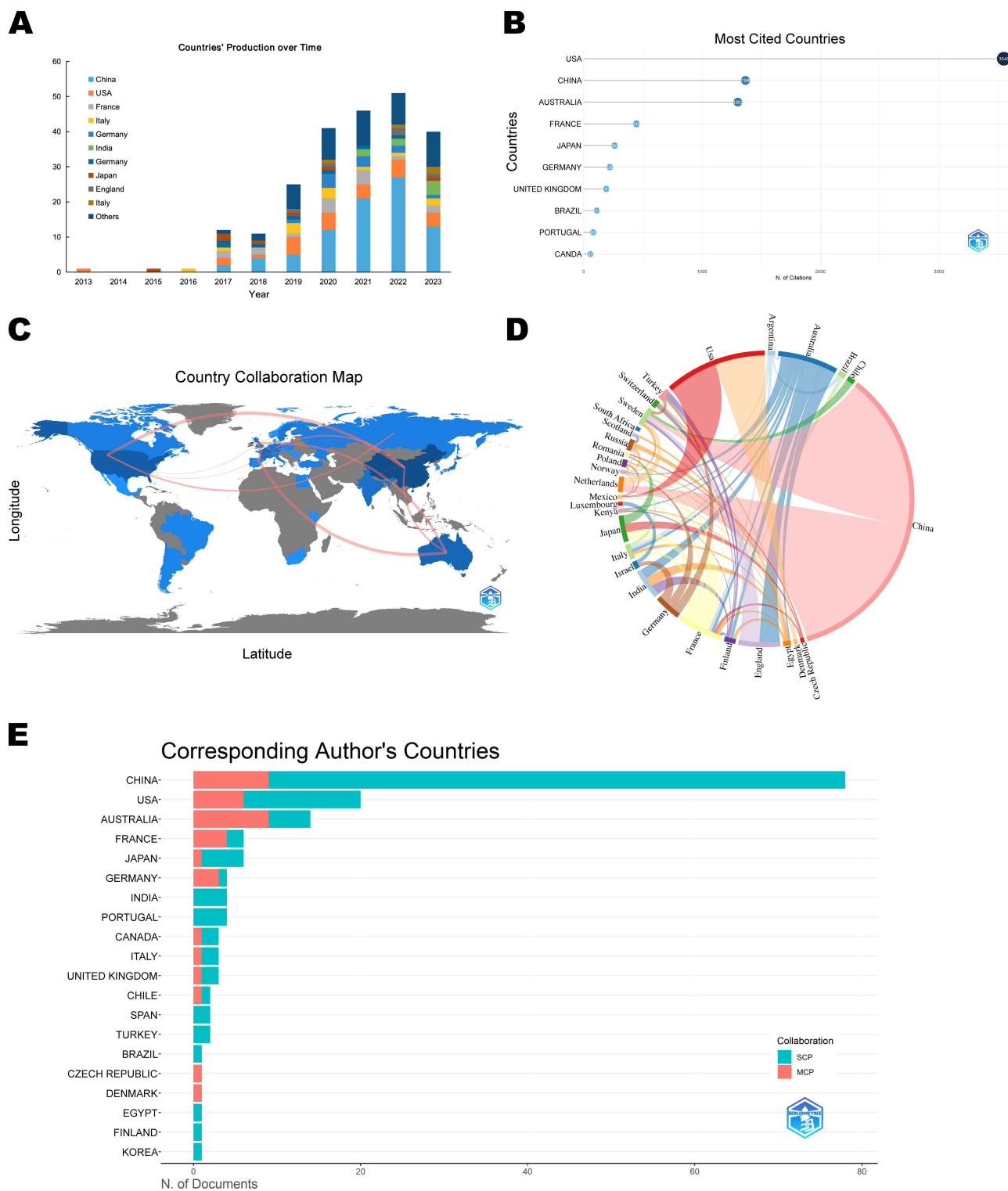


Figure 3 Visualization map of the contributions of various countries to related research. **(A)** World map of countries' literature publications. **(B)** Top 10 cited countries in terms of literature publications. **(C)** World map of countries' cooperation. **(D)** Chord diagram evaluating international collaborations. **(E)** The 20 countries with the most corresponding authors.

results indicated the formation of 4 closely collaborating academic groups in this field, including Zhu ML, Devos D, Cao J, and Huang DY. Their research focused on experimental studies of Sorting Nexin 5,^{16,17} lipid metabolism,^{18,19} DJ-1 proteins,²⁰ and iron chelators²¹ in regulating ferroptosis in PD.

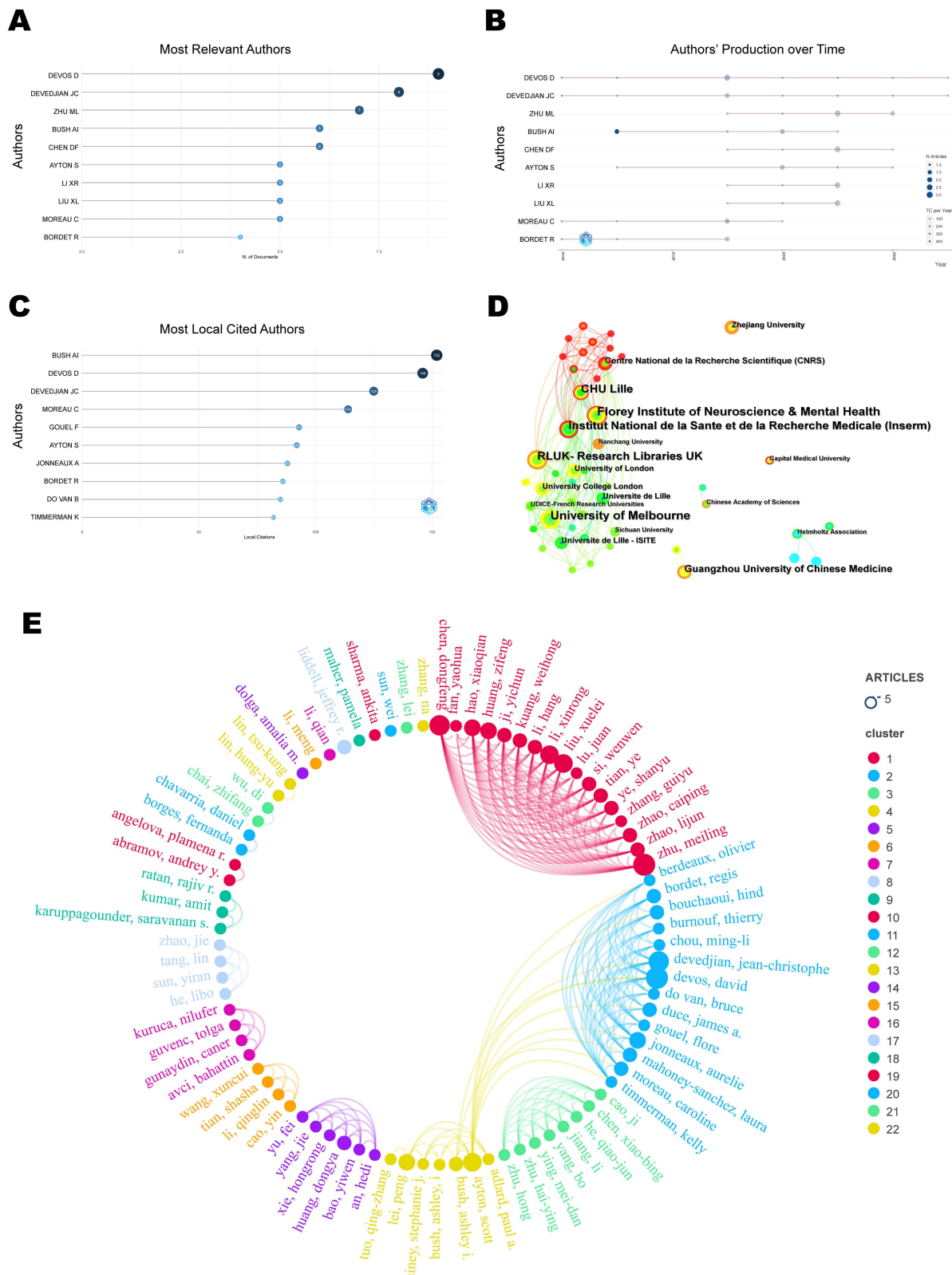


Figure 4 Visualization Map of Authors and Institutions. **(A)** Top 10 authors in publication terms. **(B)** Annual publication trends of the top 10 authors in publication terms. **(C)** Top 10 cited authors in publication terms. **(D)** Distribution map of inter-institutional collaboration. **(E)** Collaborative network map of core authors.

Figure 4D, a CiteSpace-based institutional co-occurrence map, contains 162 nodes and 378 lines. Each institution is symbolized by a node, with a larger node signifying higher productivity of the institution. Lines connecting the nodes indicate institutional cooperation, and their color and thickness represent the duration and intensity of the cooperation. Betweenness centrality (BC) represents the importance of the node in the network. The top 10 institutions out of a total of 162 institutions conducting ferroptosis in PD by volume and centrality are listed in Table 1. The University of Melbourne had the highest publication volume with 12 articles, followed by Florey Institute of Neuroscience & Mental Health and Research Libraries UK (RLUK), while the top three institutions in terms of centrality were RLUK, Institut National de la Sante et de la Recherche Medicale (Inserm) and University of Melbourne. University of Melbourne, the Florey Institute of Neuroscience & Mental Health, Inserm and Centre National de la Recherche Scientifique (CNRS), among others, were found to possess closer co-operations. These findings demonstrated that the majority of institutions were universities from various nations, with a higher rate of collaboration observed among institutions in Europe and Oceania.

Co-Cited References Analysis

Highly cited papers assist in detecting pioneering research within a research field and are used within the WOS to identify the most influential research papers. The top 1% of papers by cited frequency were listed in Figure 5A. Citation burst refers to a sharp frequency increase in the citations of a specific article during a particular time period and serves to unearth the latest high-interest research topics in related fields. The 20 cited references with the highest citation bursts are presented in Figure 5B, where the blue line depicts the interval of time with citation emergence, and the red line indicates the period of time when a citation burst of a reference was detected.²² Cocitation refers to that two or more articles are cited by one or more papers at the same time, and the two articles are considered to be a cocitation relationship. As a result, 16 highly cited papers (Figure 5A), 20 references with the strongest citation burst (Figure 5B), and 32 papers with co-citation frequency not less than 20 (Figure 5C) were extracted, which we refer to as a, b, and c for convenience. Through Venn analysis (Figure 5D), it was found that 1 paper is in a, b, and c simultaneously, which was published by Do Van B on *NEUROBIOL DIS* in 2016 and is the first to emphasize the role of ferroptosis in PD,²³ making it one of the most influential papers. 6 papers in both a and c; 14 papers in both b and c. The detailed information, in particular the main highlights and contributions of each paper, is listed in Table 2.

The thematic coupling analysis of the co-cited literature (Figure 5E) identified a total of five clusters: the blue cluster contained most of the articles on the mechanisms of ferroptosis,^{38,65} the red cluster mainly focused on ferroptosis-targeted therapies,^{23,39} the green cluster concentrated on iron metabolism in neurodegenerative pathologies,⁴¹ the yellow cluster included articles with content primarily related to mitochondrial dysfunction,^{45,66} and the purple cluster featured researches on molecular therapeutics of PD.^{19,67}

Clustering analysis of co-cited references proves to be an effective method for uncovering the cutting-edge topics of the field.⁶⁸ Further clustering results for these references are displayed in Figure 5F, and in Figure 5G, each cluster label is matched

Table 1 Top 10 Institutions by Output (Left) and Centrality (Right)

Rank	Affiliations	Publications	Rank	Affiliations	Betweenness Centrality
1	University of Melbourne	12	1	RLUK- Research Libraries UK	0.05
2	Florey Institute of Neuroscience & Mental Health	11	2	Institut National de la Sante et de la Recherche Medicale (Inserm)	0.04
3	RLUK- Research Libraries UK	10	3	University of Melbourne	0.02
4	Centre Hospitalier Universitaire de Lille (CHU Lille)	9	4	Centre National de la Recherche Scientifique (CNRS)	0.02
5	Institut National de la Sante et de la Recherche Medicale (Inserm)	9	5	Florey Institute of Neuroscience & Mental Health	0.01
6	Guangzhou University of Chinese Medicine	7	6	Centre Hospitalier Universitaire de Lille(CHU Lille)	0.01
7	Centre National de la Recherche Scientifique (CNRS)	5	7	UDICE-French Research Universities	0.04
8	University of London	4	8	University of Cambridge	0.02
9	Universite de Lille - ISITE	4	9	Hebrew University of Jerusalem	0.01
10	University College London	4	10	Pennsylvania Commonwealth System of Higher Education (PCSHE)	0.01

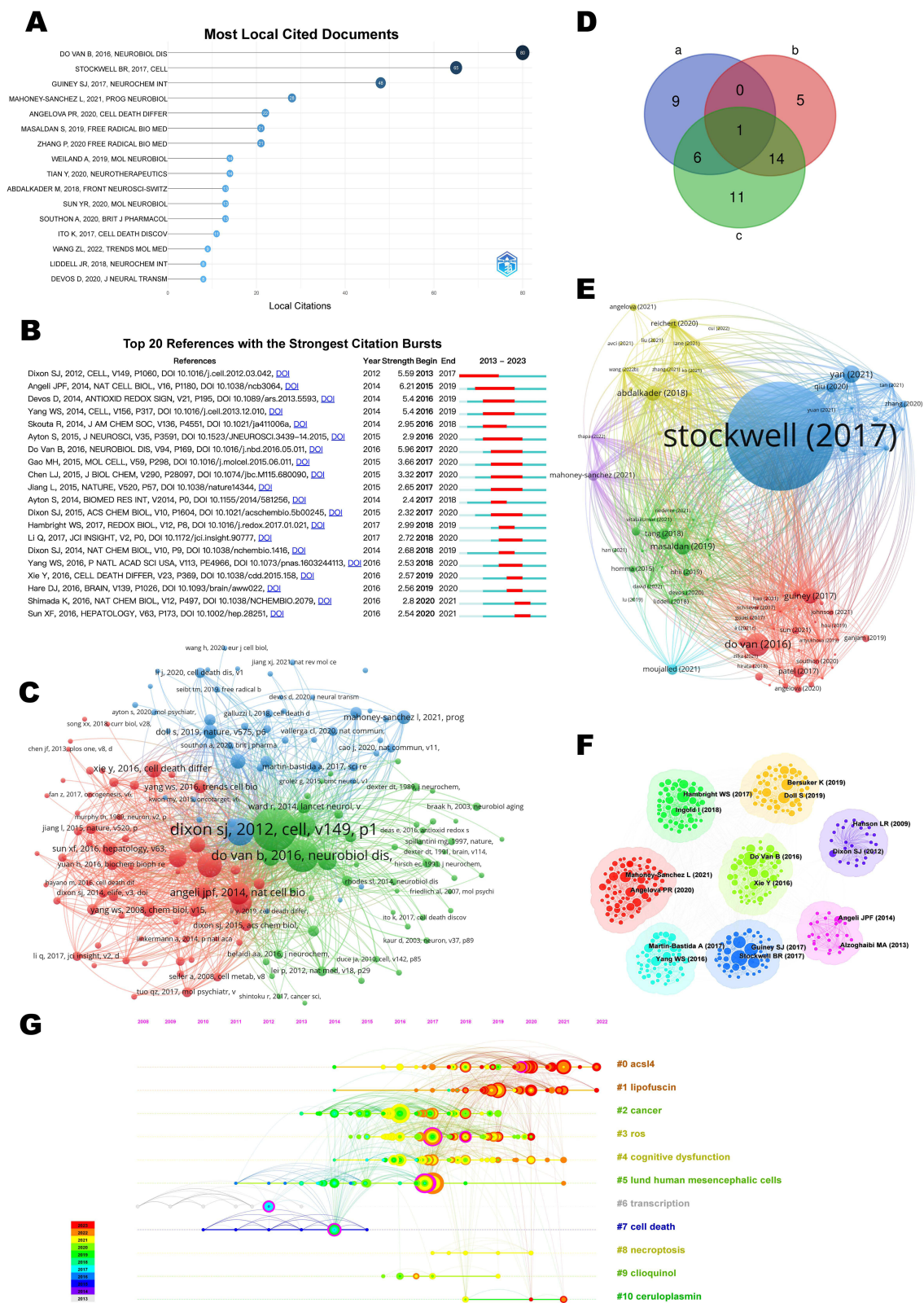


Figure 5 Visualization Map of Cited Literature. (A) Highly cited papers. (B) The 20 references having the highest citation burst. (C) Network of 32 papers with co-citation frequency not less than 20. (D) Venn outline for three of them. a, the collection of highly cited papers; b, the collection of references with the strongest citation burst; c, the collection of papers with co-citation frequency not less than 20. (E) Network of cited references. (F) Clustered network map of co-cited references. (G) Timeline map of co-cited references with their cluster labels on the right.

Table 2 The Detailed Information of the 16 Highly Cited Papers, 20 References with the Strongest Citation Burst, and 33 Papers with Co-Citation Frequency Not Less Than 20

Relationship with a, b, and c	References	Main Highlights and Contributions	Corresponding Author	Institute/Country	Periodical	
Papers in a, b, and c, simultaneously	Do Van B et al, 2016 ²³	First study to emphasize the importance of ferroptosis dysregulation in PD and to prove Fer-1 derivatives and PKC inhibitors as strong drug candidates to modulate the ferroptotic signaling cascade.	Devedjian JC	Lille Nord de France University, France	Neurobiol Dis	
	Dixon SJ et al, 2012 ²⁴	Demonstrated the role of cystine uptake by system xc ⁻ in ferroptosis	Stockwell BR	Columbia University, USA	Cell	
	Friedmann Angeli JP et al, 2014 ²⁵	Provided direct genetic evidence that the knockout of Gpx4 causes ferroptosis.	Conrad M	Helmholtz Zentrum München, Germany	Nat Cell Biol	
	Devos D et al, 2014 ²⁶	A moderate iron chelation regimen that avoids changes in systemic iron levels may constitute a novel therapeutic modality for PD.	Devos D	Lille Nord de France University, France.	Antioxid Redox Signal	
	Yang WS et al, 2016 ²⁷	Proved the necessity of PUFA oxidation by lipoxygenases for ferroptosis.	Stockwell BR	St. John's University, USA.	Proc Natl Acad Sci USA	
	Yang WS et al, 2013 ²⁸	Identified Gpx4 as a central regulator of ferroptotic cancer cell death.	Stockwell BR	Columbia University, USA	Cell	
	Skouta R et al, 2014 ²⁹	Developed a mechanistic model to explain the activity of Fer-1	Stockwell BR	Columbia University, USA	J Am Chem Soc	
	Gao M et al, 2015 ³⁰	Provided a potential therapeutic approach for treating ischemia/reperfusion-induced heart injury by inhibiting glutaminolysis.	Jiang X	Memorial Sloan-Kettering Cancer Center, USA	Mol Cell	
	Ayton S et al, 2015 ³¹	Explained how elevated NO causes iron-dependent neurodegeneration in PD	Bush AI	University of Melbourne, Australia	J Neurosci	
	Jiang L et al, 2015 ³²	Uncovered a new mode of tumour suppression based on p53 regulation of cystine metabolism, ROS responses and ferroptosis.	Gu W	Columbia University, USA	Nature	
	Dixon SJ et al, 2015 ³³	Revealed the genetic regulation of cell death and highlight the central role of lipid metabolism in nonapoptotic cell death.	Dixon SJ, Superti-Furga G, Stockwell BR	Columbia University, USA	ACS Chem Biol	
	Hambright WS et al, 2017 ³⁴	Indicated that forebrain neurons are susceptible to ferroptosis.	Ran Q	University of Texas, USA	Redox Biol	
	Dixon SJ et al, 2014 ³⁵	Reviewed the role of iron and reactive oxygen species in cell death.	Stockwell BR	Columbia University, USA	Nat Chem Biol	
	Papers in a and c, simultaneously	Xie Y et al, 2016 ³⁶	Reviewed the regulation signaling pathways of ferroptosis and discuss the role of ferroptosis in disease.	Kang R, Tang D	University of Pittsburgh, USA	Cell Death Differ
		Sun X et al, 2016 ³⁷	Demonstrated novel molecular mechanisms of ferroptosis(p62-Keap1-NRF2 Pathway).	Tang D	Guangzhou Medical University, China	Hepatology
Stockwell BR et al, 2017 ³⁸		Reviewed the connections between ferroptosis and other areas of biology and medicine.	Stockwell BR	Columbia University, USA	Cell	
Guiney SJ et al, 2017 ³⁹		Reviewed the potential to therapeutically target ferroptosis to slow the progression of PD.	Ayton S	University of Melbourne, Australia	Neurochem Int	
Mahoney-Sánchez L et al, 2021 ¹³		Addressed the known pathological features of PD in relation to the ferroptosis pathway with therapeutic implications of targeting ferroptosis.	Devos D, Duce JA	Lille University, France	Prog Neurobiol	
Angelova PR et al, 2020 ⁴⁰		Reported a new mechanism of lipid peroxidation-induced cell death, emphasising the role of ferroptosis in PD.	Abramov AY, Gandhi S	UCL Queen Square Institute of Neurology, UK	Cell Death Differ	
Masaldan S et al, 2019 ⁴¹		Described the iron metabolism and ferroptosis in neurodegeneration.	Bush AI	Melbourne Dementia Research Centre, Australia	Free Radic Biol Med	
Zhang P et al, 2020 ⁴²		Presented ferroptosis is more initial in cell death caused by iron overload which is associated with the p53 signalling pathway.	Jiao Q, Jiang H	Qingdao University, China	Free Radic Biol Med	

Papers only in a	Weiland A et al, 2019 ⁴³	Summarized the underlying mechanisms of ferroptosis, and its role in diverse neurologic diseases.	Li Q, Wang J	Johns Hopkins University, USA.	Mol Neurobiol
	Tian Y et al, 2020 ⁴⁴	Discovery of the role of FTH1 in linking ferritinophagy and ferroptosis in the 6-OHDA model of PD.	Chen D, Zhu M	Guangzhou University of Chinese Medicine, China	Neurotherapeutics
	Abdalkader M et al, 2018 ⁴⁵	Proposed targeting Nrf2 as a rational therapy for ferroptotic neurodegeneration.	Liddell JR	University of Eastern Finland, Finland	Front Neurosci
	Sun Y et al, 2020 ⁴⁶	Presented a potential therapy of PD combining targeting the p62-Keap1-Nrf2 pathway and inhibiting ferroptosis.	Tang L	Sichuan University, China	Mol Neurobiol
	Southon A et al, 2020 ⁴⁷	Demonstrated that Cull(at5m) is a promising therapeutic candidate for ferroptosis-related diseases including ALS and PD.	Bush AI	University of Melbourne, Australia	Br J Pharmacol
	Ito K et al, 2017 ⁴⁸	MPP+-induced cell death and ferroptosis are two distinct mechanisms with common features.	Imagawa Y, Tsujimoto Y	Osaka University, Japan	Cell Death Discov
	Wang ZL et al, 2022 ¹⁴	Reviewed the crosstalk between glia and neurons to explore novel therapeutic interventions for PD.	Li JY	China Medical University, China	Trends Mol Med
	Liddell JR et al, 2017 ⁴⁹	Summarised the nexus between mitochondrial function, iron, copper and glutathione in PD.	Liddell JR	University of Melbourne, Australia	Neurochem Int
	Devos D et al, 2020 ⁵⁰	Reviewed the efficacy and safety of conservative iron chelation for neurodegenerative diseases	Devos D	Lille Nord de France University, France	J Neural Transm
	Papers only in b	Chen L et al, 2015 ⁵¹	Presented that ferroptosis inhibition by GPX4 is essential for motor neuron health and survival in vivo.	Ran Q	University of Texas, USA
Ayton S et al, 2014 ⁵²		Reviewed the evidence that prooxidant iron elevation in the SNc is an invariable feature of sporadic and familial PD forms	Lei P	University of Melbourne, Australia	Biomed Res Int
Li Q et al, 2017 ⁵³		Presented that ferrostatin-1 protects hemorrhagic brain, and cyclooxygenase-2 could be a biomarker of ferroptosis.	Wang J	Columbia University, USA.	JCI Insight
Hare DJ et al, 2016 ⁵⁴		Reviewed redox couple formed by iron and dopamine that induces neurodegeneration in PD.	Double KL	University of Technology Sydney, Broadway, Australia	Brain
Shimada K et al, 2016 ⁵⁵		Revealed that FIN56 activates ferroptosis in a manner independent of GPX4 degradation.	Stockwell BR	Columbia University, USA	Nat Chem Biol

(Continued)

Table 2 (Continued).

Relationship with a, b, and c	References	Main Highlights and Contributions	Corresponding Author	Institute/Country	Periodical
Papers only in c	Doll S et al, 2017 ⁵⁶	Proved that Acsl4 inhibition is a viable therapeutic approach to prevent ferroptosis-related diseases.	Angeli JP, Conrad M	Helmholtz Zentrum München, Germany	Nat Chem Biol
	Kagan VE et al, 2017 ⁵⁷	Vitamin E poses a homeostatic physiological effect. This oxidative PE death pathway may also represent a target for drug discovery.	Conrad M, Bayir H	University of Pittsburgh, Germany	Nat Chem Biol
	Bersuker K et al, 2019 ¹²	Identified FSP1 as a key component of a non-mitochondrial CoQ antioxidant system that acts in parallel to the canonical glutathione-based GPX4 pathway.	Olzmann JA	University of California, Berkeley, USA	Nature
	Doll S et al, 2019 ⁵⁸	Identified FSP1–CoQ10–NAD(P)H pathway exists as a stand-alone parallel system, which co-operates with GPX4 and glutathione to suppress phospholipid peroxidation and ferroptosis.	Angeli JPF, Conrad M	Helmholtz Zentrum München, Germany	Nature
	Yang WS et al, 2008 ⁵⁹	Identify two compounds named RSL3 and RSL5, and defined aspects of their action mechanism.	Stockwell BR	Columbia University, USA	Chem Biol
	Ward RJ et al, 2014 ⁶⁰	Reviewed the role of iron in brain ageing and neurodegenerative disorders	Zecca L	Imperial College London, UK	Lancet Neurol
	Yang WS et al, 2016 ⁶¹	Summarized the discovery of ferroptosis, the mechanism of ferroptosis regulation, and its relevance to pathological physiology.	Stockwell BR	Columbia University, USA	Trends Cell Biol
	Martin-Bastida A et al, 2017 ⁶²	A phase 2 randomised double-blinded placebo controlled clinical trial of Brain iron chelation by deferiprone in PD	Dexter DT	Imperial College London, UK	Sci Rep
	Sian J et al, 1994 ¹⁰	Investigated alterations in glutathione levels in PD and other neurodegenerative disorders affecting basal ganglia	Jenner P	King's College London, UK	Ann Neurol
	Yagoda N et al, 2007 ⁶³	Demonstrated that ligands to VDAC proteins can induce non-apoptotic cell death selectively in some tumour cells harbouring activating mutations in the RAS–RAF–MEK pathway.	Stockwell BR	Columbia University, USA	Nature
Yuan H et al, 2016 ⁶⁴	Demonstrated that ACSL4 is a sensitive monitor and an important contributor of ferroptosis.	Tang D	Jilin University, China	Biochem Biophys Res Commun	

by the corresponding timeline. Clusters #0 and #1 indicated that ACSL4 inhibitors (ferroptosis inhibitors) and lipofuscin remain the ongoing focal points of research to date. Clusters #0 ACSL4 inhibitors, #1 lipofuscin, #3 ROS regulation, #9 chloroquine, and #10 ceruloplasmin emerge as significant therapeutic targets; Clusters #2 cancer and #4 cognitive dysfunction are other domains having dependencies; Clusters #5 neuronal cells, #6 transcription, #7 cell death, and #8 necrosis are related to the corresponding mechanisms under investigation.

Keywords Analysis

Keywords Co-Occurrence Analysis

The analysis of keywords portrays the professional focus of an article or an author, providing an overall synopsis of the corresponding research pattern.⁶⁹ High-frequency keywords signify a widely explored topic of investigation, and high-centrality keywords highlight the significance and impact of the related research content within this particular field.⁷⁰

As shown in Figure 6A-C, 50 keywords appeared more than 5 times in total. Remarkably, in addition to ferroptosis and PD, OS/Reactive oxygen species (ROS), iron/iron metabolism, lipid peroxidation/polyunsaturated fatty acids,

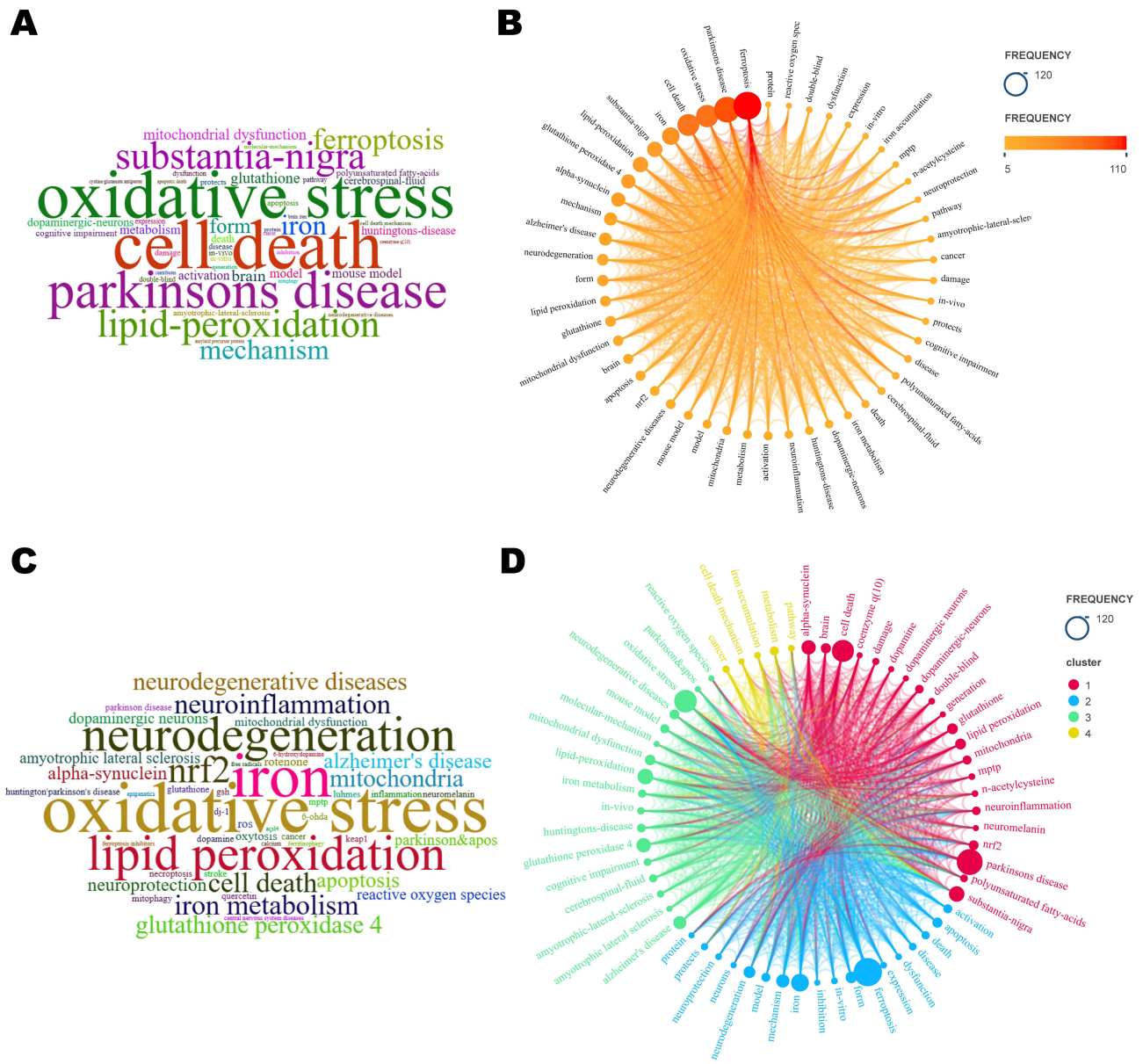


Figure 6 Visualization Map of Keyword Frequency and Co-occurrence Analysis. (A) Word cloud of keywords. (B) Keyword frequency distribution. (C) Word cloud of Author Keywords. (D) Keyword Co-occurrence Analysis.

glutathione peroxidase 4 (GPX4)/n-acetylcysteine (NAC), α -syn, mitochondrial dysfunction, nuclear factor E2-related factor 2 (Nrf2), and mouse/in vivo/in vitro models were all ranked. Combined keyword co-occurrence analysis (Figure 6D) reveals a research emphasis on in vivo experiments, mechanism of action and targeted therapy. Among the animal models implemented in the field, mouse models, particularly 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) models, were the most frequently employed. Additional animal models included the 6-OHDA model, rotenone model, α -Syn model, LPS model, and PINK1 knockout model, among others. In terms of mechanistic studies, the primary focus was on the molecular regulation or signaling pathways that play a role in regulating apoptosis, OS, lipid peroxidation, iron metabolism, and mitochondrial function, thereby affecting cellular ferroptosis in PD. Commonly used drugs and drug targets in experimental studies based on cellular, mouse and other models included glutathione (GSH), GPX4, Nrf2, protein kinase C (PKC) inhibitors, lipoxygenase (LOX) inhibitors, and iron chelators.

Keyword Citation Burst Analysis

By analyzing the emergent keywords, it is feasible to identify the focal themes of research in the field over time and to predict research trends. As illustrated in Figure 7A, with the blue line denoting the time interval and the red line signifying the duration during which the keyword bursts were detected, the keywords demonstrating the strongest emergence intensity were mitochondrial dysfunction and iron metabolism. Furthermore, iron accumulation, cognitive disorders, and antioxidants remain research hotspots to date.

Combining the keyword time zone map, timeline map and topic trend, as shown in Figure 7B-D, the evolution of research hotspots in this field is divided into 3 time phases: (1) from 2013–2016, only research-related basic terms, such as Parkinson's disease, iron, mouse model, OS and apoptosis, appeared in the keywords, indicating that academics had started researching in the field, but the heat is lacking; (2) from 2017–2020, keywords including in vivo experiments, targeting GPX4, and mitochondrial dysfunction garnered significant attention, leading to an apparent boom in research on antioxidant effects; and (3) from 2021–2023, the α -Syn model, double-blind trials, and iron accumulation have successively become research hotspots, indicating a shift towards clinical trials of targeted therapies. Based on this, it is predicted that antioxidant therapies, clinical trials, and specific molecular targets will be the hotspots of future research in the field of ferroptosis and PD after 2023.

Discussion

This paper employs software tools such as CiteSpace, VOSviewer, and the RStudio, to summarize and collate a total of 160 publications related to ferroptosis in PD from the WOSCC database, with records up to May 23, 2023. By creating knowledge maps, the paper provides a visual representation of the publication status, journal sources, research authors, institutional collaboration networks, related keywords, and citation situations in this field for the ten years since the first relevant article was published in 2013. Ferroptosis, a novel modality of cell death, has received widespread attention and has shown a steady growth trend in publication volume over the past decade. Currently, the United States, China, and Australia are leading in this research field. Specifically, the United States has the most published and most cited journals (*Free Radical Biology and Medicine*, *J Biol Chem*), making it the most cited country, with the second-highest overall number of publications. China leads in the total number of publications, with citation counts second only to the United States. The University of Melbourne is the institution with the most publications, and Bush AI from this university is the author with the most citations and the highest influence.

The types of publications in this field mainly include in vitro and in vivo experiments, reviews, and information from public databases, with reviews accounting for approximately half of the publications. These reviews tended to describe the molecular pathways between cellular ferroptosis and PD along with potential treatment strategies based on these pathways, reflecting the current focus of researchers on developing a scientific basis and potential new targets for treating PD based on ferroptosis. Current relevant experimental researches primarily aim to explore the scientific validity and feasibility of various compounds, especially natural small molecule compounds, as potential inhibitors of PD-related ferroptosis. Keyword analysis has indicated that current research hotspots are the mechanisms of iron metabolism disorders, lipid peroxidation, and imbalanced antioxidant regulation, involving specific targets such as GPX4, NRF2,

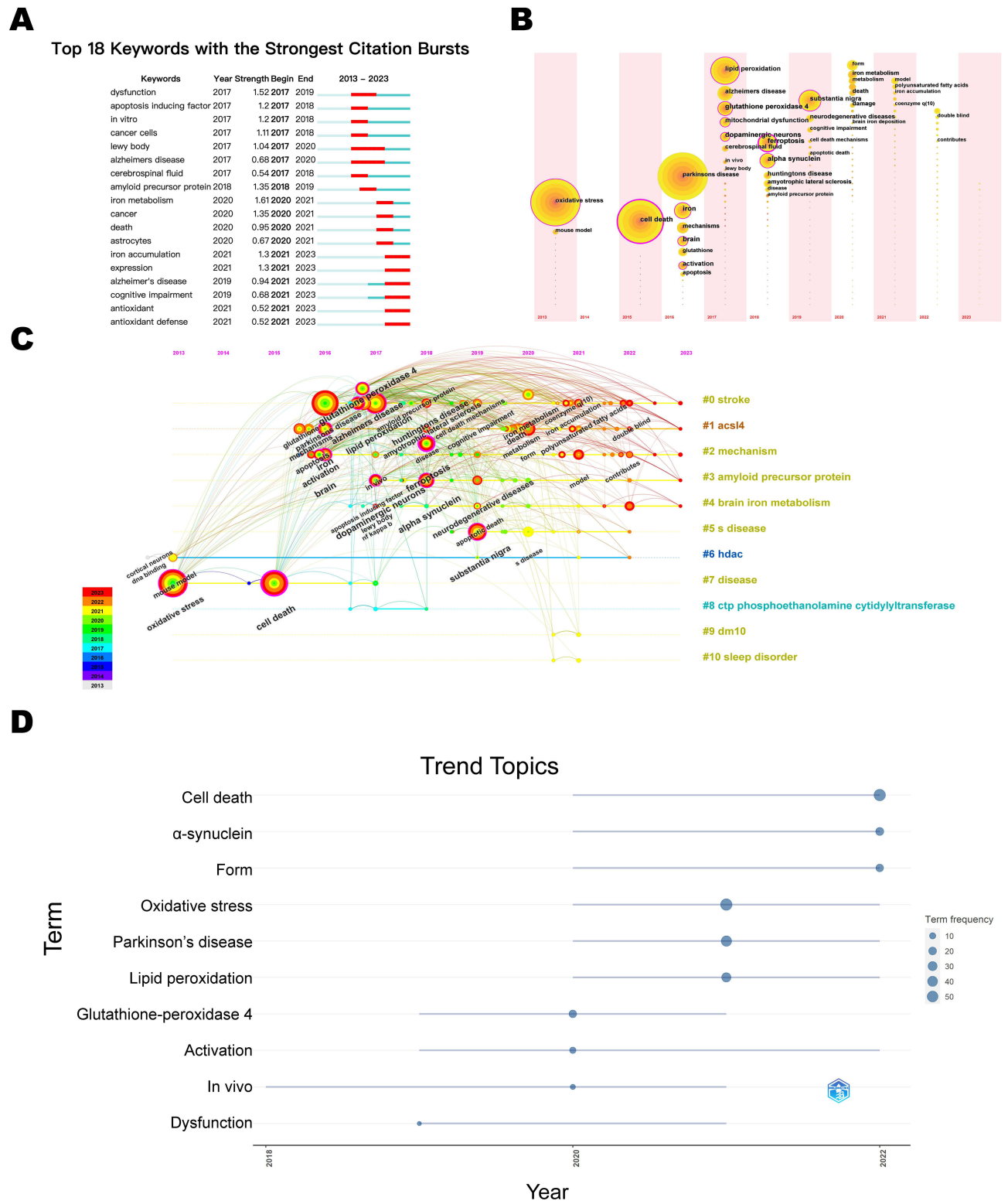


Figure 7 Visualization Map of Keyword bursts and time zone Analysis. **(A)** Keyword Emergence. **(B)** Keyword timeline. **(C)** Keyword Time Zone. **(D)** Trends in thematic terms.

and ACSL4. It should be highlighted that clinical research aimed at treating PD by targeting ferroptosis is an important direction and ultimate goal for future investigation and remains in its preliminary stages.

The Correlation Between Ferroptosis and the Pathological Mechanism of PD

The results of keyword co-occurrence and emergence analysis showed that the keywords iron accumulation, α -syn, mitochondrial dysfunction, OS, lipid peroxidation and antioxidant had a high co-occurrence frequency and emergence intensity, indicating that the exploration of the ferroptosis pathway in PD is the hotspot and trend of current research, which is conducive to the search for a new therapeutic target targeting ferroptosis.

Iron Accumulation

In the central nervous system, the ability of iron to circulate in its oxidized state and to form ligand bonds makes it an important cofactor for numerous enzymes involved in a variety of fundamental physiological processes. However, overloaded iron breaks down peroxides by triggering the Fenton reaction, resulting in the production of high levels of hydroxyl radicals that cause oxidative damage to cells. Iron also acts as a LOX enzyme family cofactor, enabling the formation of lipid peroxides and playing a central role in cellular ferroptosis.^{71,72} Several studies have shown that cellular iron overload leads to the accumulation of lipofuscin, intralysosomal aggregates mainly composed of lipids and oxidized proteins, and the amount of iron contained in lipofuscin plays a crucial role in its cytotoxicity.^{73,74} The iron in lipofuscin catalyzes the formation of free radicals, jeopardizes the stability of the lysosome, triggers apoptosis and induces mitochondrial dysfunction.^{75–78} Shi L et al found that lipofuscin accumulated significantly in the SN neurons and the accumulation levels were positively correlated with iron content, DA neuron loss and PD scores, suggesting that MPTP-induced oxidative stress, marked by lipofuscin, leads to the accumulation of iron, which in turn creates a feed-forward loop that exacerbates the toxicity of MPTP.⁷⁹ Meanwhile, excessive iron accumulation in the SN represents a key pathological characteristic of PD. Iron is deposited selectively in certain brain regions, including the SN, caudate nucleus and pallidum, as humans age, and this phenomenon is particularly severe in PD patients,⁸⁰ with iron levels positively correlating with the PD process and its associated motor dysfunction.^{81,82} Inductively coupled plasma spectroscopy,⁸³ magnetic resonance imaging,⁸⁴ laser microprobe mass spectrometry,⁸⁵ susceptibility-weighted imaging,^{86,87} enhanced T2-weighted angiography,⁸⁸ and single photon emission tomography of the dopamine transporter⁸⁹ are all complementary diagnostic tools that confirmed a link between dopaminergic striatal impairment and nigrostriatal iron deposition in PD patients. Ferroptosis was found to precede apoptosis in dopaminergic cells treated with the iron fortifier ferric ammonium citrate (FAC).⁴² Abnormalities in iron metabolism, including the down-regulation of iron transport protein (FPN),⁹⁰ up-regulation of divalent metal transfer protein 1 (DMT1),⁹¹ and reduced plasma cuprocytin activity of iron oxidase, have also been reported in animal models and PD patients.^{92,93} Furthermore, iron chelation therapies have demonstrated the capability to attenuate motor deficits and cognitive impairment in tau-knockout and MPTP-induced PD mouse models.^{26,94,95} The iron chelator DFO rescued FAC-induced iron overload and MPP⁺-induced ferroptosis in nerve growth factor (NGF) treated PC12 cells.²¹ Additionally, a pilot clinical study evidenced enhanced GPX activity in cerebrospinal fluid and improvements in motor symptoms in PD patients by iron chelation therapy.²⁶ This evidence also reinforced the pathological link between iron-dependent cell death and PD at a therapeutic level.

Oxidative Stress

OS is one of the major factors in the progressive loss of dopaminergic neurons in PD. OS arises from an imbalance in the redox state, necessitating both an accumulation of ROS products in the cell and a dysregulation of antioxidant protection mechanisms. Excessive amounts of free Fe²⁺ and H₂O₂ present in the cytoplasm can generate OH⁻ radicals via the Fenton reaction, and OH⁻ is one of the most unstable ROS products. Meanwhile, an antioxidant system operates within the cell to reduce ROS activity products, thereby maintaining redox balance and defending against cell death caused by OS reactions. GPX4 is a crucial GSH-dependent antioxidant enzyme, and decreased levels of GSH¹⁰ and GPX4^{96,97} were observed in the brain tissues of PD patients. A recent blood-based PD holomethylation association study⁹⁸ showed that hypermethylation of the promoter region of the SLC7A11 (system xc-) gene was associated with the risk of PD. System xc-, an antiporter for cellular uptake of cystine, has a function directly related to intracellular GSH levels. The classic ferroptosis inducer (FIN)

erastin triggers ferroptosis by depleting GSH using system xc⁻ as the molecular target, while another type of FIN, like RSL3, acts by directly inhibiting GPX4. The antioxidant enzyme DJ-1 maintains cysteine and GSH biosynthesis by safeguarding the transsulphur pathway, and loss-of-function mutations in the DJ-1 gene have been evidenced to be associated with autosomal recessive early-onset PD.⁹⁹ Meanwhile, DJ-1 depletion enhances cellular susceptibility to ferroptosis,¹⁰⁰ and DJ-1 overexpression markedly inhibits erastin-induced ferroptosis.²⁰ Nrf2 is a transcription factor with antioxidant effects, offering protection against oxidative damage by activating the gene and protein expression of detoxification enzymes and antioxidant proteins. Activation and nuclear translocation of Nrf2 ameliorates pathological phenotypic changes and motor deficits in rat and *Drosophila* PD models¹⁰¹ and attenuates neuronal damage induced by MPP⁺, 6-OHDA, etc.^{37,102} Furthermore, Nrf2 deficiency leads to the up-regulation of iron death markers in PD-associated brain regions, and a vicious cycle of α -syn overexpression and NRF2 inhibition results in increased ferroptosis sensitivity of neuronal cells.¹⁰³ Coenzyme Q10 (CoQ10) and its reduced state (CoQ10-H2) are potent mitochondrial and lipid antioxidants and are considered to be the second endogenous mechanism for inhibiting ferroptosis, functioning independently of GPX4.^{12,104} Additionally, reduced CoQ10 has been observed in PD patients and animal models, and CoQ10 supplementation has been found to attenuate PD-associated degenerative changes.^{105–107}

Lipid Peroxidation

Lipid metabolism and cellular lipid structure are major determinants of ferroptosis susceptibility in cells. Evidence from in vitro and in vivo PD models induced by commonly used neurotoxins, including MPTP, rotenone, paraquat (PQ) and 6-OHDA, has shown that abnormalities in lipid metabolism play a key role in driving ferroptosis.²³ Brain autopsy analyses have shown reduced levels of PUFAs and increased levels of malondialdehyde (MDA), a lipid peroxidation (LPO) product, and plasma lipid hydroperoxides (LH) in the SN of PD patients.^{108,109} According to relative reports, the levels of LH, MDA and 1-hydroxynonenal (4-HNE) in the peripheral blood of PD patients increased with the clinical progression of PD, with MDA and 4-HNE having a higher prognostic value.¹¹⁰ It was also found that membrane lipids doped with activated PUFAs (eg, phospholipids) are peroxidative substrates necessary for ferroptosis, a process requiring the involvement of specific enzymes.^{18,57} Acetyl coenzyme A (CoA) synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) participate in the activation and incorporation of PUFAs into membrane-localized lipids and were the earliest identified ferroptosis-promoting gene products whose inactivation was proven to render cells resistant to RSL3- and ML162-induced ferroptosis.^{33,56} ACSL4 expression was increased in the SN of MPTP-treated PD mice and PD patients, and ACSL4 inhibition specifically blocked lipid ROS elevation and ameliorated the PD phenotype.¹¹¹ It has been suggested that β -hydroxybutyrate and the probiotic strain *L. lactis* MG1363-pMG36e-GLP-1 have the potential to modulate lipid peroxidation-driven ferroptosis by targeting ACSL4, thereby benefiting the treatment of PD.^{112,113} Additionally, phospholipase iPLA2 β (PLA2G6) was shown to inhibit ROS-induced ferroptosis by scavenging oxidized PUFA tails in phospholipids,^{114,115} and its inactivation or deficiency leads to PD-related motor deficits.¹¹⁶

α -Synuclein Aggregation

Abnormal aggregation of α -syn to form Lewy bodies (LB) is one of the hallmark pathological features of PD. Various studies have demonstrated that α -syn plays a role in regulating iron and lipid metabolism, reinforcing the link between PD, as a synucleinopathy, and ferroptosis. Iron deposition in the PD midbrain has been shown to colocalize with α -syn,^{117,118} and redox-active iron and α -syn were found together in the midbrain LB.¹¹⁹ Both Fe²⁺ and Fe³⁺ exhibit robust binding affinities toward α -synuclein, eliciting conformational shifts that lead to the subsequent oligomerization of α -synuclein upon interaction with iron.^{120–123} Iron-regulatory proteins (IRPs) inhibit the translation of α -syn mRNA by binding to the sequence of iron-responsive elements (IREs),^{124,125} a process reversed by iron accumulation.¹²⁶ Evidence has also shown that Fe²⁺ inhibits autophagosome-lysosome fusion, thereby increasing α -syn spreading between dopaminergic neurons.¹¹⁹ Furthermore, α -synuclein is considered an iron reductase whose overexpression can elevate Fe²⁺ levels and augment its catalyzed Fenton reaction.¹²⁷ Meanwhile, conditions like OS and excess Fe²⁺ promote the further formation of toxic α -syn oligomers or protofibrils,^{128–130} creating a vicious cycle between iron and α -synuclein.¹³¹ α -Syn can also directly regulate cellular iron

intake by promoting the uptake of transferrin-bound iron (Tf-Fe)¹³² and reducing the degradation of divalent metal transporter 1 (DMT1).¹³³

Studies have shown that iron tends to cause increased neural damage and motor defects in PD *Drosophila* and mouse models overexpressing mutant α -syn.^{134,135} Various iron chelators have demonstrated the ability to decrease pathological α -syn and ameliorate motor function in *in vivo* experiments.^{136,137} Angelova et al discovered that α -syn oligomers can bind to cell membranes and induce ferroptosis by driving lipid peroxidation.⁴⁰ Furthermore, research findings indicate that α -syn plays a role in metabolizing essential membrane PUFAs like arachidonic acid (AA),^{6,138} including increasing its membrane fluidity and regulating vesicle assembly and synaptic transmission.^{109,138,139} A recent study utilizing transmission electron microscopy (TEM) and optical microscopy imaging technologies suggested that the immunoreactivity of α -syn in LB is closely linked to high levels of membrane lipids, fragmented organelles, and vesicles.¹⁴⁰ All these results support ferroptosis as a key pathological mechanism in α -synucleinopathy.

Mitochondrial Dysfunction

Mitochondrial dysfunction has long been recognized as a significant initiating factor for the loss of dopaminergic neurons, with its pathological link to PD traced back to 1982.¹⁴¹ Numerous PD risk genes have been found to be related to vital mitochondrial functions such as biogenesis, fusion/fission, transport, and autophagy, including ATP13A2 (PARK9), PRKN (PARK2), PINK1 (PARK6), PLA2G6 (PARK14), VPS13C (PARK23), VPS35 (PARK17), DJ-1 (PARK7), FBXO7 (PARK15), LRRK2 (PARK8), and SNCA (PARK1),^{142–149} supporting the importance of mitochondria in PD from a genetic perspective. Distinct morphological alterations characterizing ferroptosis include mitochondrial shrinkage, increased membrane density, crista diminution, and membrane potential dissipation, implying the onset of mitochondrial dysfunction.^{150,151} The electron transport chain (ETC) located on the mitochondrial inner membrane generates superoxide and H₂O₂ due to electron leakage,^{152,153} while inhibition of ETC complexes I to IV reduces ROS accumulation and ferroptosis, indicating the involvement of the ETC in ferroptosis.¹⁵⁴ Mitochondria harbour iron homeostasis-regulating molecules like Mitoferrin (FtMt), Cysteine Desulfurase (NFS1), and Heme Oxygenase-1 (Hmox1). Overexpression of FtMt can increase storage for excess iron, mitigate oxidative damage, and inhibit erastin-induced ferroptosis,¹⁵⁵ along with a significant up-regulation of FtMt immunoreactivity in dopaminergic neurons in PD patients.¹⁵⁶ While inhibited NFS1 and activated Hmox1 have been found to cause mitochondrial iron overload, generating excessive ROS and triggering mitochondrial membrane potential (MMP) depolarization,¹⁵⁷ ultimately promoting ferroptosis.¹⁵⁸ Mitochondrial DHODH and CoQ10 inhibit ferroptosis induced by cysteine starvation and glutathione depletion,^{159,160} highlighting the role of mitochondria in ferroptosis. Studies have found that the expression of voltage-dependent anion channel (VDAC), a major component of the mitochondrial outer membrane, increases in PD cell models induced by rotenone,¹⁶¹ MPP⁺,¹⁶² and 6-OHDA.¹⁶³ Inhibition of VDAC1 oligomerization can prevent erastin-induced cell death,¹⁶⁴ pointing to the noteworthy role of mitochondria in the pathological mechanism of ferroptosis in PD.

Relevant Experimental Models

From the results of keyword analysis, it is clear that *in vivo*, *in vitro*, model, mouse model, and MPTP all have a high frequency of occurrence. To gain insight into the pathophysiological mechanisms of PD and evaluate the efficacy of PD-targeted drugs, sophisticated models have been developed using a series of chemicals typified by PQ, MPTP/MPP⁺, rotenone, and 6-OHDA (Figure 8), mimicking and replicating the neurodegenerative process of PD.¹⁶⁵ The main modeling subjects include mice, rats, *Drosophila melanogaster*, PC12 cells, SH-SY5Y cells, and LUHMES cells, among others. Designing an appropriate experimental model that aligns with research objectives and modeling characteristics can help harvest compelling indicative results.^{166,167} Importantly, the current study indicates that PD-inducing chemicals lead to the onset of cellular ferroptosis in various PD models.

PQ-induced dopaminergic neurotoxicity stems from elevations in cellular OS and neuroinflammation, leading to α -syn aggregation and lipid peroxidation,^{168–173} as well as mitochondrial dysfunction and impairment.¹⁷⁴ PQ in combination with maneb has been demonstrated to induce ferroptosis in SH-SY5Y cells, which can be inhibited by

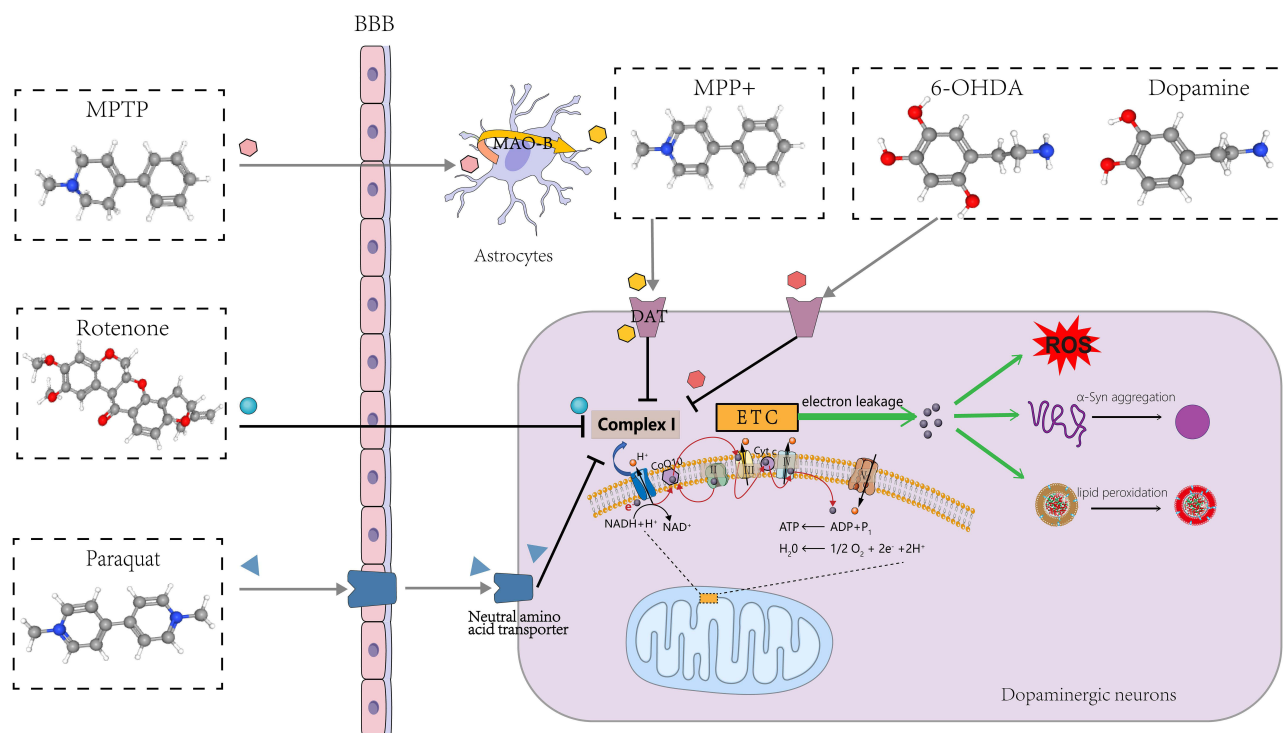


Figure 8 Chemicals used to create PD models.

ferrostatin-1, lipoxstatin-1, or deferoxamine.¹⁷⁵ This model better reflects the characteristics of PD-like progression, especially early pathological changes,¹⁷⁶ and may serve as a candidate model for the mechanism of ferroptosis.

With high lipophilicity, rotenone freely passes through the blood–brain barrier (BBB) and various cell membranes and exerts its mitochondrial toxicity and mitotic inhibitory effects^{177,178} to striatal, pallidum and substantia nigra striatal dopaminergic neurons.^{179,180} Kabiraj et al found that Fer-1 inhibits rotenone-induced SH-SY5Y cell death, attenuating α -syn aggregation and endoplasmic reticulum stress.¹⁸¹ Meanwhile, rotenone-induced rat models of PD effectively exhibited ferroptosis features such as abnormal iron metabolism, lipid peroxidation, GSH depletion, and OS, which can be rescued by DL-3-n-butylphthalide (NBP),¹⁸² erucic acid,¹⁸³ idebenone,¹⁸⁴ NAC,¹⁸⁵ and resveratrol.¹⁸⁶

MPTP has been extensively employed in developing PD models, especially mouse models.¹⁶⁶ MPTP models have been proven to induce significant α -syn accumulation and motor impairments,¹⁸⁷ with notable loss of dopaminergic neurons and extensive astrocyte hyperplasia.¹⁸⁸ The first animal model of PD in which ferroptosis was found was induced by MPTP, and the toxicity of MPTP was inhibited by Fer-1, a specific ferroptosis inhibitor, as reported by multiple sources.^{23,111,113} Liangqin Shi et al established a stable MPTP-induced monkey model of PD by adopting a long-term gradual regimen and demonstrated that CQ can help to reduce iron concentration and ROS levels in the SN, block p53-mediated cellular ferroptosis, and improve motor and nonmotor deficits in PD monkeys.¹⁸⁹ In addition, LUHMES, SH-SY5Y, and PC12 cells also experienced ferroptosis induced by MPP⁺.^{23,48,190,191}

6-OHDA is a highly oxidisable catecholamine analogue structurally similar to DA. The 6-OHDA model is the first animal model of PD and one of the most commonly applied drug models.^{192,193} Sun et al demonstrated that 6-OHDA-induced ferroptosis can be observed in both a zebrafish model and an SH-SY5Y cell model and could be attenuated by Fer-1 treatment.⁹³ Huang and Si et al found that Sorting Nexin 5 (SNX5) plays an important role in PD ferroptosis by establishing an in vivo model of rats and an in vitro model of PC-12 using 6-OHDA.^{16,17} It has also been reported that maprotiline, teicoplanin A (Th A), a polyphenolic compound, and iron chelators can rescue 6-OHDA-induced ferroptosis in various PD models,^{194–196} providing new insights and potential for investigating pharmacological targets in PD.

PD Drug Research Targeting Ferroptosis

Currently, there are no effective treatments to halt the progression of PD, and interventions regulating ferroptosis present significant therapeutic potential.⁶⁷ Insights into the pathological mechanism of ferroptosis in PD neurons may help to identify new targets and therapeutic drug approaches to overcome the obstacles in providing safe and effective treatments for PD.

Compounds targeting ferroptosis have been reported to show positive therapeutic effects in several preclinical settings and in patients with PD, and in particular, natural small molecule compounds have become of significant interest, exerting neuroprotective effects through modulation of ferroptosis-mediated neuronal cell death in both in vitro and in vivo experiments (Table 3). Clinical trials of non-dopaminergic PD drugs against ferroptosis are still in their initial stages but present promising prospects.¹³¹

The high-affinity iron chelator deferoxamine has been shown to significantly reduce nigral iron deposition and improve motor symptoms in PD patients in two phase II clinical trials (NCT00943748, NCT01539837),^{45,62,211} while an ongoing randomized, double-blind, placebo-controlled phase II clinical trial (NCT02728843) assessed the effects of four different doses of deferiprone and placebo on 140 PD patients diagnosed within the last 3 years and being treated with anti-Parkinsonian drugs. Based on the therapeutic efficacy of deferiprone demonstrated in cells, animal models, and early-stage PD patients in previous

Table 3 PD-Therapeutic Compounds Targeting Ferroptosis

Agent	In vitro and in vivo Model	Target	Pharmacologic Action	Ref
SK4/DFO	FAC/MPP+ induced PC12-NGF cells	Intracellular free iron ions	ROS↓;DMT1↓, TfR1↓, GPX4↑, FTH1↑, ACSL4↓	[21]
Paeoniflorin	MPP-treated primary dopaminergic neurons	Akt/Nrf2/GPX4 pathway	Lipid ROS↓;Nrf2↑, p-Akt↑, GPX4↑	[197]
Alpha-Lipoic acid	MPP+-induced PC12 cells	The PI3K/Akt/Nrf2 pathway	MDA,4-HNE, iron, ROS↓, GSH↑, SLC7A11, GPX 4↓; p-pi3k, p-akt, Nrf2↑	[198]
Hinokitiol	RSL3/6-OHDA- induced PC12 cells; 6-OHDA-treated zebrafish model	Iron; Nrf2	ROS, lipid peroxidation, MDA↓;TfR1, FPN↑, FTH↓;Nrf2↑, Keap1/Nrf2↓, SLC7A11, GPX4, HO-1↑	[199]
Quercetin	Erastin-induced M17 cells; MPP-/ MPTP-induced PC12 cells/mice; MPP+-induced SH-SY5Y cells	Nrf2	Total and nuclear Nrf2↑;GPX4, FTH, SLC7A11, GPX4↑;MDA↓, GSH, SOD↑; NCOA4↓	[191,200,201]
DL-3-n-butylphthalide	Rotenone-induced rat model	Iron-related protein	xCT, GPX4, GSH↑, iron, MDA↓, TfR, Ft-L↓, Fpn1↑	[182]
Sinapic acid	Rotenone-induced rat model	Iron	Iron and transferrin↓, serum HO-1↑, brain HO-1↓, GPx-4↑, SOD, CAT↑	[183]
MGI363-pMG36e-GLP-1	MPTP-induced PD mice	Keap1/Nrf2/GPX4 pathway	ACSL4, ROS, MDA, DMT1↓, Nrf2, Keap1, GPX4, TfR1, FSP1↑	[112]
Ketone Body β-Hydroxybutyric Acid	MPP+/MPTP-inducedSN4741 cells and C57BL/6 mice	Zinc finger pro-tein 36 (ZFP36)/ACSL4 axis	MDA↓, GSH↑, α-syn, ACSL4↓, TH, GPX4, FTH1↑, ZFP36↑	[113]
Clioquinol	MPTP-induced rhesus monkeys/SK-N-SH cells	Iron;AKT/mTOR pathway	p-p53, iron, TFR2, MDA,4-HNE↓, FPN1, GSH, SOD, p-mTOR, p-AKT, Bcl-2/Bax↑	[189]
Idebenone Apoferritin	Rotenone-induced rat model MPTP-induced PD mice model	Lipid peroxidation Iron;ACSL4, FSP1	GSH, SOD, NAD(P)H, GPx-4, TH↑, MDA↓ Iba-1, DMT1, iron, ACSL4↓, TfR1, FSP1↑	[184] [202]
Cu-II(atSm), CuATSP	RSL3/erastin-induced neuronal cell model	Lipid radical	Lipid peroxidation↓	[47,203]
Maprotiline	6-OHDA-induced SH-SY5Y neuronal cells	Nrf2	ROS, MDA, Fe2+, LDH, FPN, PTGS2, ACSL4↓, Ferritin, Nrf2↑	[194]

(Continued)

Table 3 (Continued).

Agent	In vitro and in vivo Model	Target	Pharmacologic Action	Ref
Thonningianin A (Th A)	6-OHDA-induced zebrafish/ SH-SY5Y cells	Nrf2;Keap1-Nrf2 PPI	Nrf2 nuclear translocation, HO-1, GSH, GSH↑, Keap1, Keap1-Nrf2 PPI, α -syn, iron↓	[195]
TC derivatives	Primary cultures of DA neurons derived from midbrain tissue of E13.5 Swiss mouse embryos	Intracellular oxidative stress and mitochondrial membrane depolarization	ROS↓, TH, $\Delta\Psi_m$ ↑	[204]
Epigallocatechin- 3-gallate	6-OHDA-induced N27 cells	Hepcidin	DMT1, hepcidin, TH, Tfr2, H-ferritin↑, caspase-3, Fpn1, TFR1↓	[205,206]
GIF-0726-r	Glutamate-/erastin-/ tunicamycin- induced HT22 cells	ROS, Ca2+, ARE	ROS accumulation, Ca2+ influx, p-PERK, p-IRE1 α , LDH, GADD153, Grp78, the spliced form of XBP1↓, antioxidant response element (ARE)↑	[207]
Resveratrol	Rotenone-induced microglial BV-2 cells	STAT1; Nrf2/Keap1/ SLC7A11 pathway	STAT2, Keap1, IL-6, IL-1 β , TNF- α ↓, Nrf1, SLC2A7, free iron, ROS, MDA↑	[186]
HPLs	Erastin-/MPP+/-menadione- induced LUHMES cells	The Akt/MEK pathways	TH, NSE↑, LDH, lipid peroxidation, oxidative stress↓	[208,209]
DI- 3-n-Butylphthalide(NBP)	MPP+ induced N2A cells	P53 signaling pathway	P53, Bax↓	[182,210]

experiments,^{45,109,212} the FAIRPARK-II study was conducted as a European multicentre, parallel-group, international clinical trial (NCT02655315), which enrolled a total of 372 patients with early-stage PD who did not receive any dopaminergic therapy but showed that after 36 weeks of treatment, the nigrostriatal iron content decreased more in the deferiprone group than in the placebo group, but the total MDS-UPDRS score, the main index, was worse than that of the placebo group,²¹³ which needs to be further verified by longer treatment duration clinical trials with iron chelators as a dopaminergic supplementation therapy. The CuII complex, Cu(II)ATSM, as a radical scavenger with anti-lipid peroxidation effects,¹⁴ and a phase I study (NCT03204929) provided preliminary evidence of its efficacy in patients with early idiopathic PD. The antioxidant intranasal GSH was shown to be beneficial in PD patients in a phase I clinical study (NCT01398748). Two phase II clinical trials (NCT01470027 and NCT02212678) were also conducted on the therapeutic effects of the GSH precursor n-acetylcysteine NAC in patients with PD. The antioxidant CoQ10 has shown efficacy in improving activities of daily living and locomotor symptoms in PD patients in phase II and III clinical trials (NCT01892176, NCT00004731, and NCT00180037),^{214–216} and CoQ10 is generally used in combination with vitamin E to provide a synergistic antioxidant effect that enhances absorption. Oral administration of EPI-743 (vitamin E-based), a designed p-benzoquinone analogue with a more than 1000-fold increase in antioxidant protection over CoQ10 and idebenone,²¹⁷ significantly improved motor function in PD patients in a phase IIb study (NCT01923584). However, some clinical trials investigating the aforementioned antioxidant therapies for PD have produced inconclusive or adverse outcomes, underscoring the necessity for more extensive and pertinent studies to furnish objective evidence of their efficacy and to refine drug development and supplement co-administration.^{218–220}

Limitations

This article analyzed and synthesized 160 relevant literatures to forecast future research trends and directions using visualization techniques. The output supports researchers in comprehending related research deemed germane to this field, identifying research hotspots and development trends, characterizing the structure of the field, and locating collaboration opportunities. Nevertheless, this research approach harbours certain inherent limitations. The amount of published literature in this area is limited. This paper primarily comprises pertinent literature obtained from the WOSCC database, which has limitations in both the source and quantity of literature. As a result, some potential information in the data may not be fully reflected. Additionally, certain authors or institutions within the WOSCC database may have differing name formats, resulting in a dispersion of

retrieved research results that can ultimately impact analysis outcomes to some degree. Meanwhile, CiteSpace conducts optimal clustering using its pre-set algorithm, but it cannot analyze the literature content. The analyzed data depend on the database statistics, which can struggle to represent the entire research content accurately. Hence, to enhance the comprehensiveness and accuracy of the research results, future studies should expand the scope of the literature search to encompass superior quality basic experimental and real-world research data, as well as strive to employ multiple metrology software programs for comparative analyses. While there are certain limitations to this study, it still offers insights into research trends and focal points within this field, providing valuable references and information for selecting topics and identifying future frontiers in related studies.

Conclusion

This research evaluated the worldwide status of PD and ferroptosis-related research based on an analysis of 160 publications in the WOSCC database from 2013 to 2023. The study employed bibliometric and visual methods using CiteSpace, VOSviewer, and the RStudio. The analysis results indicate that there has been a continued increase in literature within the related field over the past decade. The most prolific countries in terms of article production are China, the USA, and Australia, whereas the journals *Free Radical Biol. Med.* and *J Biol Chem* have published the highest number of articles and have been cited extensively, indicating their significant impact within the field. Additionally, our comprehensive analysis of the keywords and cited references has reviewed the research progress on ferroptosis in PD. Our findings demonstrate that the pathogenesis and treatment of PD based on ferroptosis remains a prominent topic in the field in recent years. Despite limitations in the database search scope, sources, and literature, this study provides new insights and directions for future research and topic selection in this field.

Data Sharing Statement

All data used or analyzed during the study were included in this article. Further inquiries about the data are available from the corresponding author on reasonable request.

Author Contributions

All authors made significant contributions to this study, both in terms of conceptualization, study design, data acquisition, analysis and interpretation; and were involved in drafting or revising the article, agreeing on the journal to which the article should be submitted, and ultimately approving the version to be published, and agreeing to take responsibility 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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