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The crossroads of Amantadine from antiviral to neurotherapeutic: Bibliometric mapping of six decades of therapeutic evolution

Razan Naji[1], Ibrahim Albokhadaim[1], Yassir A. Almofti[1], Mohammed Al-Rasheed[2], Maryam Mahmoud[3], Mahmoud Kandeel[1]

[1]Department of Biomedical Sciences, College of Veterinary Medicine, King Faisal University, Al-Ahsa, Saudi Arabia.
[2]Department of Clinical Sciences, College of Veterinary Medicine, King Faisal University, Al-Ahsa, Saudi Arabia.
[3]Faculty of Medicine, Delta University for Science and Technology, Gamasa, Egypt.

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ABSTRACT

To analyze six decades of global research on amantadine, identifying trends, thematic clusters, key contributors, and the drug's evolving role from antiviral to neurotherapeutic agent. A bibliometric analysis was conducted using the Scopus database, covering publications from 1964 to April 2025. A total of 1,540 English-language research articles were analyzed. Data were processed using R (Bibliometrix package) and VOSviewer to assess publication trends, thematic evolution, citation impact, collaboration networks, and keyword co-occurrence. The research output on amantadine has grown steadily, with significant increases in the 2000s and a peak in 2022. Four major thematic clusters emerged: (1) molecular and preclinical studies, (2) neurological symptoms and mechanisms, (3) antiviral research, and (4) clinical trials and drug effects. Amantadine's use in Parkinson's disease and its repurposing for viral infections, including COVID-19, were key themes. Highly cited studies emphasized both antiviral mechanisms and neurological applications. Classical themes in amantadine research include its antiviral activity against influenza A and its established use in managing Parkinson's disease symptoms. Emerging themes focus on its neuroprotective and anti-inflammatory properties, as well as its potential repurposing for conditions such as COVID-19 and traumatic brain injury. Amantadine has transitioned from a narrow antiviral application to a multifaceted therapeutic agent with growing importance in neurology and drug repurposing. Continued exploration in pharmacogenomics, molecular mechanisms, and clinical trials is essential to unlock its full therapeutic potential in emerging viral and neuroinflammatory diseases.

INTRODUCTION

Amantadine is a tricyclic amine compound that has exhibited remarkable pharmacological versatility since its discovery in the early 1960s [1]. Amantadine possesses antiviral properties, specifically against the influenza A virus [2]. In 1966, it became the first FDA-approved antiviral medication for influenza A prophylaxis [3]. Amantadine acts by blocking the viral M2 proton channel, thereby preventing viral uncoating and replication [4,5].

The therapeutic applications of amantadine expanded unexpectedly in 1968 when Schwab *et al.* [6] reported motor symptom improvement in Parkinson's disease patients. Subsequent studies revealed that amantadine exerts a multifaceted effect on the central nervous system through enhancement of dopamine release [7], inhibition of dopamine reuptake [8], N-methyl-D-aspartate (NMDA) receptor antagonism [9], and possible dopaminergic receptor agonism [10]. These properties contributed to its use in Parkinson's disease [11].

During the 1980s and 1990s, clinical trials demonstrated amantadine's utility in managing fatigue in multiple sclerosis and improving attention and arousal in patients with various neurological disorders [12,13]. By the early 2000s, controlled studies, such as those by Giacino *et al.* [14], confirmed its efficacy in accelerating recovery in patients

*Corresponding Author
Mahmoud Kandeel, Department of Biomedical Sciences, College of Veterinary Medicine, King Faisal University, Al-Ahsa, Saudi Arabia.
E-mail: mkandeel @ kfu.edu.sa

with traumatic brain injury emerging from minimally conscious or vegetative states.

In recent years, attention has turned to amantadine's anti-inflammatory and neuroprotective effects [15]. *In vitro* studies indicate it reduces pro-inflammatory cytokine production, such as TNF-α and IL-1β, and may modulate microglial activation [15,16]. These findings suggest potential applications in neurodegenerative and neuroinflammatory conditions.

In addition to its established clinical roles, amantadine has been the subject of numerous preclinical studies involving rodent models to investigate its effects on ion transport [17], hippocampal function, and dopaminergic signaling pathways [8–10]. These molecular insights have contributed to understanding its neuropharmacological mechanisms, particularly in relation to learning, memory, and synaptic plasticity. Moreover, like many central nervous system-active drugs, amantadine is associated with side effects such as dizziness, nervousness, and insomnia [18], which are important considerations in both therapeutic decisions.

This bibliometric analysis comprehensively maps the evolution of amantadine research from 1964 to April 2025, focusing on publication trends, international collaboration, therapeutic advancements, and emerging mechanistic insights that continue to shape its role in clinical pharmacology and neuroscience.

METHODS

Data source and search strategy

This bibliometric analysis draws on data sourced from the Scopus database, a comprehensive repository of academic literature. This bibliometric study was conducted and reported in accordance with the BIBLIO guidelines proposed by Montazeri *et al.* [19], with all key methodological decisions transparently described to ensure clarity and reproducibility.

The search process was conducted on April 12, 2025, targeting all published research on amantadine conducted globally, which retrieved data from 1964 to April 2025. The search strategy utilized the following terms and conditions: (((TITLE(Amantadine))) AND (EXCLUDE (SRCTYPE,"Undefined")) AND (EXCLUDE (AFFILCOUNTRY,"Undefined")) AND (EXCLUDE (PREFNAMEAUID,"Undefined")) AND (EXCLUDE (SUBJAREA,"Undefined"))AND(LIMIT-TO(DOCTYPE,"ar")) AND (LIMIT-TO (LANGUAGE,"English"))). The scope was restricted to English-language publications to ensure consistency in analysis. To ensure high specificity, we restricted the search to records with "Amantadine" in the article title. This approach minimizes the inclusion of studies where amantadine is only mentioned peripherally in the abstract or keywords, thereby focusing the dataset on research in which amantadine is the principal subject. Review articles were excluded to avoid duplication of primary data and secondary citation clustering. This allowed the bibliometric analysis to reflect original research output rather than synthesized summaries.

Inclusion and exclusion criteria

This study focused on research publications that specifically addressed amantadine, retrieved from the Scopus database. Inclusion criteria were as follows: (i) articles published between 1964 and April 2025; (ii) English-language publications only; (iii) documents explicitly containing "Amantadine" in the title; and (iv) limited to original research articles (Scopus document type "ar") to ensure scientific rigor. Exclusion criteria included (i) non-English articles to avoid inconsistencies in translation; (ii) non-research items such as reviews, editorials, letters, conference proceedings, and book chapters; and (iii) articles lacking metadata such as author names, affiliations, or publication year, or classified as "Undefined" under subject area or source type.

Data cleaning and preprocessing

The data retrieved from Scopus were exported in CSV format and underwent a stepwise cleaning process before analysis. Initially, the search of the Scopus database using "Amantadine" as the query yielded 2,417 articles. Within this initial set, there were 51 records with undefined authors, 367 records with undefined country information, and five records from undefined sources. These incomplete entries were excluded. Subsequently, we removed non-article document types (e.g., reviews, editorials, conference papers) and non-English publications, which resulted in a final dataset of 1,540 articles used for bibliometric analysis. The final search query, which yielded the final number of retrieved articles, is provided in the "Data source and search strategy" section. Standardization procedures were applied to harmonize author names, journal titles, and keywords by correcting for case sensitivity and typographical inconsistencies.

Bibliometric analysis

The analysis employed VOSviewer (v1.6.20) [20] and the Bibliometrix (R package) [21] to explore the intellectual structure of amantadine research. VOSviewer was employed to generate visual maps for co-authorship and keyword co-occurrence, enabling the identification of intellectual and social structures within the field. Bibliometrix facilitated quantitative assessments, including annual publication output, citation analysis, author productivity, and institutional contributions. Key bibliometric parameters analyzed included total number of publications, average citations per document, h-index, and thematic evolution based on keyword trends.

RESULTS

This study utilized the Scopus database to identify English-language publications related to the keyword "Amantadine," covering the period from 1964 to April 12, 2025. Data was retrieved on April 12, 2025, yielding a total of 1,540 records.

Annual scientific production

The bibliometric analysis of amantadine research from 1964 to April 2025 reveals a dynamic publication history. Starting with just one article in 1964, output grew modestly,

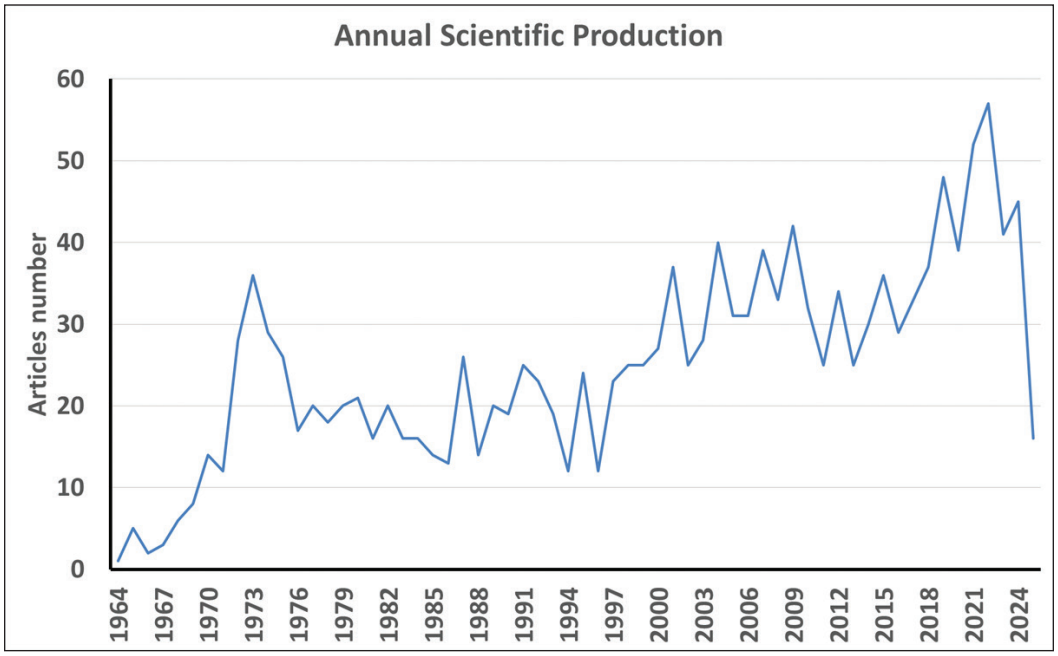

Figure 1. The annual scientific production from 1964 to April 2025.

Table 1. Most relevant sources. Leading journals publishing amantadine-related research from 1964 to 2025.

Sources	Articles
Clinical Neuropharmacology	27
European Journal of Pharmacology	21
Neurology	21
Journal of Infectious Diseases	18
Movement Disorders	18
Journal of Pharmacology and Experimental Therapeutics	17
Antimicrobial Agents and Chemotherapy	16
Journal of Neural Transmission	15
Brain Injury	14
Virology	12

Table 2. Authors' local impact by H-index.

Author	h_index
Wang Z	15
Wang J	14
Sitar DS	13
Rogóz Z	12
JR	11
Li Y	11
Wang S	11
Danysz W	10
Saito R	10
Hauser RA	9

reaching five articles by 1965. The 1970s experienced a notable rise, with publications peaking at 36 in 1973, following 29 in 1974, and 28 in 1972. A slight decline followed, with 17 articles in 1976, and the 1980s maintained a steady output. The 2000s marked another rise, with 40 articles in 2004 and a high of 57 in 2022. The years 2021 and 2023 sustained strong activity with 52 and 41 articles, respectively, while 2025 recorded 16, indicating ongoing interest (Fig. 1).

Most relevant sources

The Clinical Neuropharmacology, European Journal of Pharmacology, and Neurology emerged as the most active publication sources on amantadine. Journals focusing on both neurological and antiviral research, such as the Journal of Infectious Diseases and Movement Disorders, also showed strong contributions. Further details can be found in Table 1.

Author local impact

Key researchers have significantly shaped the research landscape surrounding amantadine. Among them, Z. Wang stands out with 18 publications since 2011, accumulating 567 citations and an h-index of 15, reflecting consistent scholarly impact. J. Wang, active since 2004, has authored 17 papers that have garnered 1,065 citations, with an h-index of 14, indicating a broad research reach. Another influential author, D.S. Sitar, has been publishing on the topic since 1978, contributing 31 papers and receiving 459 citations, with an h-index of 13. Other contributors can be found in Table 2.

Most relevant affiliations

Amantadine research is widely distributed across global institutions, with China Agricultural University leading the field with 121 published articles. The Institute of

Pharmacology follows with 55 publications, emphasizing drug development, while Niigata University in Japan has contributed 54 articles. Another major contributor from China, Tianjin University of Science and Technology, produced 49 articles. Further details are shown in Table 3.

Table 3. Most relevant affiliations.

Affiliation	Articles
China Agricultural University	121
Institute of Pharmacology	55
Niigata University	54
Tianjin University of Science and Technology	49
Ocean University of China	39
Liaoning University	36
Shandong Marine Resource and Environment Research Institute	34
University of Pittsburgh	33
Tehran University of Medical Sciences	32
Islamic Azad University	31

Table 4. Corresponding authors' countries. The top 10 countries.

Country	Number of articles	Percentage %	SCP	MCP	MCP %
USA	170	11.04%	145	25	14.71%
China	140	9.09%	132	8	5.71%
Japan	57	3.70%	54	3	5.26%
Germany	56	3.64%	43	13	23.21%
Iran	44	2.86%	40	4	9.09%
Poland	34	2.21%	29	5	14.71%
Italy	32	2.08%	25	7	21.88%
Canada	30	1.95%	24	6	20.00%
India	21	1.36%	20	1	4.76%
United Kingdom	20	1.30%	14	6	30.00%

Table 5. Highly cited articles on amantadine, highlighting foundational studies in antiviral and neurotherapeutic applications.

Paper	DOI	Total Citations
Davies *et al.*, 1964 Science [22]	10.1126/science.144.3620.862	695
Giacino *et al.*, 2012, New Engl J Med [14]	10.1056/NEJMoa1102609	656
Schwab *et al.*, 1969, JAMA [6]	10.1001/jama.1969.03160070046011	598
Cady *et al.*, 2010, Nature [4]	10.1038/nature08722	557
Verhagen Metman *et al.*, 1998, Neurology [12]	10.1212/wnl.50.5.1323	530
Wang *et al.*, 1993, J Virol [5]	10.1128/JVI.67.9.5585-5594.1993	462
Dolin *et al.*, 1982, New Engl J Med [23]	10.1056/NEJM198209023071002	400

Corresponding authors' countries and the country's scientific production

Based on the affiliations of corresponding authors, the USA leads amantadine research with 170 articles, with 145 single-country and 25 multi-country publications (Table 4). China follows with 140 articles, including 132 single-country and eight multi-country efforts. Japan contributed 57 articles, Germany 56 (3.64%), and Iran 44 (2.86%). Poland (34 articles),

Table 6. Key recurring and emerging research topics in amantadine literature based on keyword frequency and median appearance year.

Term	Frequency	Year (Q1)	Year (median)	Year (Q3)
Catecholamines	9	1972	1975	2000
Catalepsy	5	1972	1979	1994
Apomorphine	7	1975	1983	1989
L-dopa	9	1973	1987	1995
Reserpine	7	1980	1989	1994
Cocaine	7	1988	1996	2004
Parkinsonism	8	1975	1999	2019
Amantadine sulfate	6	1996	2002	2007
NMDA antagonist	5	1997	2002	2016
Dopamine	38	1995	2003	2012
Interferon	16	2003	2003	2004
Chronic hepatitis C	25	2001	2004	2005
Ribavirin	24	2003	2004	2007
Serotonin	8	2002	2005	2010
Microdialysis	7	1998	2005	2008
Memantine	21	1998	2006	2012
Influenza	16	2000	2006	2008
Glutamate	27	2004	2007	2015
Antiviral resistance	5	2006	2007	2016
Amantadine hydrochloride	29	1996	2008	2020
Amantadine sulfate	7	2004	2008	2015
NMDA	9	2005	2009	2015
Oseltamivir	7	2008	2009	2011
Parkinson's disease	66	2000	2010	2018
Influenza A virus	13	2000	2010	2016
Amantadine	606	2001	2011	2020
Levodopa	7	2004	2011	2020
Treatment	15	2006	2012	2021
Amantadine resistance	14	2008	2012	2017
Dyskinesia	16	2009	2013	2020
Drug resistance	5	2007	2013	2017
Rimantadine	17	2007	2014	2018

Continued

Term	Frequency	Year (Q1)	Year (median)	Year (Q3)
Depression	7	1998	2015	2022
Neuroprotection	7	2006	2015	2023
Cognition	11	2008	2016	2020
Crystal structure	11	2010	2016	2018
Parkinson's disease	11	2012	2017	2022
Synthesis	9	2013	2017	2019
Adamantane	7	2016	2018	2022
Apoptosis	7	2012	2018	2020
Traumatic brain injury	19	2015	2019	2021
Morris water maze	5	2019	2019	2024
Drug delivery	6	2018	2020	2022
Disorders of consciousness	5	2020	2020	2022
Covid-19	17	2021	2021	2022
Multiple sclerosis	14	2014	2021	2022
Adsorption	8	2018	2023	2023
Coma	6	2016	2023	2024

Italy (32), Canada (30), India (21), and the UK (20) also feature prominently.

Most globally cited papers

The most cited papers on amantadine highlight its transition from an antiviral to a neurological therapeutic, significantly influencing clinical practice (Table 5) [23]. Davies *et al.* [22] received 695 citations (11.21/year) for demonstrating amantadine's inhibition of influenza A virus replication. Giacino *et al.* [14] received 656 citations (46.86/year) from a trial showing that amantadine accelerated functional recovery in 184 patients with severe traumatic brain injury in vegetative or minimally conscious states. Schwab *et al.* [6] gained 598 citations (10.49/year) for reporting that 66% of 163 Parkinson's disease patients experienced improvements in akinesia, rigidity, and tremor. Cady *et al.* [4] achieved 557 citations (34.81/year) by explaining amantadine's binding to the influenza M2 proton channel through nuclear magnetic resonance spectroscopy. Verhagen Metman *et al.* [12] received 530 citations (18.93/year) by confirming that amantadine reduced levodopa-induced dyskinesias in advanced Parkinson's disease. Further details are shown in Table 6.

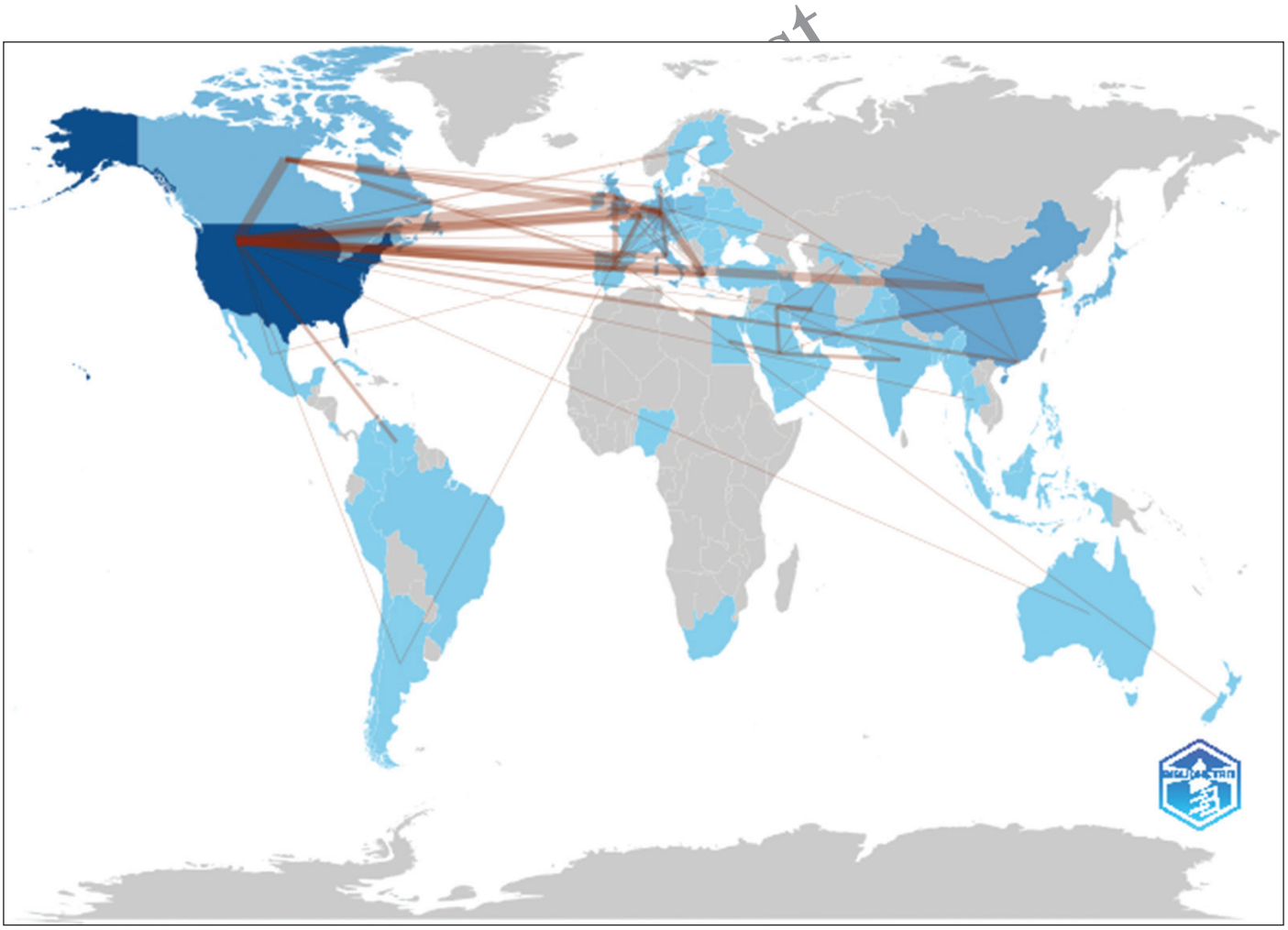

Figure 2. The global collaboration networks.

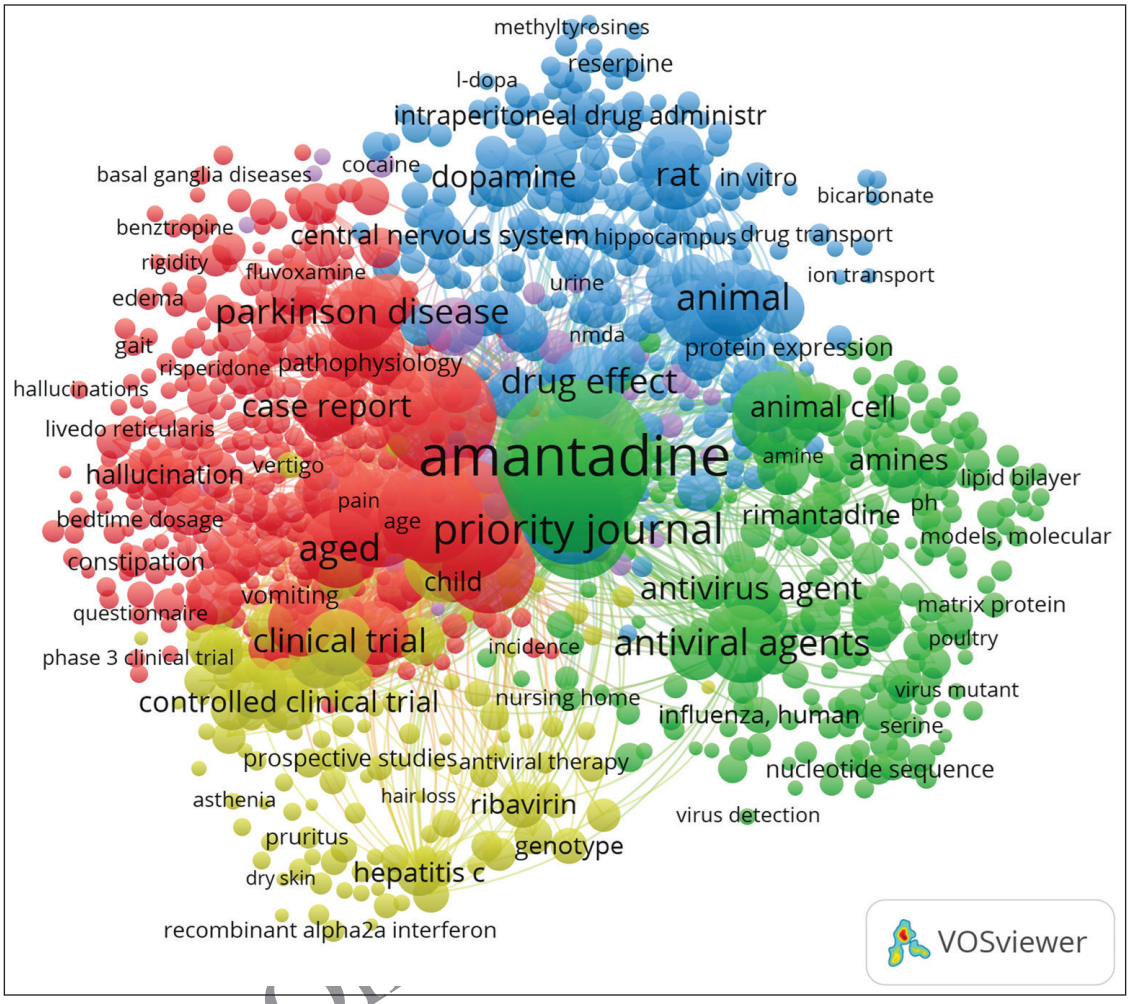

Figure 3. Overlay visualization of keyword co-occurrence in amantadine research.

Trend topics

Trending topics include "Parkinson's disease" (66 occurrences, median year 2010) and "amantadine" (606, median 2011), with early terms like "catecholamines" (median 1975), "traumatic brain injury" (2019), "COVID-19" (2021), and "coma" (2023). Topics like "dopamine" (38, median 2003), "glutamate" (27, median 2007), "antiviral resistance" (2012), and "neuroprotection" (2015) reflect evolving pharmacological and clinical focus, showcasing amantadine's transition from antiviral to neurological and emerging applications (Table 6).

The global collaboration networks

The global collaboration network for amantadine research reveals a vibrant, interconnected scientific community (Fig. 2). The United States leads with strong ties, notably 13 collaborations each with Canada and Germany, 12 with the United Kingdom, and 10 with China, reflecting strong transatlantic and transpacific partnerships. Germany also emerges as a key hub, collaborating frequently with Greece (6), Canada (5), and the UK (4). European connections exist, with the UK and France sharing five collaborations, and Spain and Belgium linking four times. Emerging research hubs like Iran and Iraq (four collaborations) and India and Saudi Arabia (3) highlight growing contributions from the Middle East and South Asia.

Visualization of keyword co-occurrence in amantadine research

Figure 3 displays a co-occurrence network of keywords in amantadine research, organized into five distinct color-coded clusters. The graph is centered on "amantadine." The blue cluster links to molecular and animal studies, encompassing "rat," "ion transport," "dopamine," "hippocampus," and "protein expression." The red cluster focuses on neurological aspects, featuring "pain," "hallucinations," and "pathophysiology." The green cluster highlights antiviral research, with "influenza," "antiviral agent," and "virus detection" as prominent terms. The yellow cluster focuses on clinical trials and effects, including "controlled clinical trial," "vomiting," and "drug effect."

DISCUSSION

The bibliometric analysis of amantadine research spanning 1964 to April 2025 illuminates a dynamic and evolving field, marked by significant growth in publication output,

international collaboration, and diversification of therapeutic applications. The study revealed a steady increase in research productivity, particularly since the early 2000s, with a peak in 2022, reflecting heightened global interest in amantadine's multifaceted pharmacological properties. The increase in publications aligns with expanded clinical applications [24], from its initial role as an antiviral agent [25,26] to its established use in neurological disorders and emerging potential in neuroprotection and anti-inflammatory contexts [27]. A notable surge in amantadine-related publications began in 2004 and continued through the following two decades, peaking in 2022. Several factors may explain this rise. First, renewed clinical attention was directed toward amantadine's efficacy in managing Parkinson's disease [11,28]. Second, the emergence of viral epidemics—including SARS, H1N1, and COVID-19 [16,29,30]—revived interest in amantadine's antiviral properties and repurposing potential.

A key finding is the pivotal role of international collaboration in driving amantadine research. The United States, China, and Japan emerge as leading contributors, with robust networks connecting North America, Europe, and Asia. These collaborations have facilitated knowledge exchange, as evidenced by the high proportion of multi-country publications. The prominence of institutions such as China Agricultural University in amantadine-related research may reflect multiple converging factors. As a leading agricultural and life sciences university, China Agricultural University likely engages in both experimental pharmacology and antiviral research related to animal health, where amantadine has applications in veterinary virology.

The thematic evolution of amantadine research highlights its transition from antiviral applications to neurological and neuroprotective roles. Early studies, such as Davies *et al.* [23], focused on influenza A prophylaxis, laying the foundation for amantadine's antiviral legacy. Subsequent decades saw a shift toward neurological applications, with landmark studies like Schwab *et al.* [6] and Giacino *et al.* [14] establishing its efficacy in Parkinson's disease and traumatic brain injury, respectively. More recent trends, particularly post-2010, emphasize neuroprotection and anti-inflammatory effects [16,24]. Emerging topics like COVID-19 and coma reflect amantadine's adaptability to contemporary health challenges [16], though these areas remain underexplored compared to established themes like Parkinson's disease and dopamine modulation.

The thematic clusters identified in the keyword co-occurrence analysis provide insight into the intellectual structure of the field. A cluster centered on "amantadine" and "Parkinson's disease," [6,12,28] represents the core of clinical research, while another underscores the enduring relevance of antiviral studies [22,24]. Additional clusters focusing on neurological mechanisms and clinical trial outcomes highlight the field's interdisciplinary nature [29,30]. A separate cluster with terms like "rat" and "protein expression" points to a growing emphasis on preclinical and molecular studies, which could pave the way for novel derivatives with enhanced selectivity [31].

In a clinical context, the thematic clusters underscore amantadine's dual role as both an antiviral and neurotherapeutic agent. The green cluster, centered on antiviral terms such as "influenza" and "antiviral agent," reflects its well-documented action as an influenza A treatment. The reappearance of these terms in recent years, alongside "COVID-19," suggests renewed interest in repurposing amantadine amid emerging viral threats. The red and blue clusters, rich in neurological and molecular terms such as "dopamine," "NMDA," "hallucinations," and "ion transport," mirror amantadine's pharmacodynamic effects on dopaminergic transmission and NMDA receptor antagonism. These mechanisms underlie its clinical efficacy in managing motor symptoms and dyskinesia in Parkinson's disease and cognitive dysfunction post-traumatic brain injury. The inclusion of "pain" and "pathophysiology" points to its expanding application in neuroinflammation and central sensitization, with growing preclinical evidence supporting its anti-inflammatory effects via microglial modulation and cytokine suppression. The yellow cluster, focusing on terms like "controlled clinical trial" and "drug effect," aligns with efforts in assessing amantadine in structured clinical settings, including trials for fatigue in multiple sclerosis, disorders of consciousness, and post-viral fatigue syndromes.

Despite its strengths, this study has limitations. A notable limitation of this study is the exclusive reliance on the Scopus database. While Scopus offers comprehensive coverage of peer-reviewed literature, it may omit relevant articles indexed in other platforms or regional databases. This could result in an underrepresentation of publications from grey literature. The focus on English-language publications may also overlook valuable studies in other languages, such as Spanish, Chinese, or Japanese, which could offer unique perspectives. Future studies could complement this analysis with qualitative assessments to evaluate real-world applications.

The analysis identifies several research gaps and future directions. While neurological applications are well-developed, molecular and pharmacogenomic studies remain underrepresented. Further exploration of genetic factors influencing amantadine response could personalize treatment strategies, particularly for Parkinson's disease and traumatic brain injury [32]. The potential of amantadine in neuroinflammatory and neurodegenerative conditions, supported by *in vitro* evidence of cytokine modulation, warrants larger clinical trials [31]. Additionally, the limited focus on amantadine's role in emerging viral diseases, such as COVID-19, suggests an opportunity to reconsider its antiviral properties in the context of global health threats.

CONCLUSION

This bibliometric analysis of amantadine research from 1964 to 2025 reveals a significant and evolving scientific work spanning antiviral, neurological, and emerging therapeutic applications. The publication trend shows steady growth over six decades, with a marked increase in output during the 2000s and a peak in 2022, reflecting sustained global interest. The thematic analysis identified major clusters, including molecular/preclinical studies, neurological mechanisms, antiviral research, and clinical trials assessing drug effects. Highly cited papers

and keyword trends demonstrate a progressive shift in research focus from amantadine's traditional antiviral use toward neurotherapeutic indications, including its role in dopamine modulation, NMDA antagonism, and neuroprotection. The United States and China led in scientific productivity and international collaboration, while key institutions such as China Agricultural University and the University of Pittsburgh were prominent contributors. Despite extensive research into neurological disorders and antiviral efficacy, underexplored areas remain, particularly pharmacogenomic profiling, its role in COVID-19 treatment, and the development of novel derivatives.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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REFERENCES

1. Martin WJ, Rabinowitz LG. Amantadine. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, *et al.*, editors. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993.
2. Zhirnov OP, Klenk HD, Wright PF. Aprotinin and similar protease inhibitors as drugs against influenza. Antiviral Res. 2011;92(1):27–36. doi: https://doi.org/10.1016/j.antiviral.2011.07.014
3. De Clercq E, Li G. Approved antiviral drugs over the past 50 years. Clin Microbiol Rev. 2016;29(3):695–747. doi: https://doi.org/10.1128/cmr.00102-15
4. Cady SD, Schmidt-Rohr K, Wang J, Soto CS, Degrado WF, Hong M. Structure of the amantadine binding site of influenza M2 proton channels in lipid bilayers. Nature 2010;463(7281):689–92. doi: https://doi.org/10.1038/nature08722
5. Wang C, Takeuchi K, Pinto LH, Lamb RA. Ion channel activity of influenza A virus M2 protein: characterization of the amantadine block. J Virol. 1993;67(9):5585–94. doi: https://doi.org/10.1128/jvi.67.9.5585-5594.1993
6. Schwab RS, England AC Jr, Poskanzer DC, Young RR. Amantadine in the treatment of Parkinson's disease. JAMA 1969;208(7):1168–70. doi: https://doi.org/10.1001/jama.1969.03160070046011
7. Dekundy A, Pichler G, El Badry R, Scheschonka A, Danysz W. Amantadine for traumatic brain injury-supporting evidence and mode of action. Biomedicines 2024;12(7):1558. doi: https://doi.org/10.3390/biomedicines12071558
8. Heikkila RE, Cohen G. Evaluation of amantadine as a releasing agent or uptake blocker for H3-dopamine in rat brain slices. Eur J Pharmacol. 1972;20(2):156–60. doi: https://doi.org/10.1016/0014-2999(72)90144-6
9. Blanpied TA, Clarke RJ, Johnson JW. Amantadine inhibits NMDA receptors by accelerating channel closure during channel block. J Neurosci. 2005;25(13):3312–22. doi: https://doi.org/10.1523/jneurosci.4262-04.2005
10. Peeters M, Page G, Maloteaux J-M, Hermans E. Hypersensitivity of dopamine transmission in the rat striatum after treatment with the NMDA receptor antagonist amantadine. Brain Res. 2002;949(1):32–41. doi: https://doi.org/10.1016/S0006-8993(02)02961-X
11. Crosby NJ, Deane KH, Clarke CE. Amantadine for dyskinesia in Parkinson's disease. Cochrane Database Syst Rev. 2003;2003(2):Cd003467. doi: https://doi.org/10.1002/14651858.Cd003467
12. Verhagen Metman L, Del Dotto P, van den Munckhof P, Fang J, Mouradian MM, Chase TN. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. Neurology 1998;50(5):1323–6. doi: https://doi.org/10.1212/wnl.50.5.1323
13. Rosenberg GA, Appenzeller O. Amantadine, fatigue, and multiple sclerosis. Arch Neurol. 1988;45(10):1104–6. doi: https://doi.org/10.1001/archneur.1988.00520340058012
14. Giacino JT, Whyte J, Bagiella E, Kalmar K, Childs N, Khademi A, *et al.* Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med. 2012;366(9):819–26. doi: https://doi.org/10.1056/NEJMoa1102609
15. Unluer C, Bektasoglu PK, Erguder BI, Arikok AT, Ermutlu I, Gurer B, *et al*. Amantadine's neuroprotective effects in rabbit spinal cord ischemia/reperfusion model. Turk Neurosurg. 2024;34(6):1133. doi: https://doi.org/10.5137/1019-5149.Jtn.45875-23.3
16. Jiménez-Jiménez FJ, Alonso-Navarro H, García-Martín E, Agúndez JAG. Anti-inflammatory effects of amantadine and memantine: possible therapeutics for the treatment of Covid-19? J Pers Med. 2020;10(4):217. doi: https://doi.org/10.3390/jpm10040217
17. Takeda M, Pekosz A, Shuck K, Pinto LH, Lamb RA. Influenza a virus M2 ion channel activity is essential for efficient replication in tissue culture. J Virol. 2002;76(3):1391–9. doi: https://doi.org/10.1128/jvi.76.3.1391-1399.2002
18. Bryson YJ, Monahan C, Pollack M, Shields WD. A prospective double-blind study of side effects associated with the administration of amantadine for influenza A virus prophylaxis. J Infect Dis. 1980;141(5):543–7. doi: https://doi.org/10.1093/infdis/141.5.543
19. Montazeri A, Mohammadi S, Hesari PM, Ghaemi M, Riazi H, Sheikhi-Mobarakeh Z. Preliminary guideline for reporting bibliometric reviews of the biomedical literature (BIBLIO): a minimum requirements. Syst Rev. 2023;12(1):239. doi: https://doi.org/10.1186/s13643-023-02410-2
20. van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics 2010;84(2):523–38. doi: https://doi.org/10.1007/s11192-009-0146-3

21. Darvish H. Bibliometric analysis using bibliometrix an R package. J Scientometric Res. 2020;8:156–60. doi: https://doi.org/10.5530/jscires.8.3.32
22. Davies WL, Grunert RR, Haff RF, McGahen JW, Neumayer EM, Paulshock M, *et al*. Antiviral activity of 1-adamantanamine (amantadine). Science 1964;144(3620):862–3. doi: https://doi.org/10.1126/science.144.3620.862
23. Dolin R, Reichman RC, Madore HP, Maynard R, Linton PN, Webber-Jones J. A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. N Engl J Med. 1982;307(10):580–4.
24. Danysz W, Dekundy A, Scheschonka A, Riederer P. Amantadine: reappraisal of the timeless diamond-target updates and novel therapeutic potentials. J Neural Transm (Vienna). 2021;128(2):127–69. doi: https://doi.org/10.1007/s00702-021-02306-2
25. Torre F, Campo N, Giusto R, Ansaldi F, Icardi GC, Picciotto A. Antiviral activity of amantadine in elderly patients with chronic hepatitis C. Gerontology 2001;47(6):330–3. doi: https://doi.org/10.1159/000052823
26. Sasaki -Tanaka R, Shibata T, Moriyama M, Okamoto H, Kogure H, Kanda T. Amantadine and rimantadine inhibit hepatitis A virus replication through the induction of autophagy. J Virol. 2022;96(18):e0064622. doi: https://doi.org/10.1128/jvi.00646-22
27. Hofmann A, Blum C, Single C, Adeyemi K, Schwarz P, Siokas V, *et al.* Amantadine for NeuroenhaNcement in acutE patients Study - a protocol for a prospective pilot proof of concept phase IIb study in intensive and intermediate care unit patients (ANNES). BMC Neurol. 2023;23(1):308. doi: https://doi.org/10.1186/s12883-023-03345-w
28. Sharma VD, Lyons KE, Pahwa R. Amantadine extended-release capsules for levodopa-induced dyskinesia in patients with Parkinson's disease. Ther Clin Risk Manag. 2018;14:665–73. doi: https://doi.org/10.2147/tcrm.S144481
29. Harandi AA, Pakdaman H, Medghalchi A, Kimia N, Kazemian A, Siavoshi F, *et al*. A randomized open-label clinical trial on the effect of Amantadine on post Covid 19 fatigue. Sci Rep. 2024;14(1):1343. doi: https://doi.org/10.1038/s41598-024-51904-z
30. Weis N, Bollerup S, Sund JD, Glamann JB, Vinten C, Jensen LR, *et al*. Amantadine for COVID-19 treatment (ACT) study: a randomized, double-blinded, placebo-controlled clinical trial. Clin Microbiol Infect. 2023;29(10):1313–9. doi: https://doi.org/10.1016/j.cmi.2023.06.023
31. Piątkowska-Chmiel I, Gawrońska-Grzywacz M, Popiołek Ł, Herbet M, Dudka J. The novel adamantane derivatives as potential mediators of inflammation and neural plasticity in diabetes mice with cognitive impairment. Sci Rep. 2022;12(1):6708. doi: https://doi.org/10.1038/s41598-022-10187-y
32. Liu JS, Chen Y, Shi DD, Zhang BR, Pu JL. Pharmacogenomics—a new frontier for individualized treatment of Parkinson's disease. Curr Neuropharmacol. 2023;21(3):536–46.

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