RESEARCH ARTICLE

Trends in Ubiquitination Research in Brain Diseases from 1999 to 2024: A Bibliometric Analysis

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Abstract: ***Background*:** Ubiquitination is a fundamental biological process that plays several critical roles in cellular regulation. In recent years, extensive research worldwide has investigated the involvement of ubiquitination in the pathogenesis of various brain diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), ischemic stroke, and glioblastoma (GBM). However, to date, no comprehensive bibliometric analysis has systematically examined the research landscape concerning the role of ubiquitination in brain diseases.

***Methods*:** A detailed exploration of the Web of Science Core Collection (WoSCC) database was carried out, encompassing studies from 1999 to 2024, to evaluate the interplay between ubiquitination mechanisms and various brain disorders. The database was retrieved on January 20, 2025. Bibliometric and visualization analyses were performed using various tools such as Microsoft Excel, VOSviewer, CiteSpace, the R package 'bibliometrix', and an online bibliometric platform.

***Results*:** A marked growth in scholarly articles investigating ubiquitination's role in brain diseases has been observed over the 25-year period from 1999 through 2024. A total of 1,658 articles were published in 539 journals. The United States leads in national research output, with the Chinese Academy of Sciences ranking first among all institutions in terms of publication output. Among authors, Ted M. Dawson has contributed the most articles, and the Journal of Biological Chemistry has the highest number of publications. Research on ubiquitination in brain diseases primarily focuses on AD, PD, ischemic stroke, and GBM.

***Discussion*:** The rapid expansion of this field highlights ubiquitination as a key regulatory mechanism in brain diseases. Future studies should focus on mechanistic depth and translational potential, particularly targeting ubiquitin related pathways for therapeutic intervention.

***Conclusion*:** Increasing attention is being paid to the research field exploring the relationship between brain diseases and ubiquitination. The insights from our findings may serve as a valuable reference for scholars interested in investigating ubiquitination in brain disorders in the future.

ARTICLE HISTORY

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1. INTRODUCTION

A universally conserved small protein, ubiquitin (Ub), exists in every type of eukaryotic cell. The ubiquitination process involves the covalent attachment of Ub to target proteins through a series of enzymatic reactions. This process involves three enzymatic steps mediated by E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ubiquitin-ligase enzymes working in sequence [1]. Initially, E1 ubiquitin-activating enzymes activate Ub using ATP, forming a Ub-E1 intermediate. E1 ubiquitin-activating enzymes then transfer Ub to E2 ubiquitin-conjugating enzymes, creating a Ub-E2 intermediate. Finally, E3 ubiquitin-ligase enzymes facilitate the transfer of Ub from E2 ubiquitin-conjugating enzymes to the target protein [2]. Following this initial monoubiquitination event, additional Ub molecules are progressively attached to the previously conjugated Ub, typically *via* its Lys48 or Lys63 residues, leading to the assembly of polyubiquitin chains [3]. The 26S proteasome then recognizes and degrades the polyubiquitin chain, generating small peptides and free Ub, which can be recycled. Together with the ubiquitination process, this constitutes the ubiquitin-proteasome system (UPS), a crucial pathway for degrading misfolded proteins and maintaining protein homeostasis in eukaryotic cells [4, 5]. Through the UPS, cells regulate a wide array of biological processes, including proliferation control, apoptotic mechanisms, differentiation pathways, repair systems, inflammatory signaling, and immune responses [6].

Beyond its well-established role in targeting unwanted or misfolded proteins for proteasomal degradation, ubiquitination also fulfills a wide range of non-proteolytic functions. These include cell signaling, DNA replication and repair [7], endocytosis, autophagy [8], and regulation of inflammation [9-12]. The ubiquitination process is bidirectional, with deubiquitinating enzymes capable of reversing the modification by catalyzing the detachment of Ub molecules from their target proteins. Dysregulation of ubiquitination can have profound consequences, contributing to the onset and progression of various severe diseases that are often associated with poor prognosis and substantial healthcare costs. These diseases include neurodegenerative disorders, malignant tumors, ischemic stroke, and others. Notably, neurodegenerative disorders, including Alzheimer's disease (AD) [13-15], Parkinson's disease (PD) [1, 16, 17], and amyotrophic lateral sclerosis [18, 19], are hallmarked by the accumulation of misfolded protein aggregates that disrupt cellular homeostasis and compromise neuronal integrity. Dysfunctions in the UPS are closely linked to impaired proteostasis, facilitating aggregate persistence, exacerbating their neurotoxic effects, and ultimately driving progressive neuronal degeneration. Hence, this article will focus on the role of ubiquitination within the UPS in the pathogenesis of human brain diseases.

Bibliometrics is a cross-disciplinary area that utilizes computational and analytical methods to quantitatively assess the features of publications in a particular field over a defined timeframe [20]. The previous bibliometric analyses focused on ubiquitination in other diseases, such as hepatocellular carcinoma [21], diabetes [22], and breast cancer [23], but did not include studies on brain diseases. Besides, there are numerous reviews that have explored ubiquitination from the perspective of specific brain diseases [24], yet there is still a significant lack of bibliometric analysis specifically focusing on the role of ubiquitination in brain diseases. In this study, we provide a comprehensive bibliometric analysis that bridges ubiquitination research with a wide range of brain diseases, including neurodegenerative diseases, stroke, and glioma. By integrating multi-dimensional bibliometric indicators, we offer a novel perspective on how ubiquitination-related research has progressed, where current hotspots are concentrated, and how these trends may inform future mechanistic and translational studies.

2. METHODS

2.1. Data Collection and Search Strategy

The Web of Science is considered one of the most powerful databases globally, containing a vast collection of high-quality academic journals from around the world [25-27]. It is widely utilized in bibliometric studies to conduct comprehensive and visually intuitive analyses of recent research advancements, emerging hotspots, and evolving trends in the field of ubiquitination and brain disorders. All research articles utilized in this study were sourced from the Web of Science Core Collection (WoSCC). The dataset was retrieved on January 20, 2025, to prevent alterations in search outcomes due to database updates and to maintain the originality and consistency of the data. The entire process, including data retrieval and screening, was conducted collaboratively by two authors. The search strategy was as follows: TS=(ubiquitination OR ubiquitylation OR ubiquitinate) AND TS=(brain OR cerebrovascular). This strategy was intentionally adopted to maintain conceptual coherence, reproducibility, and consistency across the bibliometric dataset. A total of 1,658 articles were retrieved for analysis in this study. The selection criteria included publications from

1999 to 2024, articles written in English, and limited to articles and reviews (Fig. **1**).

2.2. Visualized Analysis of Data

Five types of software were used to visualize research on ubiquitination in brain diseases: Microsoft Excel Office (2021), VOSviewer (1.6.19), CiteSpace (6.2.R4), the R (4.3.1) package "bibliometrix," and the online bibliometric platform (https://bibliometric.com). Microsoft Excel was used to compile statistical data and generate visualizations illustrating annual publication trends. In addition, VOSviewer was employed to conduct visual analyses of the most influential and productive countries, institutions, journals, publications, co-cited references, and keywords [28]. We utilized CiteSpace to analyze research foundations, development trends, research hotspots, and research fronts in the field, including co-cited authors, citation bursts, and timeline plots [29]. We used the R package bibliometrix to analyze the most frequently used keywords and identify core journals according to Bradford's law [30]. Specifically, we created a country collaboration map using this package. To analyze cooperation between different countries, we also utilized the web tool available on the online bibliometric platform. By integrating these software tools, we aimed to provide a comprehensive visualization and analysis of the research landscape concerning ubiquitination in brain diseases.

3. RESULTS

3.1. Document Types and Annual Publication Tendency

After screening, a total of 1658 articles on ubiquitination in brain diseases were identified, comprising 1458 research papers (87.9% of the total) and 200 review articles (12.1% of the total). The annual publication volume from 1999 to 2024 can be divided into three stages (Fig. **2**). The first stage (1999-2010) was characterized by a modest volume of publications, reflecting the early developmental phase of research on ubiquitination in brain diseases. In the second stage (2011-2018), the annual publication volume doubled, reflecting growing research interest in this emerging topic. In the third stage (2019-2024), there was rapid growth in the annual publication volume, with over 100 articles published each year since 2019, peaking at 151 articles in 2024. These findings indicate that research in this field remains highly active, underscoring its continued growth and substantial future potential.

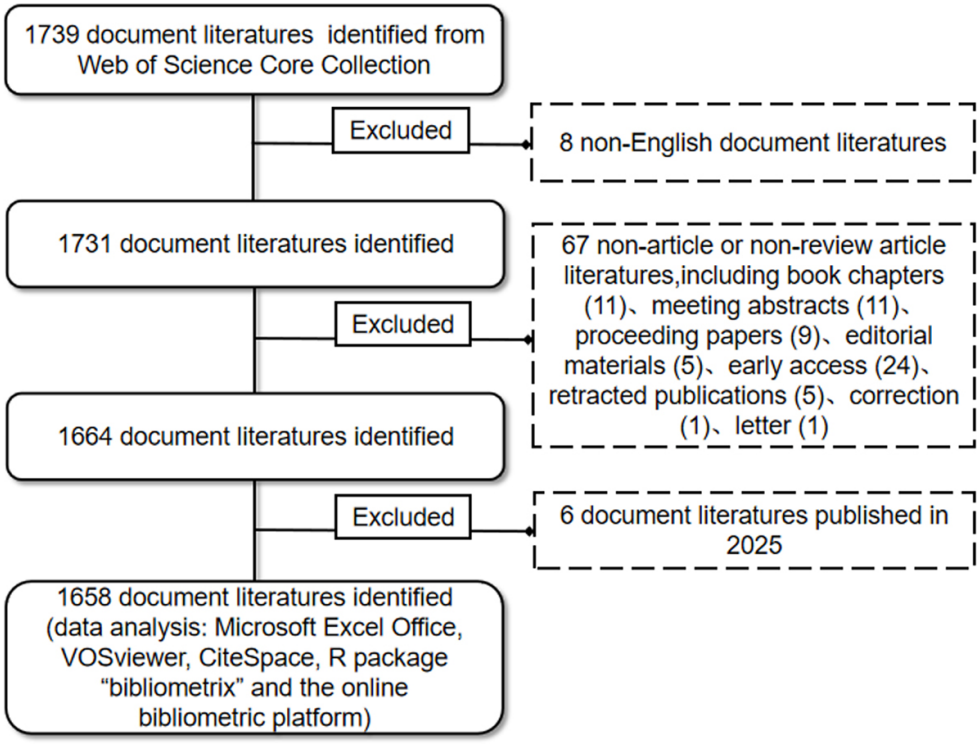


Fig. (1). Flow chart of literature screening on the study of ubiquitination in brain diseases.

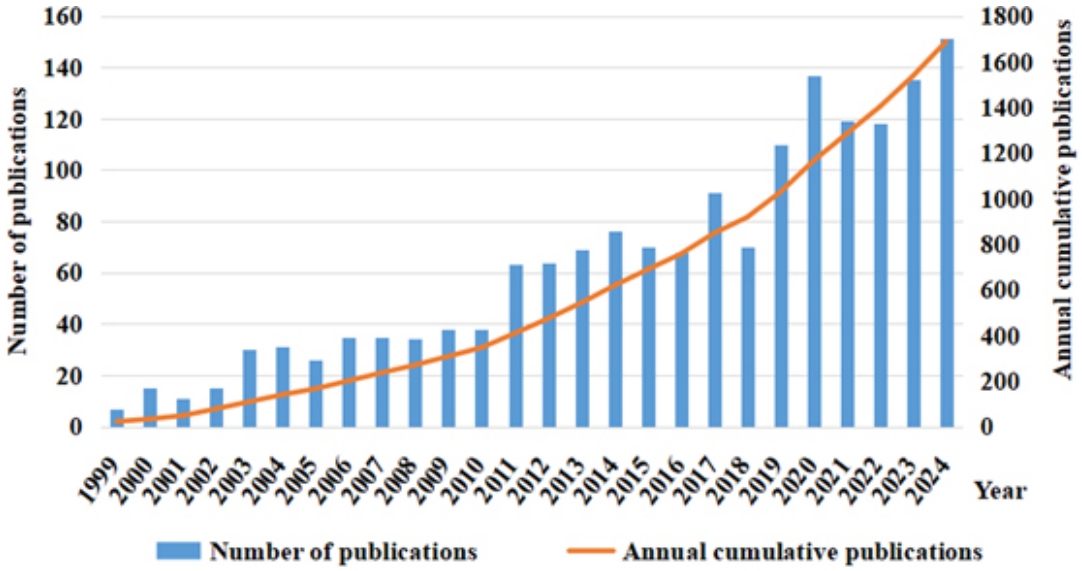


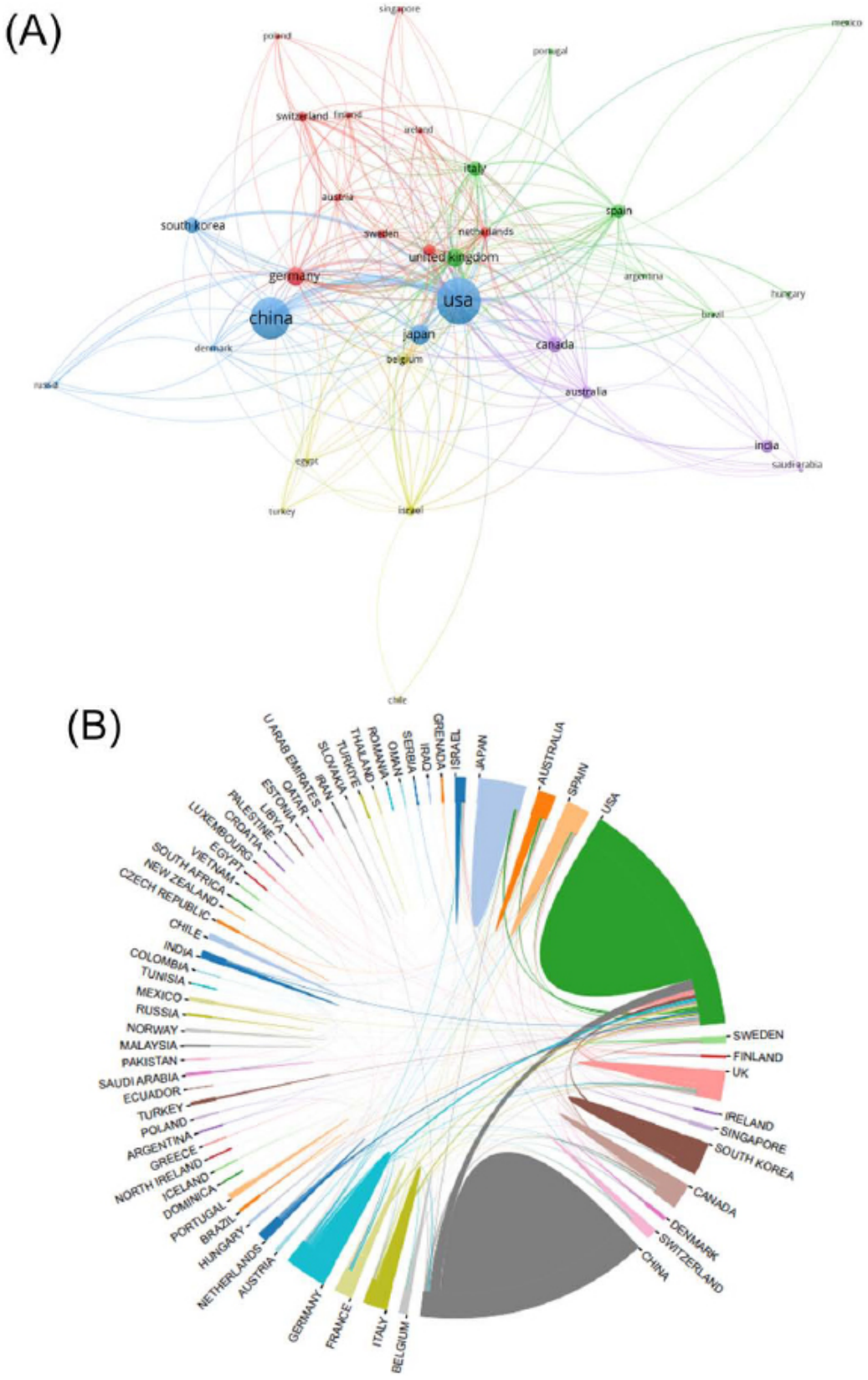
Fig. (2). Distribution of publications from 1999 to 2024 on the study of ubiquitination in brain diseases. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. The top 15 most published countries on the study of ubiquitination in brain diseases.

Rank	Country	Documents(n%)	Citations	Citations Per Document
1	USA	638(38.48)	38047	59.63
2	China	517(31.18)	11013	21.30
3	Japan	130(7.84)	5941	45.70
4	UK	110(6.63)	5344	48.58
5	Germany	110(6.63)	5037	45.79
6	South korea	81(4.89)	2804	34.62
7	Canada	74(4.46)	3419	46.20
8	Italy	70(4.22)	3371	48.16
9	Spain	59(3.56)	1896	32.14
10	India	50(3.02)	999	19.98
11	Australia	49(2.96)	3418	69.76
12	France	47(2.83)	2284	48.60
13	Israel	35(2.11)	1422	40.63
14	Switzerland	34(2.05)	1885	55.44
15	Netherlands	34(2.05)	1332	39.18

3.2. The Analysis of National Contributions

To understand the contributions of each country to the study of ubiquitination in brain diseases, we conducted a visual analysis. In Table **1**, the top 15 nations are listed based on their contribution to the literature on this theme. The United States leads with 638 articles (38.48% of the total) and a total citation count of 38047, followed by China (including Taiwan, 31.18% of the total) and Japan (7.84% of the total). It is noteworthy that Australia, despite having a lower publication count, achieves the highest citation rate per article, reflecting the exceptional quality of its research contributions. A visualization analysis was performed for countries with five or more publications (Fig. **3A**). The countries that cooperate most with the United States are China, the United Kingdom, South Korea, Canada, Japan, and Australia, with the strongest collaboration observed with China. China ranks second in terms of the number of articles compared to the United States, but it does not cooperate much with other countries (Fig. **3B** and Fig. **3C**). As illustrated, the largest node is the United States, which has the highest intensity of cooperation with other countries. Other countries, such as China and Japan, also contributed high-quality research.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LIBYA
CROATIA
LUXEMBOURG
EGYPT
VIETNAM
SOUTH AFRICA
NEW ZEALAND
CZECH REPUBLIC
CHILE
INDIA
COLOMBIA
TUNISIA
MEXICO
RUSSIA
NORWAY
MALAYSIA
PAKISTAN
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ICELAND
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BRAZIL
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NETHERLANDS
AUSTRIA
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Fig. (3). Contd....

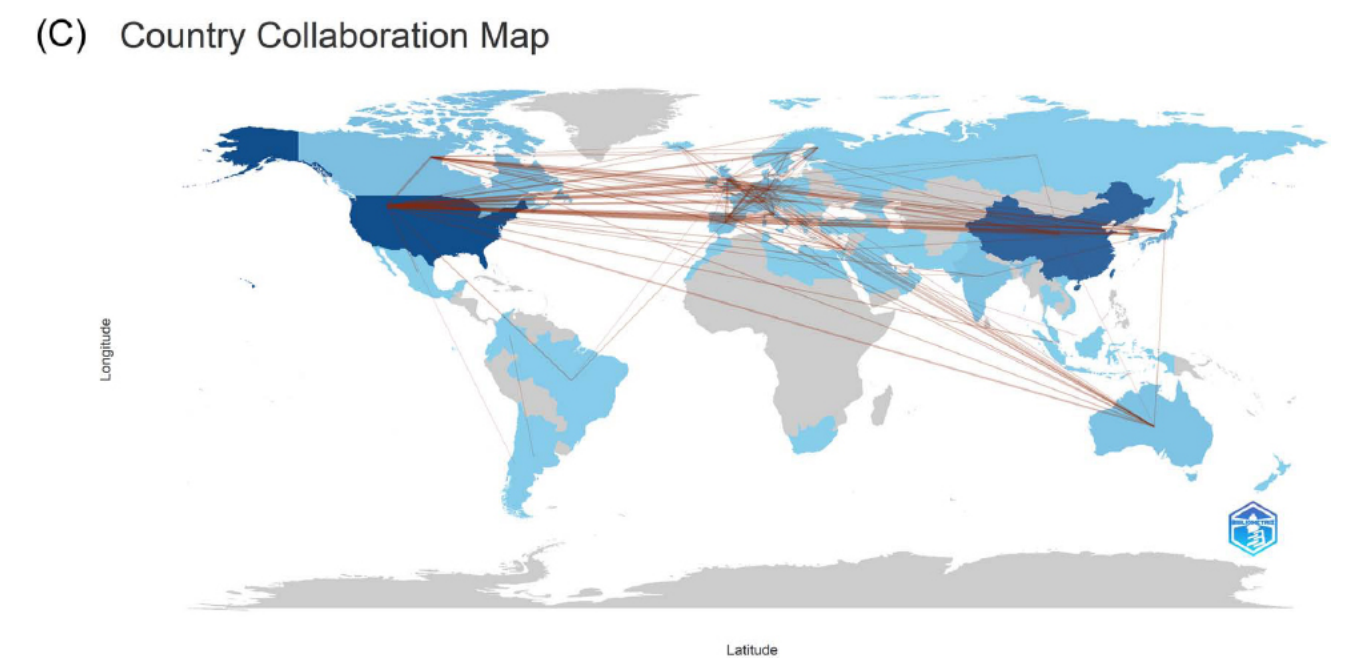


Fig. (3). Visualization analysis of cooperation between countries. (**A**). Network visualization of countries involved in ubiquitination research in brain diseases. (**B**). Analysis of linkages among nations on the study of ubiquitination in brain diseases. (**C**). Country collaboration map of ubiquitination research in brain diseases. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

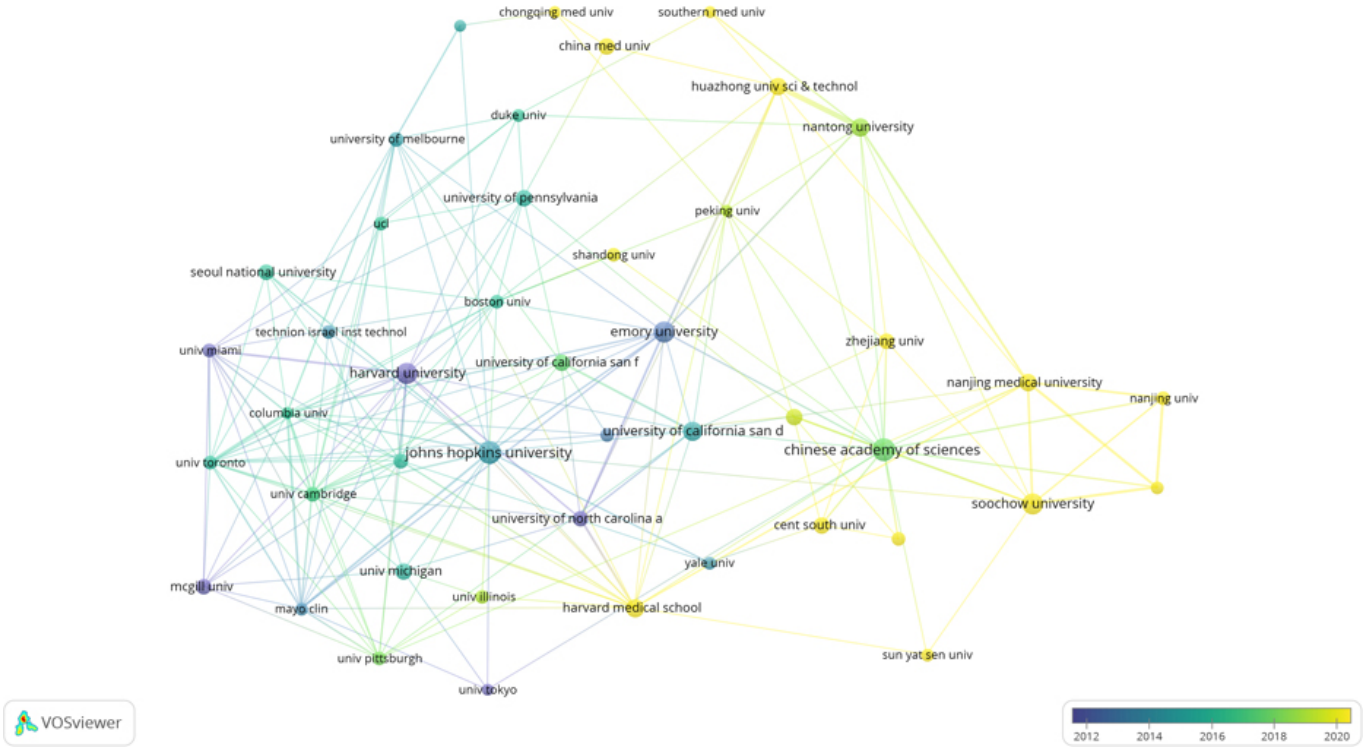


Fig. (4). Overlay Visualization of major institutions involved in ubiquitination research in brain diseases. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.3. The Analysis of Institutions' Contributions

Between 1999 and 2024, five Chinese institutions ranked within the top 10 global contributors to ubiquitination research in brain diseases: the Chinese Academy of Sciences, Nantong University, Nanjing Medical University, Fudan University, and Huazhong University of Science and Technology (Table **2**). These institutions collectively received 3083 citations, which is just over half the number of citations garnered by the top-ranked Johns Hopkins University. Johns Hopkins University led with 33 articles and 4,573 citations, averaging 138 citations per document. Although Chinese institutions have a relatively low citation rate in this field, the number of institutions participating in ubiquitination research related to brain diseases has increased in recent years. The time overlay visualization reveals that before 2016, articles were predominantly produced by Johns Hopkins University, Harvard University, and Emory University. However, since 2016, Chinese institutions, including the Chinese Academy of Sciences, Fudan University, and Nanjing Medical University, have begun to emerge and actively engage in this research (Fig. **4**). This indicates a growing interest in the study of ubiquitination in brain diseases within the Chinese medical community. Notably, Nantong University and Huazhong University of Science and Technology demonstrated the most cohesive collaboration. Overall, while the citation impact of Chinese institutions in ubiquitination research of brain diseases has been relatively low, their involvement and contributions have been on the rise, indicating a promising trend for future research and collaboration in this field.

3.4. The Analysis of Authors and Co-cited Authors

The top 10 authors by the number of publications on ubiquitination in brain diseases are listed in Table **3**. Leading the list is Ted M. Dawson from Johns Hopkins University School of Medicine in the United States, with 15 articles and a total of 3700 citations, averaging 246 citations per article. Notably, the article titled "PARIS (ZNF746) Repression of PGC-1α Contributes to Neurodegeneration in Parkinson's Disease," with Ted M. Dawson as the corresponding author and Joo-Ho Shin as the first author, has received the highest number of citations (877) and was published in the high-impact journal Cell, which has an impact factor of 45.6 [31]. Following Ted M. Dawson, authors Valina L. Dawson, Han Seok Ko, Yunjong Lee, and Joo-Ho Shin have also received over 200 citations per article. Interestingly, all these authors are affiliated with Johns Hopkins University School of Medicine, highlighting the institution's strong emphasis on research in ubiquitination and brain diseases and the recognition it has received from the broader research community. Furthermore, 60 authors have published more than five articles each. The most influential collaborative cluster consisted of the authors from Johns Hopkins University School of Medicine as described above (Fig. **5A**). Author co-citation describes the occurrence of two authors being consistently cited together within scholarly publications. The network analysis of co-cited authors revealed that 11 authors were cited more than 50 times, led by Yi Zhang, Avram Hershko, and Hideki Shimura in descending order. (Table **4**), which indicates that these three are authoritative scholars in this field and that their published articles are of high quality. Additionally, Yi Zhang maintains a strong co-citation relationship with Hideki Shimura, Aaron Ciechanover, Avram Hershko, Tohru Kitada, and Kenny K. K. Chung. Yi Zhang, Avram Hershko, and Aaron Ciechanover were identified as co-cited authors with high centrality (Fig. **5B**).

Table 2. The top 10 most published institutions on the study of ubiquitination in brain diseases.

Rank	Institution	Documents(n%)	Citations	Citations Per Document
1	Chinese Academy of Sciences	34(2.05)	779	22.91
2	Johns Hopkins University	33(1.99)	4573	138.58
3	Harvard University	29(1.75)	4011	138.31
4	Emory University	29(1.75)	3348	115.45
5	Soochow University	29(1.75)	724	24.97
6	University of California San Diego	25(1.51)	1632	65.28
7	Harvard Medical School	24(1.45)	1014	42.25
8	Nantong University	24(1.45)	846	35.25
9	Nanjing Medical University	23(1.39)	726	31.57
10	Huazhong University of Science and Technology	22(1.33)	732	33.27

Table 3. The top 10 most published authors on the study of ubiquitination in brain diseases.

Rank	Author	Documents(n%)	Citations	Citations Per Document
1	Ted M. Dawson	15(0.90)	3700	246.67
2	Valina L. Dawson	14(0.84)	3609	257.79
3	Gang Chen	11(0.66)	278	25.27
4	Jian-Zhi Wang	10(0.60)	535	53.50
5	Heng-Ye Man	10(0.60)	450	45.00
6	Jason Howitt	9(0.54)	582	64.67
7	Seong-Seng Tan	9(0.54)	582	64.67
8	Xiang Li	9(0.54)	173	19.22
9	Yan Liu	8(0.48)	287	35.88
10	Nien-Pei Tsai	8(0.48)	171	21.38

Table 4. The top 10 most co-cited authors on the study of ubiquitination in brain diseases.

Rank	Co-cited Author	Count	Centrality
1	Yi Zhang	159	0.42
2	Avram Hershko	112	0.21
3	Hideki Shimura	105	0.19
4	Aaron Ciechanover	89	0.30
5	Cecile M. Pickart	75	0.08
6	Tohru Kitada	73	0.11
7	David Komander	70	0.06
8	Yang Li	59	0.07
9	Y. Wang	57	0.02
10	J. Wang	54	0.05

3.5. The Analysis of Journals and Co-cited Journals

The literature on ubiquitination in brain diseases has been published across 539 journals. According to Bradford's law, there are 25 core journals (Fig. **6A**). The top 4 journals by publication volume are the Journal of Biological Chemistry (87 articles, 5.25% of the total 1658 articles), Proceedings of the National Academy of Sciences of the United States of America (41 articles, 2.47%), Journal of Neuroscience (39 articles, 2.35%), and Human Molecular Genetics (33 articles, 1.99%), collectively accounting for 12.06% of all published articles (Table **5**). These 4 journals also have the highest citation counts. Among the top 15 journals by publication volume, 9 are classified as Q1 in the Journal Citation Reports: Proceedings of the National Academy of Sciences of the United States of America, Journal of Neuroscience, Plos One, Molecular Neurobiology, International Journal of Molecular Sciences, Nature Communications, Cell Death & Disease, Scientific Reports, and Neurobiology of Disease. Together, these Q1 journals account for 14% of all publications. The remaining 6 journals are classified as Q2/Q3. Notably, Nature Communications has the highest impact factor among these journals, at 14.7. In network visualizations, the Journal of Neuroscience and Human Molecular Genetics exhibits the strongest collaboration with the Journal of Biological Chemistry (Fig. **6B**). The Journal of Biological Chemistry, Proceedings of the National Academy of Sciences of the United States of America, and Nature are the three most frequently co-cited journals in research on brain diseases related to ubiquitination (Table **6**). Seven of these journals are classified as Q1. In the visualization of the co-citation journal network, the far-reaching relationship and influence between these journals can be more obvious(Fig. **6C**).

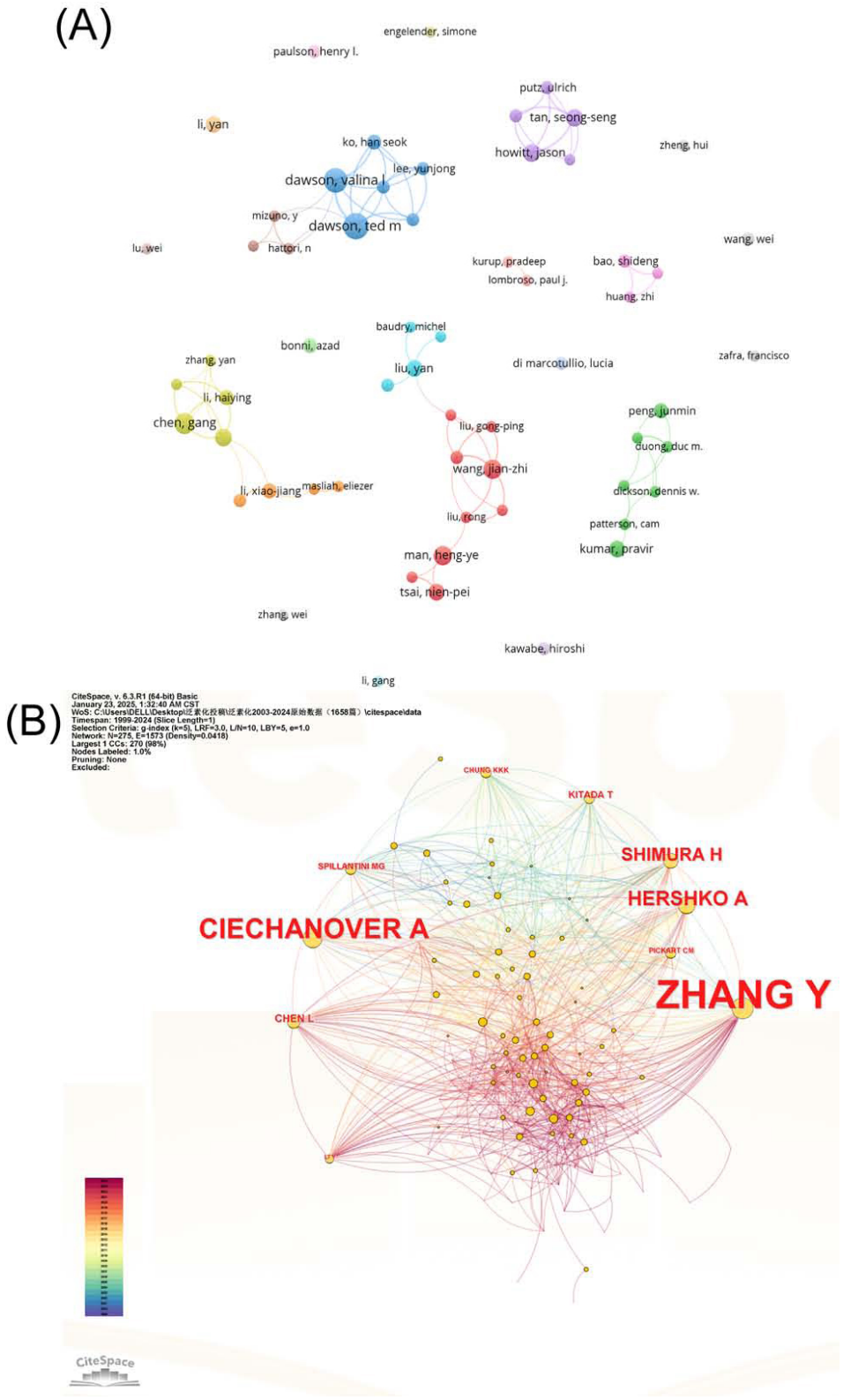


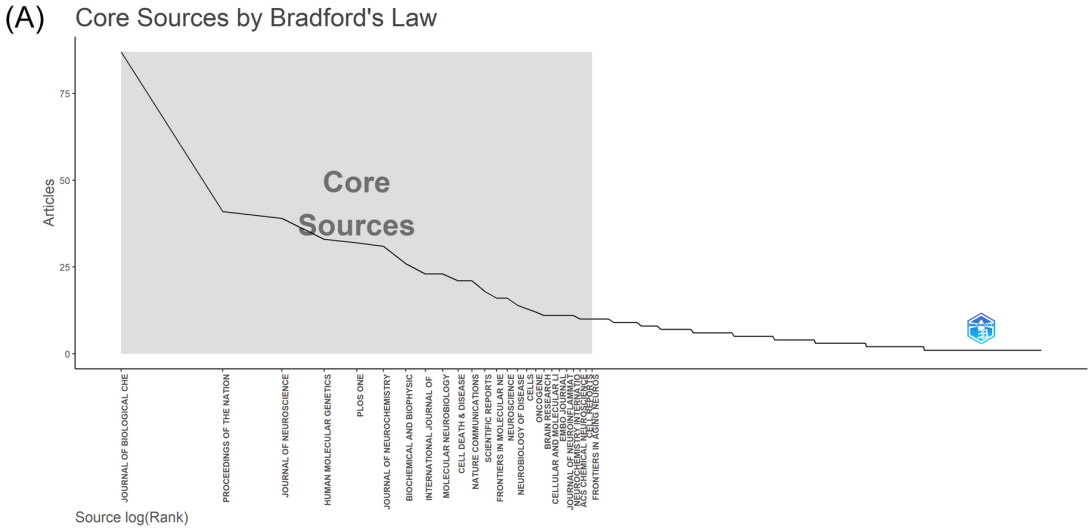
Fig. (5). Visualization analysis of cooperation between authors and co-cited authors. (**A**). Network visualization of authors involved in ubiquitination research in brain diseases. (**B**). Network visualization of co-cited authors involved in ubiquitination research in brain diseases. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 5. The top 15 most published journals on the study of ubiquitination in brain diseases.

Rank	Journal	Documents(n%)	Citations	Citations Per Document	2023 JCR Subarea(JIF)
1	Journal of Biological Chemistry	87(5.25)	6761	77.71	Q2(4.0)
2	Proceedings of The National Academy of Sciences of The United States of America	41(2.47)	3353	81.78	Q1(9.4)
3	Journal of Neuroscience	39(2.35)	4632	118.77	Q1(4.4)
4	Human Molecular Genetics	33(1.99)	2692	81.58	Q3(3.1)
5	Plos One	32(1.93)	786	24.56	Q1(2.9)
6	Journal of Neurochemistry	31(1.87)	1036	33.42	Q2(4.2)
7	Biochemical and Biophysical Research Communications	26(1.57)	521	20.04	Q3(2.5)
8	Molecular Neurobiology	23(1.39)	325	14.13	Q1(4.6)
9	International Journal of Molecular Sciences	23(1.39)	338	14.70	Q1(4.9)
10	Nature Communications	21(1.27)	1059	50.43	Q1(14.7)
11	Cell Death & Disease	21(1.27)	707	33.67	Q1(8.1)
12	Scientific Reports	18(1.09)	422	23.44	Q1(3.8)
13	Frontiers in Molecular Neuroscience	16(0.97)	425	26.56	Q2(3.5)
14	Neuroscience	16(0.97)	288	18.00	Q2(2.9)
15	Neurobiology of disease	14(0.84)	414	29.57	Q1(5.1)

Table 6. The top 10 most co-cited journals on the study of ubiquitination in brain diseases.

Rank	Co-cited Journal	Citations	2023 JCR Subarea(JIF)
1	Journal of Biological Chemistry	5570	Q2(4.0)
2	Proceedings of The National Academy of Sciences of The United States of America	3833	Q1(9.4)
3	Nature	3086	Q1(50.5)
4	Journal of Neuroscience	2979	Q1(4.4)
5	Cell	2683	Q1(45.6)
6	Science	2356	Q1(44.8)
7	Neuron	2105	Q1(14.7)
8	Journal of Neurochemistry	1488	Q2(4.2)
9	Plos One	1356	Q1(2.9)
10	Human Molecular Genetics	1319	Q3(3.1)



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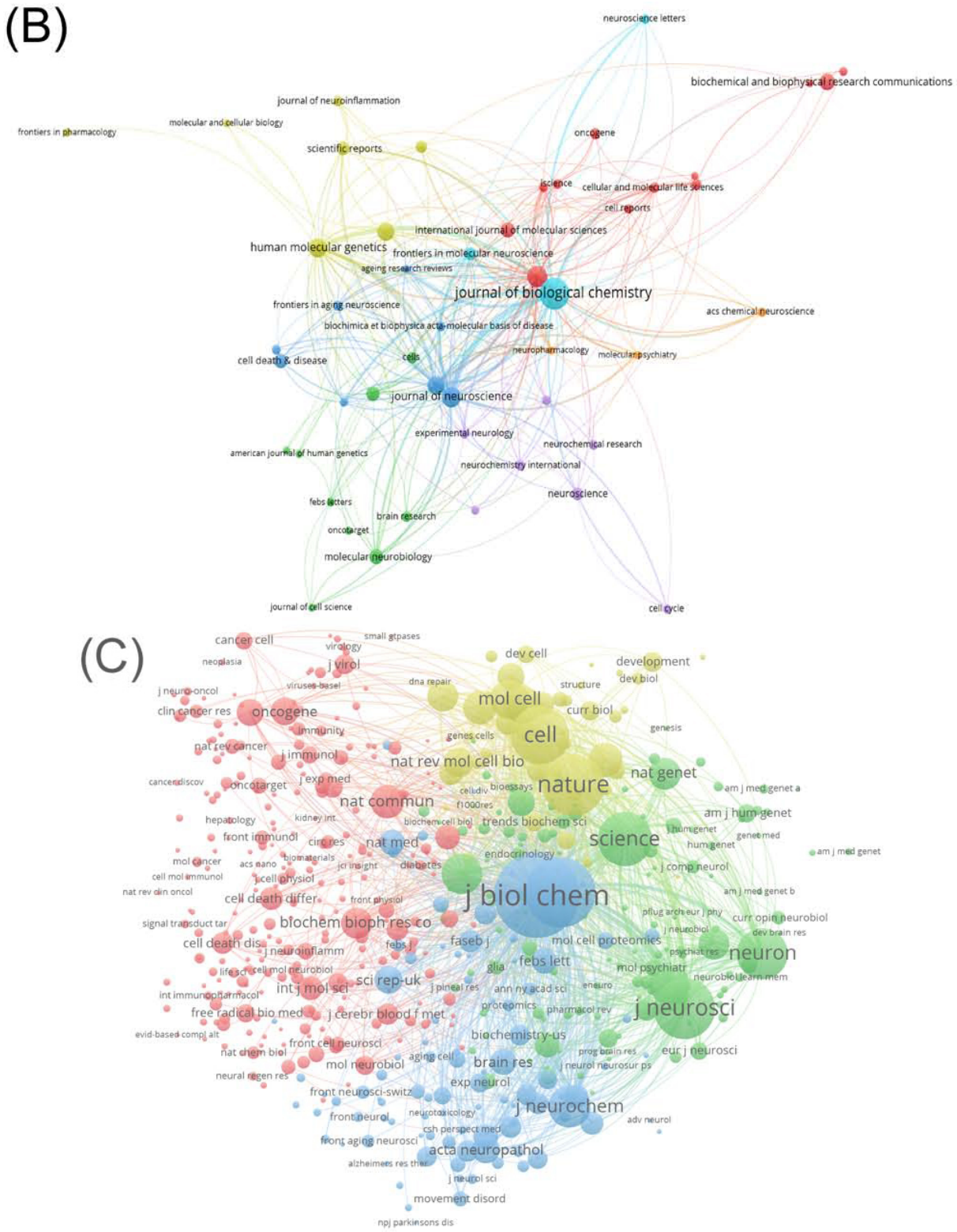


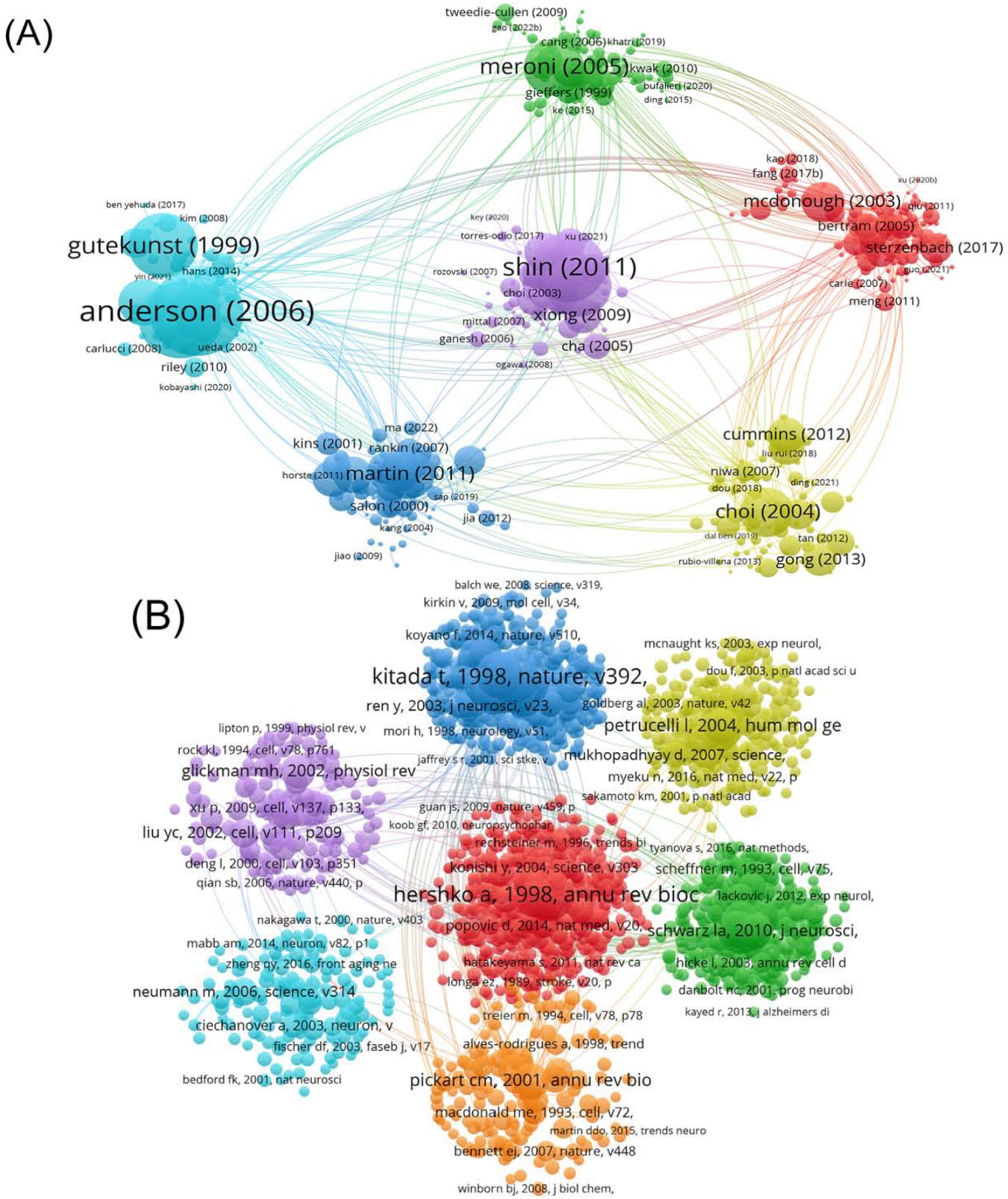
Fig. (6). Visualization analysis of cooperation between journals and co-cited journals. (**A**). Core journals of ubiquitination research in brain diseases. (**B**). Network visualization of journals involved in ubiquitination research in brain diseases. (**C**). Network visualization of co-cited journals involved in ubiquitination research in brain diseases. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.6. The Analysis of Articles and Co-cited References

A statistical analysis of 1,658 articles revealed that 6 documents received more than 500 citations each. The publication with the highest citation count is by John P. Anderson, titled "Phosphorylation of Ser-129 is the dominant pathological modification of α-synuclein in familial and sporadic Lewy body disease," which has been cited 1051 times and was published in the Journal of Biological Chemistry [32]. This is followed by a publication by Hideki Shimura (887 citations, published in Science) [33] and another by Joo-Ho Shin (773 citations, published in Cell) [31]. The high citation frequencies of these documents highlight their significant impact in the field (Table **7**, Fig. **7A**). From the analysis, it is evident that PD and AD are frequently mentioned in the titles of highly cited articles, indicating the early prominence of research on neurodegenerative diseases and ubiquitination. The top 15 highly co-cited references are listed in Table **8**. The top 3 references with the highest co-citation counts are by Tohru Kitada (90 citations, published in Nature), Avram Hershko (88 citations, published in Annual Review of Biochemistry), and Hideki Shimura (69 citations, published in Nature Genetics). Network visualization and density visualization for the 1,658 references with five or more citations were conducted (Fig. **7B**, Fig. **7C**). The co-citation network, composed of these references, effectively demonstrates the research foundation of the field.

Table 7. The top 10 most cited articles on ubiquitination research in brain diseases.

Rank	Title	Total Citations	First Author	Publication Year	Journal
1	Phosphorylation of Ser-129 is the dominant pathological modification of α-synuclein in familial and sporadic Lewy body disease	1051	John P. Anderson	2006	Journal of Biological Chemistry
2	Ubiquitination of a new form of α-synuclein by parkin from human brain: implications for parkinson's disease	887	Hideki Shimura	2001	Science
3	PARIS (ZNF746) repression of PGC-1α contributes to neurodegeneration in Parkinson's disease	773	Joo-Ho Shin	2011	Cell
4	Nuclear and neuropil aggregates in Huntington's disease: Relationship to neuropathology	704	C. A. Gutekunst	1999	Journal of Neuroscience
5	S-nitrosylation of Parkin regulates ubiquitination and compromises Parkin's protective function	651	Kenny K. K. Chung	2004	Science
6	TRIM/RBCC, a novel class of 'single protein RING finger' E3 ubiquitin ligases	578	Germana Meroni	2005	Bioessays
7	Oxidative modifications and down-regulation of ubiquitin carboxyl-terminal hydrolase L1 associated with idiopathic Parkinson's and Alzheimer's diseases	487	Joungil Choi	2004	Journal of Biological Chemistry
8	Post-translational modifications of tau protein: Implications for Alzheimer's disease	479	Ludovic Martin	2011	Neurochemistry International
9	Neuropathology in mice expressing human α-synuclein	451	H. van der Putten	2000	Journal of Neuroscience
10	Protein quality control during aging involves recruitment of the macroautophagy pathway by BAG3	424	Martin Gamerdinger	2009	Embo Journal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mcdonough (2003)
qiu (2011)
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rubio-villena (2013)
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(B)
balch we, 2008, science, v319,
kirkin v, 2009, mol cell, v34,
koyano f, 2014, nature, v510,
kitada t, 1998, nature, v392,
ren y, 2003, j neurosci, v23,
mcnaught ks, 2003, exp neurol,
dou f, 2003, p natl acad sci u
goldberg al, 2003, nature, v42
petrucelli l, 2004, hum mol ge
lipton p, 1999, physiol rev, v
mori h, 1998, neurology, v51,
rock kl, 1994, cell, v78, p761
jaffrey s r, 2001, sci stke, v
mukhopadhyay d, 2007, science,
glickman mh, 2002, physiol rev
myeku n, 2016, nat med, v22, p
sakamoto km, 2001, p natl acad
xu p, 2009, cell, v137, p133,
guan js, 2009, nature, v459, p
liu yc, 2002, cell, v111, p209
koob gf, 2010, neuropsychophar
rechsteiner m, 1996, trends bi
tyanova s, 2016, nat methods,
deng l, 2000, cell, v103, p351
konishi y, 2004, science, v303
scheffner m, 1993, cell, v75,
qian sb, 2006, nature, v440, p
hershko a, 1998, annu rev bioc
lackovic j, 2012, exp neurol,
nakagawa t, 2000, nature, v403
popovic d, 2014, nat med, v20,
schwarz la, 2010, j neurosci,
mabb am, 2014, neuron, v82, p1
hatakeyama s, 2011, nat rev ca
hicke l, 2003, annu rev cell d
zheng qy, 2016, front aging ne
longa ez, 1989, stroke, v20, p
neumann m, 2006, science, v314
danbolt nc, 2001, prog neurobi
kayed r, 2013, j alzheimers di
treier m, 1994, cell, v78, p78
ciechanover a, 2003, neuron, v
alves-rodrigues a, 1998, trend
fischer df, 2003, faseb j, v17
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bedford fk, 2001, nat neurosci
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winborn bj, 2008, j biol chem,

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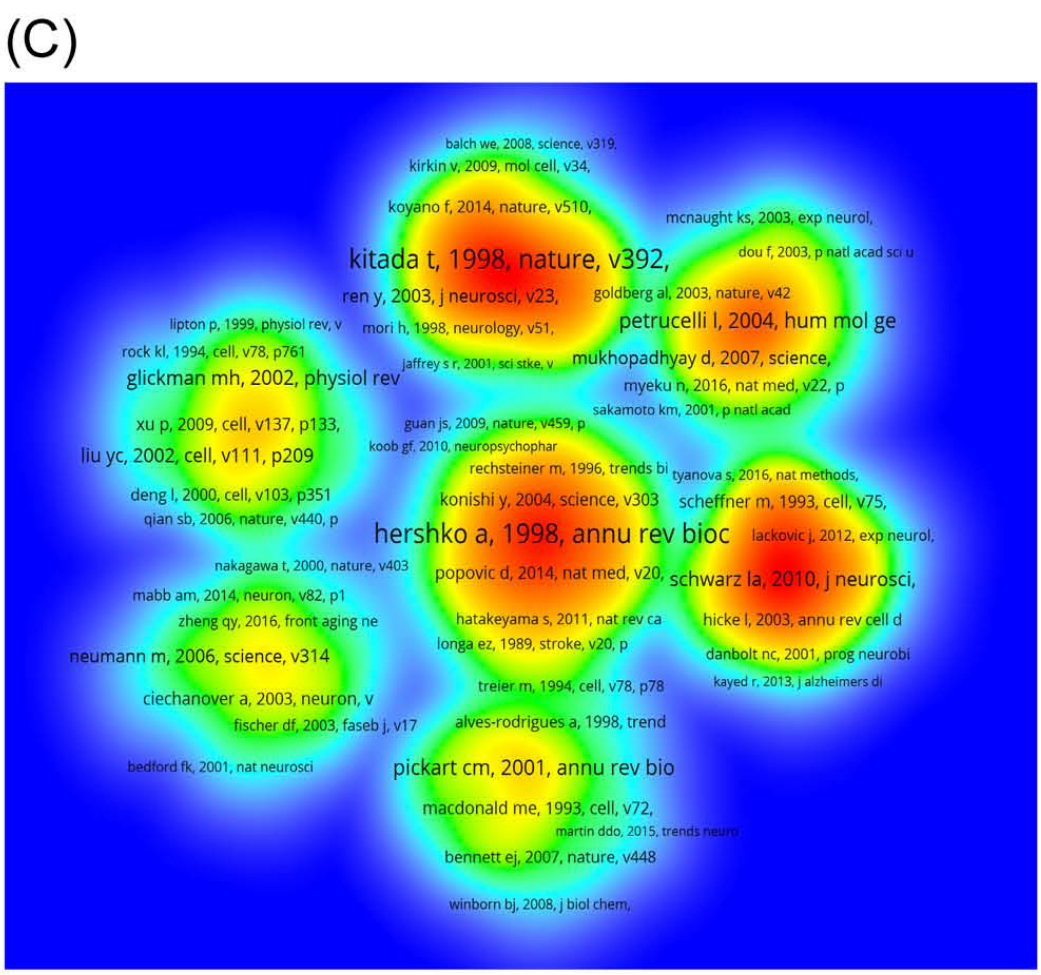


Fig. (7). Visualization analysis of articles and co-cited references with a co-occurrence network. (**A**). Network visualization of articles involved in ubiquitination research in brain diseases. (**B**). Network visualization of co-cited references involved in ubiquitination research in brain diseases. (**C**). Density visualization of co-cited references involved in ubiquitination research in brain diseases. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.7. The Analysis of Keywords

There were a total of 4,940 keywords identified, with the most frequent being expression, degradation, protein, ubiquitination, brain, activation, phosphorylation, Alzheimer's disease, gene, and disease (Fig. **8A**). Out of the total, 475 keywords were found to appear more than five times, and the network visualization graph provided an intuitive representation of their co-occurrence patterns (Fig. **8B**). Between 1999 and 2024, the top 15 keywords showing the strongest bursts in citations were analyzed (Fig. **8C**). Notably, the top-ranking keyword is "ischemic stroke." Over the past two years, it has become a prominent focus in ubiquitination research, second only to neurodegenerative disorders. Additionally, research on the ubiquitination of cancer-related diseases is gradually gaining attention and recognition from researchers. In Fig. (**8C**), we can specifically focus on the term α-synuclein. α-synuclein, a protein that is soluble and expressed within the presynaptic and perinuclear compartments of the central nervous system, has a strong association with the onset and dysfunction related to PD [34]. This highlights the significance of ubiquitination research in PD. The main clusters of keywords were visualized in the timeline plot (Fig. **8D**), revealing six clusters: "0# Parkinson's disease", "1# expression", "2# synaptic plasticity", and "3# proteins", "4# degradation", "5# oxidative stress". The timeline analysis indicates that although research interest in ubiquitination related to Parkinson's disease has shown a declining trend, Parkinson's disease remains one of the most important

Table 8. The top 15 high co-cited frequency references on ubiquitination research in brain diseases.

Rank	Title	Local Citations	First Author	Publication Year	Journal
1	Mutations in the parkin gene cause autosomal recessive juvenile Parkinsonism	90	Tohru Kitada	1998	Nature
2	The ubiquitin system	88	Avram Hershko	1998	Annual Review of Biochemistry
3	Familial parkinson disease gene product, parkin, is a ubiquitin-protein ligase	69	Hideki Shimura	2000	Nature Genetics
4	Ubiquitination of a new form of α-synuclein by parkin from human brain: implications for parkinson's disease	56	Hideki Shimura	2001	Science
5	Parkin functions as an E2-dependent ubiquitin-protein ligase and promotes the degradation of the synaptic vesicle-associated protein, CDCrel-1	51	Yi Zhang	2000	Proceedings of The National Academy of Sciences of The United States of America
6	Mutation in the α-synuclein gene identified in families with parkinson's disease	50	Mihael H. Polymeropoulos	1997	Science
7	Mechanisms underlying ubiquitination	45	Cecile M. Pickart	2001	Annual Review of Biochemistry
8	α-Synuclein in Lewy bodies	45	Maria Grazia Spillantini	1997	Nature
9	The ubiquitin code	45	David Komander	2012	Annual Review of Biochemistry
10	CHIP and Hsp70 regulate tau ubiquitination, degradation, and aggregation	42	Leonard Petrucelli	2004	Human Molecular Genetics
11	Activity-dependent ubiquitination of gluA1 mediates a distinct AMPA receptor endocytosis and sorting pathway	41	Lindsay A. Schwarz	2010	Journal of Neuroscience
12	The ubiquitin-proteasome proteolytic pathway: destruction for the sake of construction	41	Michael H. Glickman	2002	Physiological Reviews
13	Parkin ubiquitinates the α-synuclein-interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson's disease	40	Kenny K. K. Chung	2001	Nature Medicine
14	Ubiquitination regulates PSD-95 degradation and AMPA receptor surface expression	37	Marcie Colledge	2003	Neuron
15	Activity level controls postsynaptic composition and signaling *via* the ubiquitin-proteasome system	35	Michael D. Ehlers	2003	Nature Neuroscience

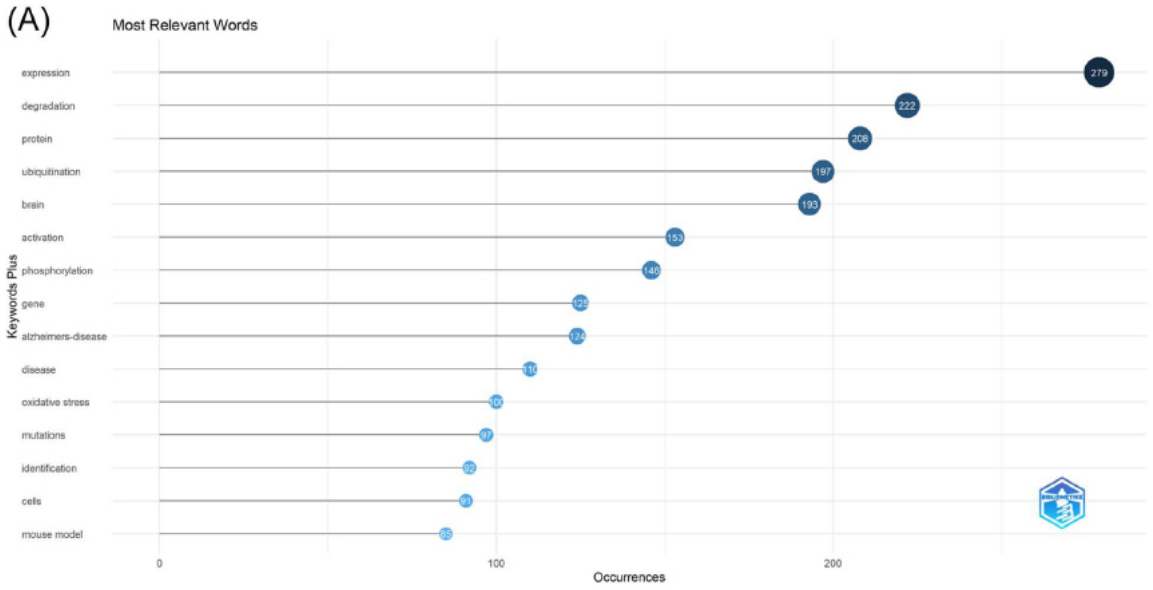
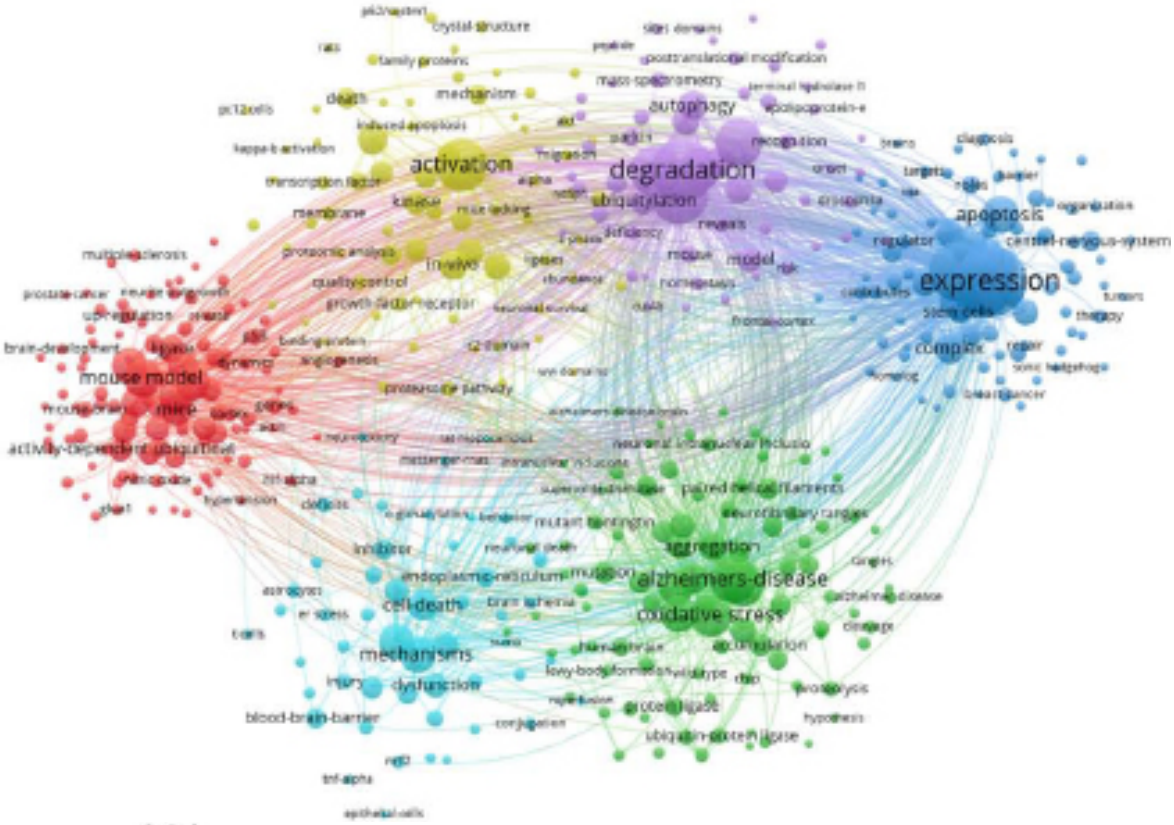


Fig. (8). Contd....

(B)



(C)

Top 15 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1999 - 2024
ischemic stroke	2021	9.49	2021	2024	
synaptic plasticity	2012	9.29	2012	2020	
gene	1999	9.15	1999	2008	
inflammation	2021	8.3	2021	2024	
ubiquitin ligase	2002	7.92	2007	2017	
cancer	2011	7.77	2022	2024	
stroke	2012	7.67	2022	2024	
in vivo	2005	7.61	2013	2017	
mutations	2001	7.58	2001	2011	
family	2001	7.55	2001	2008	
alpha synuclein	2003	6.92	2003	2010	
lewy body	2000	6.72	2000	2008	
cell death	2003	6.68	2003	2014	
mechanisms	2008	6.42	2016	2018	
parkinsons disease	2000	6.32	2003	2007	

Fig. (8). Contd....

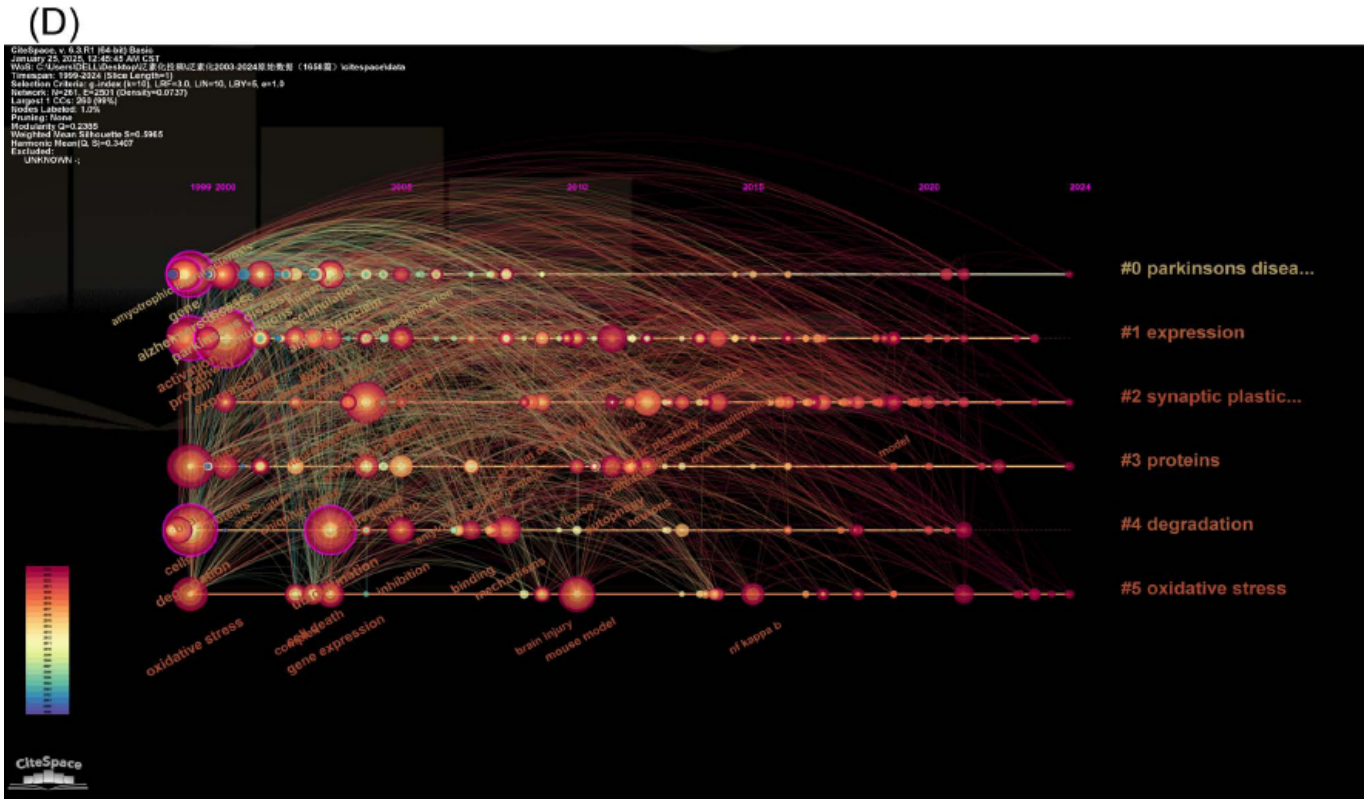


Fig. (8). Visualization analysis of keywords with a co-occurrence network. (**A**). Most relevant words in the study of ubiquitination in brain diseases. (**B**). Network visualization of keywords involved in ubiquitination research in brain diseases. (**C**). Top 15 keywords with the Strongest Citation Bursts. (**D**). Timeline plot of the keywords in the study of ubiquitination in brain diseases. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

brain disorders associated with ubiquitination. Overall, this indicates that neurodegenerative diseases, ischemic diseases, and cancer have been the primary research focus and major research topics in this field over the past 25 years.

4. DISCUSSION

4.1. General Information

In this study, we conducted a comprehensive bibliometric analysis of 1,658 articles and reviews related to ubiquitination in brain disease research published between 1999 and 2024, aiming to elucidate the knowledge structure, research dynamics, and emerging trends in this field. These publications span 69 countries and regions, encompassing contributions from thousands of institutions and more than 10,000 individual researchers, and were disseminated across 539 scholarly journals. The dataset collectively cites over 70,000 references and includes over 4,000 keywords. During the last 25 years, publications in this field have grown remarkably. The dominance of the United States in this field may be attributed to its long-standing investment in biomedical research, strong funding support from agencies such as the National Institutes of Health, and early engagement with ubiquitin-related mechanisms in neurodegenerative diseases. In contrast, China's rapid increase in publication output likely reflects recent strategic funding initiatives and expanding research capacity, although citation impact may lag due to shorter publication histories and limited international collaboration. Australia's high average citation rate, despite a smaller publication volume, may indicate a focus on high-impact, mechanism-driven studies rather than large-scale output. The delayed emergence of Chinese institutions after 2016 may reflect the maturation of national neuroscience initiatives and increased emphasis on molecular mechanisms underlying brain diseases. In contrast, early leadership by United States institutions such as Johns Hopkins University may be linked to their pioneering work in ubiquitin biology and access to advanced experimental platforms. The growing institutional collaboration observed among Chinese universities suggests an ongoing transi-

tion from quantity-driven output to more coordinated and potentially impactful research efforts. Among the authors, Ted M. Dawson has the most articles. His highly cited work, "PARIS (ZNF746) Repression of PGC-1α Contributes to Neurodegeneration in Parkinson's Disease" [31] discusses PARIS (ZNF746)'s role in PD pathogenesis. PARIS, a transcriptional repressor, interacts with the E3 ubiquitin ligase parkin, leading to the repression of PGC-1α, a crucial regulator of energy metabolism and mitochondrial function [35, 36]. This repression results in the selective loss of dopamine neurons in the substantia nigra, providing insight into the molecular mechanisms of neurodegeneration in PD and suggesting potential therapeutic targets.

The Journal of Biological Chemistry boasts the largest collection of articles. Yi Zhang's works top the list for the highest number of co-citations, a distinction also held by the Journal of Biological Chemistry in terms of co-citation frequency. The article "Phosphorylation of Ser-129 is the dominant pathological modification of α-synuclein in familial and sporadic Lewy body disease" holds the record for the most citations, while the reference "Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism" has the highest co-citation count. Ubiquitination has been extensively studied in the field of brain disease research, mainly focusing on neurodegenerative diseases such as AD and PD, ischemic stroke, and GBM. These findings are supported by multiple quantitative indicators, including a timeline plot of the keywords, keywords citation burst, and a summary of the top 10 most cited articles. Therefore, these four diseases were selected as representative focus areas to illustrate major research trends and hotspots in ubiquitination-related brain disease studies.

4.2. Role of Ubiquitination in AD

AD and PD are the most prevalent neurodegenerative disorders, with AD primarily characterized by the buildup of β-amyloid plaques and the aberrant accumulation of hyperphosphorylated tau protein [37-40]. Research on these pathological characteristics is crucial for advancing treatment strategies for AD [41]. According to quantitative and visual analysis, ubiquitination plays a pivotal role in the progression and treatment of AD. For instance, Chai *et al.* discovered that targeting the E3 ubiquitin-ligase Nedd4 may be a promising therapeutic approach for conditions characterized by the buildup of Aβ peptides, such as AD. By restoring or enhancing the expression and function of P-glycoprotein, which is facilitated by Nedd4, it may be possible to improve the clearance of Aβ peptides from the brain [42]. Hartz *et al.* further demonstrated that preventing the ubiquitination of P-glycoprotein could reduce Aβ levels in the brain and reduce the risk or severity of AD [43, 44]. Additionally, Keck *et al.* revealed that proteasomes can inhibit paired helical filament-tau in the brains of AD patients. The severity of Alzheimer's dementia is correlated with the severity of paired helical filament-tau [45]. Chu *et al.* developed a multifunctional peptide that specifically recognizes the tau protein and targets it to the UPS. This peptide enhances the ubiquitination and degradation of tau protein, offering valuable insights into potential therapeutic approaches for AD [46]. Moreover, Zhang *et al.* demonstrated that AMPA receptors mediate excitatory synaptic transmission, and their ubiquitination results in the loss of these receptors and inhibition of synaptic transmission. Therefore, maintaining appropriate levels of AMPA receptors and their synaptic localization may be a promising therapy to preserve cognitive abilities and prevent memory loss in AD patients [47]. Wang *et al.* proposed that the PINK1-Parkin-mediated ubiquitination pathway is a key mechanism for initiating Mitophagy, and that its dysregulation is associated with mitochondrial dysfunction and increased oxidative stress in patients with AD [48]. The interaction between PINK1 and Parkin is essential for regulating mitophagy in mammalian cells. PINK1 (PTEN-induced putative kinase 1) is a serine/threonine kinase, while Parkin is a component of a multiprotein E3 ubiquitin-ligase. Parkin is recruited to damaged mitochondria where PINK1 accumulates, and it ubiquitinates these damaged mitochondria to target them for degradation *via* mitophagy [49]. Therefore, enhancing the ubiquitination-dependent clearance of defective mitochondria may represent a promising therapeutic strategy for AD.

4.3. Role of Ubiquitination in PD

PD is another prevalent neurodegenerative disease, characterized by three main symptoms: resting tremors, bradykinesia, and muscle rigidity. Moreover, individuals with PD may experience freezing of gait and non-motor symptoms such as cognitive decline, pain, mood changes, and decreased sleep quality. It is important to note that PD is a progressive condition with no known cure [50, 51]. The pathological features of PD include the accumulation of α-synuclein in the brainstem, spinal cord, and cortex, the deposition of Lewy bodies, and the degeneration of dopaminergic neurons in the substantia nigra [52, 53]. McKinnon *et al.* found that overexpression of α-synuclein induces early proteasomal impairment in neurons, accompanied by dysfunction of the UPS. This finding highlights the role of α-synuclein in disrupting protein homeostasis, which

may contribute to neurodegeneration *in vivo* [54]. Tofaris *et al.* found that increasing the expression of the E3 ubiquitin-ligase Nedd4 can enhance the clearance of α-synuclein through lysosomes and promote its ubiquitination. This process ultimately reduces α-synuclein expression and mitigates the loss of dopaminergic neurons in the substantia nigra, thereby lowering the risk of PD onset [55, 56]. Furthermore, Ham *et al.* found that overexpression of the E3 ubiquitin-ligase parkin could reduce dopaminergic cell loss. In addition, a study suggested that hydrocortisone can potentially increase parkin levels, offering a potential therapeutic approach to PD [57]. Although significant research has been done, further exploration is needed to translate these findings into clinical practice. The widespread citation of these articles underscores the significance of research on ubiquitination in the treatment of PD, highlighting it as a crucial area of interest for researchers.

4.4. Role of Ubiquitination in Ischemic Stroke

Ischemic stroke is a life-threatening cerebrovascular disease [58, 59]. The removal of abnormal proteins *via* the ubiquitin-proteasome pathway is crucial following cerebral ischemia. Previous research has indicated that during focal cerebral ischemia and reperfusion, the UPS effectively removes damaged proteins, thereby promoting tissue survival. Consequently, the absence of ubiquitin-conjugated protein aggregates in post-ischemic tissue may signal severe damage at the ischemic site [60]. However, it is important to recognize that the UPS can become overwhelmed after cerebral ischemia, leading to a reduced proteasome degradation capacity. This results in the accumulation of ubiquitin--conjugated proteins in the brain, causing further damage. Enhancing proteasome activity can reduce the aggregation of these proteins [61]. On the other hand, some studies have shown that inhibiting proteasome activity can protect neurons from ischemia-induced injury. For example, Doeppner *et al.* found that proteasome inhibitors can promote long-term neurological recovery and offer neuroprotective effects by regulating peripheral immune responses and preserving the integrity of the blood-brain barrier [62]. Taken together, post-ischemic ubiquitination in the brain has a dual role, being both neurotoxic and neuroprotective. Therefore, whether ubiquitination plays a neurotoxic or neuroprotective role in a specific context depends on how the ubiquitin system is manipulated following ischemia [63]. Moreover, the mechanisms of ubiquitination in cerebral ischemia are not yet fully understood, and its effects on neurological outcomes remain unclear. Further research in this area holds great promise and warrants close attention from the scientific community.

4.5. Role of Ubiquitination in GBM

A brain tumor known for its high malignancy and rapid growth rate is glioblastoma (GBM), characterized by its aggressive nature and high mortality rates among patients. Common symptoms include persistent headaches, nausea, vomiting, neurological dysfunction, and cognitive and memory problems. Current primary treatment options for GBM include surgery, radiotherapy, and chemotherapy. However, poor surgical outcomes and resistance to radiation and chemotherapy drugs severely limit the effectiveness of GBM treatments, significantly reducing patients' quality of life [64]. Our bibliometric analysis has revealed that ubiquitination participates in the initiation and progression of GBM, offering a potential new approach for its treatment. For instance, Chen *et al.* showed that the curcumin analog ALZ003 showed promise in overcoming drug resistance in GBM by promoting the ubiquitination and subsequent degradation of the estrogen receptor [65]. Humphreys *et al.* confirmed the use of blood--brain barrier permeable proteolysis targeting chimeras (PROTACs) in GBM treatment. PROTACs facilitate the ubiquitination and degradation of specific proteins of interest through E3 ubiquitin-ligase, showing promising results in effectively targeting GBM [66]. While numerous animal studies have demonstrated the efficacy of PROTACs, there is still an absence of extensive clinical data necessary to determine their safe dosage and clinical effectiveness. Additionally, Lee *et al.* found that inhibiting ubiquitination-specific proteases could decrease the clonogenic ability and radioresistance of GBM cells [67]. Thus, this method showed promise as a novel approach for the treatment of GBM, offering new avenues for further exploration. Altogether, future research on ubiquitination will focus on conducting comprehensive studies in these four major diseases and other brain diseases. The aim is to delve into the underlying mechanisms and translate the findings into clinical research, thereby providing practical strategies for disease treatment and prevention.

5. FUTURE PERSPECTIVES

Our bibliometric analysis provides a comprehensive overview of the research landscape on ubiquitination in brain diseases. Understanding how bibliometric trends align with therapeutic innovation can bridge the gap between basic research and clinical application. Recent advances have underscored the therapeutic potential of modulating the ubiquitination system in brain di-

sorders. Aberrant activity of disease-associated E3 ubiquitin-ligases has been implicated in protein aggregation and synaptic failure in PD, AD, and ischemic brain injury [66, 68, 69]. In parallel, PROTACs represent a transformative strategy for selective protein degradation [70-73]. Future studies should focus on systematically identifying druggable E3 ubiquitin-ligases, as well as developing novel PROTAC-based molecules with improved blood-brain barrier permeability. Moreover, integrating bibliometric insights with multi-omics data could facilitate the discovery of ubiquitination-related biomarkers for early diagnosis and disease monitoring [74, 75]. By mapping high-impact keywords and disease-specific research clusters, bibliometric analysis can guide the prioritization of ubiquitination-related targets for clinical investigation. Ultimately, aligning bibliometric trends with advances in drug development and personalized medicine will be critical to accelerating translational progress in this field [76, 77].

6. LIMITATION

Firstly, CiteSpace and VOSviewer, while useful, are not complete replacements for systematic retrieval, and their limitations require attention. Secondly, the analysis was based exclusively on the WoSCC, which, although widely used in bibliometric research, does not comprehensively cover all regions. As a result, research outputs from certain countries or regions may be underrepresented. Moreover, restricting the dataset to English-language publications may introduce language bias, potentially favoring countries with established English-language publishing infrastructures. Consequently, the apparent dominance of specific countries reflects research visibility within indexed databases rather than the absolute global distribution of scientific activity. These limitations should be considered when interpreting national and institutional contributions. Lastly, we have observed that when using the search term TS=(ubiquitination OR ubiquitylation OR ubiquitinate) AND TS=(brain OR cerebrovascular), there are limitations. Future research can incorporate more extensive terms related to ubiquitination, including specific E3 ubiquitin ligases, deubiquitinating enzymes, and components of the proteasome, thereby constructing a more comprehensive research framework.

CONCLUSION

Using five types of software enabled a comprehensive bibliometric analysis of research on ubiquitination in brain diseases, providing an in-depth overview of research progress over the past 25 years and identifying emerging research hotspots. While ubiquitination has been recognized as a critical regulatory mechanism involved in AD, PD, ischemic stroke, and GBM, the underlying mechanisms remain incompletely understood. Looking forward, future studies are expected to move beyond descriptive findings and focus on mechanistic and translational research, such as characterizing druggable E3 ubiquitin-ligases, leveraging PROTAC-based targeted protein degradation technologies, and dissecting pathways like the Parkin/PINK1 pathway involved in mitophagy. Integrating these cutting-edge directions with bibliometric insights may accelerate the translation of ubiquitination-related discoveries into novel therapeutic strategies for brain diseases.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: CC, LG, and LM: writing—review and editing, methodology, supervision, resources. BW and RD: writing—original draft, software, visualization. RT and LM: writing—original draft, data curation. All the authors contributed to the article revision and read and approved the submitted version.

LIST OF ABBREVIATIONS

Ub	=	Ubiquitin
UPS	=	Ubiquitin-proteasome System
AD	=	Alzheimer's Disease
PD	=	Parkinson's Disease
WoSCC	=	Web of Science Core Collection
GBM	=	Glioblastoma
PROTACs	=	Proteolysis Targeting Chimeras
PINK1	=	PTEN-induced Putative Kinase 1

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The original contributions presented in the study are included in the article/supplementary material, and further inquiries are available by contacting the corresponding/first authors.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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