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Clemastine fumarate repurposing in neuropharmacology: bibliometric mapping of pharmacological evolution, remyelination research, and translational challenges

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Research Article

Keywords: Clemastine fumarate, bibliometric analysis, remyelination, multiple sclerosis, drug repurposing

Posted Date: June 10th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9885354/v1

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Additional Declarations: No competing interests reported.

Abstract

Purpose

Clemastine fumarate is a classical first-generation H1-antihistamine that readily crosses the blood–brain barrier. It has recently re-emerged as a candidate for neuropharmacological repurposing because of its ability to promote oligodendrocyte progenitor cell differentiation and enhance remyelination. This study aimed to map the global research trajectory underlying this pharmacological shift from an antiallergic drug to a remyelination-oriented candidate.

Methods

Publications on clemastine fumarate from 1995 to 2025 were retrieved from the Web of Science Core Collection and PubMed. Bibliometric and visualization analyses were performed using Bibliometrix, VOSviewer, CiteSpace, Microsoft Excel, Tableau, and SCImago Graphica. Publication trends, international collaboration, institutional and author productivity, keyword co-occurrence, thematic evolution, citation bursts, and pharmacology-related research shifts were analyzed. A neuropharmacological repurposing evidence layer was further constructed to interpret bibliometric signals in relation to indication, mechanism, translational maturity, and key limitations.

Results

A total of 316 publications were included. The literature showed a clear inflection after high-throughput screening identified clemastine as a promyelinating compound. Research focus gradually shifted from classical H1-antagonism, allergy, and sedation toward oligodendrocyte biology, myelin repair, neuroinflammation, and preclinical neurological disease models. Citation burst and keyword analyses highlighted an evidence chain linking high-throughput OPC screening, CHRM1/M1-related mechanisms, preclinical white-matter repair, and early clinical remyelination signals from the ReBUILD trial. Recent mechanistic studies further suggest that clemastine-mediated OPC effects cannot be fully explained by M1 antagonism alone, with additional pathways involving ERK activation, Gsta4/4-HNE signaling and H3K9 methylation.

Conclusion

Clemastine fumarate has become bibliometrically positioned as a neuropharmacological repurposing candidate, particularly in remyelination-oriented research. However, clinical translation remains constrained by limited validation, unclear CNS pharmacokinetic/pharmacodynamic relationships, disease-stage and timing dependence, tolerability issues, and uncertain clinical endpoints. Future

development should emphasize biomarker-guided, mechanism-informed, and cautiously designed translational studies.

Introduction

Clemastine fumarate is a first-generation antihistamine with high blood-brain barrier permeability, and has been clinically utilized since the 1960s to relieve allergic disorders such as urticaria and allergic rhinitis (Amonette 1981; Dockhorn and Oggel 1982; Jolliffe et al. 1985; Leurs et al. 1995; Meyrick Thomas et al. 1985; Oishi et al. 1994). For decades, clemastine was regarded as a sedating H1-receptor antagonist with limited therapeutic innovation potential, remaining largely confined to pharmacology textbooks and over-the-counter allergy medications (Oishi et al. 1994; Pushpakom et al. 2019; Schran et al. 1996). However, pharmacological landscape of this well-established compound underwent a dramatic transformation in the 2010s, catalyzed by its unexpected role in promoting central nervous system (CNS) remyelination (Chen et al. 2023; Lange et al. 2025; Liu et al. 2016; Mei et al. 2016, 2014).

The pivotal shift came from a landmark high-throughput screening study published in Nature Medicine in 2014, which identified clemastine as a potent inducer of OPC differentiation and myelin repair in animal models of demyelination (Ibrahim et al. 2024; Mei et al. 2014). This discovery repositioned clemastine from a peripheral antiallergic agent to a neuropharmacological repurposing candidate. The subsequent ReBUILD trial provided an early clinical remyelination signal in relapsing multiple sclerosis, reflected by improvement in visual-evoked potential latency rather than definitive evidence of broad clinical efficacy (Green et al. 2017). Later imaging analysis further suggested a myelin-water-fraction signal in normal-appearing white matter, supporting biomarker-based evaluation of remyelination while underscoring the need for cautious interpretation (Caverzasi et al. 2023; Yamazaki and Ohno 2025). Together, these studies created an evidence chain from screening to mechanism, clinical signal, and translational uncertainty.

Despite this renewed interest, the global scientific output on clemastine fumarate remains dispersed across diverse fields, and no systematic effort has mapped its intellectual evolution. While early research (pre-1990s) focused predominantly on pharmacokinetics, receptor binding, and adverse effects (Hildebrandt et al. 1975; Meyrick Thomas et al. 1985; Partridge and Saunders 1979), the post-1995 era captures both the consolidation of its classical profile and the emergence of novel neurological applications (Du et al. 2022; Partridge and Saunders 1979). To date, no bibliometric study has comprehensively examined the scientific landscape of clemastine fumarate. Existing reviews are either narrative or narrowly focused on mechanistic or clinical aspects, leaving a gap in our understanding of how knowledge has coalesced, who the key contributors are, and how research themes have evolved over the past three decades (Jiang et al. 2023; Yamazaki and Ohno 2025; Zhu et al. 2023b). Especially, even clemastine achieved success in the ReBUILD clinical trial, recent discussions on the differences in its efficacy among various disease phenotypes (such as the challenges posed by the TRAP-MS trial) have made a systematic review of the evolution of its research particularly urgent. Bibliometric methods

offer an objective, data-driven lens to reconstruct this intellectual journey, revealing collaboration patterns, thematic clusters, and emerging frontiers.

Therefore, this study conducts a comprehensive bibliometric analysis of peer-reviewed articles and reviews on clemastine fumarate published between January 1995 and November 2025. Rather than limiting bibliometric indicators as descriptive counts, we interpret publication trends, institutional networks, keyword co-occurrence, thematic evolution, and citation dynamics through the lens of drug repurposing and translational pharmacology. The objective is to map the global clemastine research landscape and to clarify how its pharmacological identity has evolved from H1-antihistamine use toward OPC-centered remyelination research, functional neuroprotection, and cautious clinical translation.

Methods

- Data source and search strategy

Bibliographic records were retrieved from the Web of Science Core Collection (WoSCC) and PubMed. A systematic search was performed on December 10, 2025 using the following database-specific strategy. In WoSCC, the search strategy was: TS= ("clemastine" OR "clemastine fumarate" OR "meclastine"), with language restricted to English and publication years restricted to 1995–2025. In PubMed, the search was limited to title/abstract fields (("clemastine"[Title/Abstract] OR "clemastine fumarate"[Title/Abstract] OR "meclastine"[Title/Abstract])) to improve specificity and reduce retrieval of records in which clemastine appeared only peripherally. “Meclastine” was included because it is used as an alternative name/synonym for clemastine in some bibliographic records; all retrieved records containing this term were manually checked to exclude irrelevant compounds. The publication timespan was restricted to 1995–2025, with the end date set to November 2025 to reflect the most recent indexed literature while allowing for database updating lags. Articles and reviews written in English were included because these document types represent substantive research and synthesis outputs suitable for bibliometric mapping. Records from WoSCC and PubMed were imported into Bibliometrix/Biblioshiny and merged. Duplicate records were identified and removed using available bibliographic identifiers, including DOI, PMID where available, and normalized title-based matching. Ambiguous records were manually inspected using title, first author, publication year, and journal information. The initial retrieval identified 568 records (WoSCC, n = 301; PubMed, n = 267). After de-duplication, language restriction, document-type screening, and manual eligibility review, 316 publications were retained for analysis. For pharmacology-oriented interpretation, we manually constructed a neuropharmacological repurposing evidence layer by classifying included literature according to indication, evidence type, proposed mechanism, translational maturity, and key limitation. This interpretive layer was used to link bibliometric signals to drug-repurposing and translational pharmacology questions, rather than to replace the primary bibliometric dataset. The workflow of data processing and analysis is summarized in Fig. 1.

- Analytical framework and software tools

We used an integrated bibliometric approach combining performance analysis, science mapping, and pharmacology-oriented interpretation. Bibliometrix (v5.2.1) in R was used for descriptive statistics, including annual output, source distribution, country/region productivity, institutional and author productivity, and citation indicators (Aria and Cuccurullo 2017; Chen 2017). VOSviewer (v1.6.20) was used to generate keyword co-occurrence and overlay maps. Only author keywords were used for co-occurrence analysis. Synonymous terms and spelling variants, such as “multiple sclerosis” and “multiple-sclerosis,” were manually harmonized where appropriate. Full counting was selected as the counting approach, and association strength normalization was implemented to standardize all link weights. The resolution parameter of the clustering algorithm was fixed at 1.00. A minimum occurrence threshold of 5 was set for keywords to pinpoint research hotspots, balancing network interpretability and the retention of newly emerging neuropharmacological terminology; clusters were interpreted according to dominant terms and their pharmacological meaning. CiteSpace (v6.4.R2) was used for institutional cooperation analysis and reference burst detection, allowing identification of temporal turning points in the clemastine evidence chain (Chen 2006). The detailed analytical parameters were set as listed below. The dataset was divided into one-year time slices. Network pruning was performed using the Pathfinder algorithm. Nodes were filtered via the g-index method with a scaling factor k of 25, and the gamma value was fixed at 1.0. For reference burst detection, the top 15 references with the strongest burst strength were extracted. Microsoft Excel 2024, Tableau 2025, and SCImago Graphica were used to summarize annual and cumulative publication trends, country scientific production, and collaboration patterns. Because the objective of this study was to develop a pharmacological repurposing map rather than a purely descriptive bibliometric inventory, country, institution, keyword, and burst-reference findings were interpreted in relation to allergy pharmacology, CNS exposure, OPC differentiation, remyelination mechanisms, clinical signals, and translational barriers.

Results

- Annual publications and trends

A total of 316 English-language articles published between 1995 and November 2025 were included in the analysis, consisting of 284 original research papers and 32 reviews. As shown in Fig. 2, annual publication counts are displayed as bars (left y-axis), and cumulative publications are shown as a red line (right y-axis). A linear trend line for cumulative publications ($y = 7.6403x - 2.9226$; $R^2 = 0.8865$) indicates strong overall growth. Publication output began at a moderate level (17 in 1995), declined through the late 1990s and early 2000s, and remained low and stable (~ 0–10 per year) from 2005 to 2019. A marked resurgence began in 2020 onward, with annual counts rising sharply from 12 (2020) to 36 (2025), driving cumulative totals from ~ 100 in 2019 to 316 in 2025.

This pattern reflects the field's evolution: early interest in clemastine's antihistamine applications gave way to a period of relative stagnation, followed by explosive growth post-2020, likely triggered by pivotal discoveries in remyelination (e.g., high-throughput screening in 2014 and the ReBUILD trial in 2017)

(Green et al. 2017; Mei et al. 2014). The high R^2 value confirms a robust upward trajectory, underscoring renewed momentum in neuroregenerative research and drug repurposing for demyelinating disorders.

- Geographic distribution of publications by country/region

The number of Clemastine-related articles published by various countries and regions from 1995 to 2025 is illustrated in Fig. 3. Over this period, researchers in the USA have led with the publication of the highest number of articles, followed by China. These two nations significantly outpaced others in terms of research output (Fig. 3A).

Figure 3B demonstrates the number of documents by corresponding author's country, which is further differentiated between Single Country Publications (SCP, light blue bars) and Multiple Country Publications (MCP, orange bars). The United States dominates with the highest output (60 documents), predominantly SCP (48), followed by China (49 documents, mostly SCP 42). European countries (Netherlands, Germany, Sweden, Switzerland,) and Japan each contribute 10–16 documents, with varying but generally low MCP proportions, except United Kingdom, which had more MCP than SCP. Lower-ranking nations (e.g., Canada, Egypt) published fewer than 10 documents. Overall, research leadership is concentrated in the United States and China, driven mainly by independent national efforts (high SCP ratios), while international collaboration (MCP) remains limited but more prominent in select European countries.

Figure 3C illustrates the most cited countries in clemastine fumarate research (1995–2025), ranked by total citations (TC, orange) and average article citations (blue). The United States led with the highest TC (2743) and strong average citations, followed by China with substantial TC but lower average citations. The Netherlands, Germany, Canada, Sweden, Switzerland, United Kingdom, Italy, and Japan followed, showing moderate TC and varying average citation rates. This distribution highlights the United States as the most influential contributor in terms of both volume and impact, with China emerging as a major player in publication volume. European nations exhibit solid citation performance relative to output, reflecting high-quality contributions in the field.

The network diagram (Fig. 3D) shows collaborative links between countries, with node size proportional to publication volume and link thickness indicating collaboration strength (flow intensity from 5 to 125+). The United States and China are central hubs with the strongest outgoing and incoming connections, linking extensively to Germany, Switzerland, United Kingdom, Egypt, and others (e.g., India, Iran, Spain, France, Italy, Saudi Arabia, Denmark, Brazil). Collaboration flows are dominated by ties involving the United States and China, with secondary clusters among European nations. This network reveals a core-periphery structure, in which the United States and China drive global partnerships, while emerging links to Middle Eastern, Asian, and South American countries suggest expanding international engagement in remyelination and neuroregenerative research.

- Analysis of major institutions

As shown in Fig. 4A, the University of California (UC) system is the most prolific contributor in the clemastine research field, with 56 publications, followed closely by the University of California, San Francisco (UCSF) with 51. The Army Medical University ranks third, contributing 41 articles. Other institutions, including the Egyptian Knowledge Bank (EKB), University of Illinois at Urbana–Champaign, University of Virginia, University of Zurich, Tel Aviv University, and University at Buffalo, contribute more modestly but consistently, underscoring the geographically diverse nature of clemastine research. Figure 4B illustrates the cumulative publication trajectories of the 5 leading institutions over time. Prior to 2016, clemastine-related research output was limited and relatively stable across institutions. A pronounced inflection point is observed after approximately 2017, followed by rapid growth between 2019 and 2023. The UC system and UCSF exhibit the steepest increases, suggesting sustained and expanding research programs. Notably, the Army Medical University shows a delayed but sharp rise in publications after 2018, indicating a late entry followed by accelerated engagement. In contrast, institutions such as EKB and the University of Illinois at Urbana–Champaign grew gradually with more modest absolute output, reflecting emerging or complementary research roles.

Collaboration between countries and institutions is widely recognized as an important means to improve the quality and productivity of research. We used CiteSpace software to conduct institutional cooperation analysis. The density value (0.01) was regarded as a threshold for substantial cooperation between institutions (Chen 2006); however, the analytical results showed the density value is less than 0.01 (Fig. 4C), indicating a lack of stable, frequent collaborative networks among institutions. Overall, it is necessary to break academic barriers, enhance international cooperation, and encourage communication between different research institutions and teams.

Collectively, these findings demonstrate that clemastine research is dominated by a small number of highly productive academic hubs, primarily within the United States, which also function as central nodes in the global collaboration network. The marked increase in institutional output over the past decade suggests growing scientific and translational interest in clemastine, potentially driven by expanding indications and mechanistic insights. At the same time, the participation of diverse international institutions points to a gradual globalization of research efforts in this field.

- Analysis of journals

A visual analysis of publishing and co-cited journals was conducted to identify the most active and influential journals in clemastine research. Our analysis revealed that 316 clemastine-related articles were published across 228 academic journals. The three journals with the highest number of clemastine-related publications were Glia (Np = 6), followed by Rapid Communications in Mass Spectrometry and Brain, each publishing 5 articles. The top 10 most productive journals are presented in Fig. 5A. In terms of citation impact, Nature Neuroscience ranked first with a total of 594 citations (Tc = 594), followed by The Lancet (Tc = 437) and Arthritis & Rheumatism (Tc = 389). The top 10 journals by total citations are demonstrated in Fig. 5B.

Figure 5A The top 10 journals with the largest number of publications. **B** The top 10 journals ranked by total citations. C Dual-map overlay of journals generated by CiteSpace. The left side represents citing journals and the right side represents cited journals. Curved ribbons indicate citation direction and strength; central hub (6. Molecular Biology, Genetics) highlights a key interdisciplinary nexus. Colors denote subject categories (e.g., green: medicine; yellow: molecular biology).

- Analysis of authors and cited authors

As shown in Table 1, the top three most cited authors are Jonah R Chan (TC = 1408), Feng Mei (TC = 1128), and Ruixue Li (TC = 792). Figure 6A illustrates the time graph of clemastine-related articles by authors. In this Figure, authors' names are plotted on the vertical axis and publication years are shown on the horizontal axis. The node size reflects the volume of publications, with larger circles indicating higher output, while the color intensity reflects the average annual citation count, with darker colors signifying greater citations. Ronald B Turner is considered as the pioneer in the field of clemastine research, while Lan Xiao is the most prolific author. Jonah R Chan has the highest H-index of 8 (Fig. 6B), indicating his local impact within the dataset of clemastine-related research.

Table 1
The top 10 cited authors

Ranking	Author	H-index	TC[1]	NP[2]	Institution	Country	PY[3]_start
1	Jonah R Chan	8	1408	10	University of California San Francisco	USA	2017
2	Feng Mei	6	1128	10	Army Medical University	China	2017
3	Ruixue Li	5	792	5	Army Medical University	China	2020
4	Lan Xiao	6	688	9	Army Medical University	China	2018
5	Jingfei Chen	6	625	8	Army Medical University	China	2020
6	Ari J Green	6	613	7	University of California San Francisco	USA	2017
7	Fei Wang	6	582	7	Army Medical University	China	2018
8	Ronald B. Turner	6	306	6	Medical University of South Carolina	USA	1996
9	Ulf Bondesson	5	63	5	Uppsala University	Sweden	2003
10	Mikael Hedeland	5	63	5	National Veterinary Institute (SVA)	Sweden	2003

[1]TC: Number of citations; [2]Np: Number of publications; [3]PY: The first year of publication.

- Keyword visualization and analysis

The keyword co-occurrence analysis was performed using VOSviewer. The node size reflects the frequency of occurrence (how often a keyword appears across the dataset). Larger nodes indicate more frequently used keywords. The lines (edges) indicate co-occurrence links; thicker lines mean stronger/more frequent co-occurrences between keywords. Colors represent clusters of closely related keywords (grouped by co-occurrence strength, using VOSviewer's clustering algorithm). Different colors denote distinct research sub-themes (Fig. 7A). The red cluster (right side) is centered on "antihistamine," and "double-blind." This cluster represents the traditional focus on clemastine's role as an antihistamine in allergy treatment, clinical trials for respiratory conditions, and comparative efficacy studies, emphasizing comparative efficacy and trial design. The green cluster (bottom-left) is dominated by "myelination," "myelin," "mouse model," and "rescues behavioral-changes." This cluster highlights

preclinical investigations into myelin repair mechanisms, behavioral outcomes, and animal models of neurological damage, underscoring functional recovery mechanisms. The light blue cluster (left) is focused on "oligodendrocyte," " autophagy," and "neuroinflammation." It emphasizes cellular and molecular pathways, particularly oligodendrocyte biology and inflammatory processes in demyelination. The yellow cluster (top) is led by "multiple sclerosis," and "remyelination." This cluster reflects translational and clinical applications in MS and neuroregenerative therapies, emphasizing disease-specific interventions and trial outcomes. The network demonstrates a clear thematic progression from early allergy-related research (red cluster) versus emerging neuroregenerative applications (green, blue, yellow clusters), with "remyelination" serving as a central bridging node. This structure underscores clemastine's potential therapeutic direction from peripheral antiallergic agent to CNS-targeted therapy for demyelinating disorders.

The VOSviewer overlay visualization (Fig. 7B) combines keyword co-occurrence network with a time overlay, where node colors represent the average publication year of articles containing that term. Here, all these keywords are again divided into four clusters, further illustrating clemastine’s transformation from a classic antihistamine to a promising remyelinating agent, with research increasingly focused on mechanistic depth and neurological therapeutic outcomes over the past decade.

Analysis of research trends with keywords

As demonstrated in Fig. 8A, the strategic diagram categorizes keyword clusters into four quadrants based on centrality (relevance degree, x-axis) and density (development degree, y-axis). The dominant cluster (upper-right quadrant) features high-occurrence terms with strong centrality, including "remyelination" (34 occurrences), "rescues behavioral-changes" (28), "myelination" (27), "myelin" (23), "oligodendrocyte" (22), "differentiation" (20), "multiple-sclerosis/multiple sclerosis" (combined 37), "demyelination" (18), and "prefrontal cortex" (18). These occupy basic (lower-right) and motor (upper-right) quadrants, indicating foundational and driving roles in the field. Niche themes (upper-left quadrant) are specialized with high density but low centrality, such as "adult," "middle aged," "aged," "spectrophotometric determination," "capillary-electrophoresis," and "human plasma." Emerging or declining themes (lower-left quadrant) show low centrality and density, including "acid intermediate," "clemastine/pharmacology disease models animal mice inbred c57bl," "modulation," "acth," and "anaphylaxis." Basic themes (lower-right quadrant) include transitional terms like "antihistamine," "double-blind," "histamine," "expression," "activation," and "apoptosis." This map illustrates the field's progression from early pharmacological and analytical niches to motor themes in neuroregeneration, with "remyelination" as a pivotal driver, signifying clemastine's repurposing for demyelinating disorders.

The dot plot illustrates the temporal distribution of high-frequency keywords, with the x-axis representing publication years and the y-axis listing terms ordered by median year (Fig. 8B). Each term is represented by a horizontal line spanning the interquartile range (Q1 to Q3) and a dot marking the median year, with dot size and color intensity indicating frequency (ranging from 5 to 34, as shown in the legend). Early terms (median years 1998–2006) include "cetirizine" (11; 1998–2004), "double-blind" (20; 1998–2022),

"antihistamine" (30; 1998–2017), and "histamine" (20; 2001–2019), reflecting the drug's initial focus on allergy treatment and clinical trials. Mid-period terms (median years 2007–2018) encompass analytical and pharmacological topics, such as "human plasma" (5; 2007–2013), "pharmacology" (6; 2004–2021), "spectrophotometric determination" (6; 2011–2017), and "pharmacokinetics" (9; 2013–2020). Recent terms (median years 2019–2024) highlight neurological applications, including "progenitor cells" (7; 2018–2022), "neuroinflammation" (8; 2019–2022), "rescues behavioral-changes" (28; 2020–2024), "remyelination" (34; 2021–2024), and "oligodendrocyte" (22; 2022–2025). This visualization further demonstrates a clear thematic evolution from antihistamine-related clinical and pharmacological studies in the early period to advanced neuroregenerative themes in recent years, underscoring clemastine's repurposing for remyelination and demyelinating disorders.

- Analysis of co-citation references

This CiteSpace citation burst analysis identifies the top 15 influential references in clemastine research from 1995 to 2025 (Fig. 9). Citation bursts indicate periods of sharply increased attention and help reconstruct the evidence chain underlying clemastine repurposing. The strongest bursts belong to Green AJ (2017, The Lancet, strength 14.99, burst 2018–2022) and Cree BAC (2018, Brain, strength 11.72, burst 2019–2023), highlighting the transition from preclinical remyelination to early clinical and white-matter repair signals. These bursts should be interpreted as indicators of research momentum rather than proof of clinical success. Overall, the burst pattern supports a stepwise pharmacological trajectory from screening and OPC biology to clinical remyelination signals, functional validation, and continuing uncertainty about disease stage, dosing, and endpoints.

To translate the bibliometric signals into pharmacological relevance, we additionally summarized the main therapeutic and mechanistic domains represented in the clemastine literature (Table 2). This evidence map shows that established clinical use remains allergy-related, whereas neuropharmacological repurposing is concentrated in MS/optic neuropathy, white-matter injury models, neurodegenerative disease, and exploratory cognitive or neuroinflammatory contexts. The maturity of evidence is uneven: MS has the strongest clinical signal, while most other neurological applications remain preclinical or hypothesis-generating.

Table 2
Evidence map of clemastine repurposing across pharmacological indications

Indication/domain	Evidence type	Proposed mechanism	Translational maturity	Key limitation
Allergy, urticaria, allergic rhinitis	Historical clinical use	H1-receptor antagonism	Established for original indication	Sedation and anticholinergic effects limit CNS-dose escalation
Multiple sclerosis / optic neuropathy	Clinical trial plus preclinical evidence	OPC differentiation, remyelination, myelin repair	Highest among repurposing indications	VEP and MWF signals require linkage to durable disability outcomes and patient selection
Spinal cord injury / white-matter injury	Preclinical evidence	Myelin repair, axonal support, neuroprotection	Medium-low	Animal-model dependence and uncertain timing/dosing window
Alzheimer's disease / neurodegeneration	Preclinical and hypothesis-driven evidence	Myelin renewal, autophagy, neuroinflammation modulation	Low	Clinical evidence absent and mechanism not disease-specific
Ischemic stroke / hypoxia-ischemia / perioperative cognitive dysfunction	Preclinical evidence	Myelination, anti-inflammatory and anti-apoptotic effects, white-matter preservation	Low	Timing, dose, and developmental-stage dependence remain unresolved
Depression / cognitive dysfunction / psychiatric models	Exploratory preclinical evidence	Microglial modulation, oligodendrocyte support, circuit-level effects	Exploratory	Behavioral endpoints are indirect and mechanisms overlap with other CNS pathways
Neuronal/network functional integration	Preclinical neural-interface evidence	Myelin integrity, axonal metabolic support, neuronal survival, network connectivity	Exploratory functional validation	Microelectrode performance is a functional model rather than a primary therapeutic indication

Discussion

- Global research trends and geographic evolution

The bibliometric analysis of clemastine fumarate research from 1995 to 2025 reveals a clear reorientation of the field from established antihistamine pharmacology toward CNS repurposing, remyelination biology, and translational neuropharmacology. This shift is visible in the movement from early terms related to histamine antagonism, sedation, and classical clinical use toward later terms centered on oligodendrocytes, myelination, neuroprotection, and disease models. This pattern should be interpreted as an evolving research trajectory rather than as evidence that clemastine has already achieved broad clinical validation.

Geographically, the United States and China represent the two largest contributors to clemastine research, but their contributions appear to emphasize different parts of the repurposing trajectory. The United States leads in total citations (2,743) and average citation impact, anchored by the University of California (UC) system and UC San Francisco (UCSF), where influential work helped connect high-throughput screening, remyelination biology, and early MS clinical evaluation. China has shown rapid growth in publication volume, with institutions such as the Army Medical University contributing to broader preclinical indications including AD, PND, and neuroinflammatory models. However, the global institutional collaboration network remains relatively fragmented (density < 0.01), indicating that international knowledge integration across screening, mechanism, and clinical translation remains limited.

- The paradigm shift: from allergy to neuroregeneration

The pharmacological repositioning of clemastine was catalyzed by the landmark study by Mei et al. (2014), which identified the drug as a potent inducer of OPC differentiation via a high-throughput screening platform (Mei et al. 2014). This discovery shifted research attention from classical H1-receptor antagonism toward OPC-centered remyelinating biology, initially framed around off-target M1-muscarinic receptor (CHRM1) antagonism (De Angelis et al. 2012; Yamazaki and Ohno 2025). However, recent mechanistic syntheses suggest that this shift should not be reduced to CHRM1/M1 blockade alone. Clemastine-associated OPC differentiation and remyelination may also involve ERK activation, Gsta4/4-HNE signaling, H3K9 histone methylation, and induction of NMDA receptor-rich OPC states (Yamazaki and Ohno 2025). Keyword evolution maps therefore capture not only a change in disease area, but also a broader pharmacological identity shift from symptomatic antihistamine use toward CNS-exposed, OPC-modulating, remyelination-oriented pharmacology.

This evolution illustrates a common drug repurposing pathway: a clinically familiar compound with known drawbacks is re-explored in a new mechanistic context. For clemastine, blood–brain barrier penetration was originally associated with sedation and anticholinergic burden, but later became pharmacologically relevant because CNS exposure enabled investigation of OPC differentiation, remyelination, and white-matter repair. The same property therefore creates both opportunity and constraint: CNS access supports target engagement, while first-generation antihistamine and antimuscarinic effects limit tolerability and complicate dose optimization.

- Therapeutic potential in demyelinating and neurodegenerative disorders

Multiple sclerosis (MS)

MS remains the primary clinical focus of clemastine repurposing research (Hof et al. 2024; Jiang et al. 2023; Makhzoum et al. 2025). The ReBUILD trial represented a major clinical remyelination signal rather than definitive proof of broad therapeutic efficacy, showing improvement in visual-evoked potential P100 latency in patients with chronic demyelinating optic neuropathy (Green et al. 2017). Further MRI analysis suggested that myelin water fraction of the corpus callosum and normal-appearing white matter may serve as a biomarker for treatment-associated myelin changes (Caverzasi et al. 2023; Yamazaki and Ohno 2025). These findings support early clinical validation of a remyelination signal, but they also highlight unresolved questions about patient selection, disability endpoints, CNS target engagement, and whether VEP or imaging changes translate into durable clinical benefit.

However, recent findings from the TRAP-MS trial have introduced a critical caveat: clemastine may accelerate disability accumulation in progressive MS by enhancing P2RX7-mediated pyroptosis (Kocot et al. 2025; Lee et al. 2021; Yamazaki and Ohno 2025). This "negative burst" in the literature underscores the complexity of clemastine's role in inflammatory environments and suggests that its efficacy may be phenotype-dependent (Kocot et al. 2025 Xie et al. 2021).

Alzheimer's disease (AD) and cognitive decline

Bibliometric mapping of AD and depression highlights a growing interest in multi-pathway interventions (Wang et al. 2025). Clemastine has been shown to rescue cognitive deficits in AD murine models by enhancing myelin renewal (Chen et al. 2021; Fessel 2022; Ochi et al. 2025; Zhu et al. 2023b). Beyond myelination, clemastine targets AD pathology by reducing Aβ deposition and upregulating mTOR-mediated autophagy, which facilitates the clearance of toxic protein aggregates (Jiang et al. 2023; Klionsky et al. 2012; Leyrolle et al. 2022; Li et al. 2021; Zhu et al. 2023b, 2023a). This multifaceted role positions clemastine as a potential disease-modifying strategy for neurodegeneration (Zhu et al. 2023b).

Brain injury: hypoxia, SCI, and PND

Preclinical studies report that clemastine can improve white-matter integrity or myelination-related outcomes in neonatal and adult hypoxic injury models (Chen et al. 2022; Cree et al. 2018; Feng et al. 2025; He et al. 2025; Jiang et al. 2023). The reported minimum effective dose of 7.5 mg/kg/day in neonatal mice provides a useful pharmacological benchmark, but cannot be directly translated to pediatric dosing without dedicated CNS PK/PD and safety studies (Odell et al. 2024). In spinal cord injury models, clemastine has been associated with myelin preservation, delayed axonal loss, and improved motor outcomes, whereas PND models suggest potential links with Wnt/beta-catenin signaling and neuroinflammation (Chen et al. 2023; Deshmukh et al. 2013; Dewar et al. 2003; Myatich et al. 2023; Turski et al. 2018; Wu et al. 2021). These findings broaden the translational rationale but remain model-dependent and require careful validation of timing, dose, and endpoint relevance.

Psychiatric Disorders

Emerging evidence links white matter impairment to the neuropathology of schizophrenia and major depressive disorder (MDD) (Li et al. 2015; Su et al. 2018; Wu et al. 2021). Clemastine treatment in socially isolated or cuprizone-exposed mice has been found to reverse social avoidance behaviors and rescue memory deficits (Li et al. 2015; Liu et al. 2016; Su et al. 2018). These effects are often associated with the suppression of microglial M1-like activation and the modulation of the P2X7 receptor in the hippocampus (Jiang et al. 2023; Su et al. 2018; Zhu et al. 2023b).

- Mechanistic insights: the cellular and molecular bridge

Clemastine's remyelination-related mechanism is best understood as an OPC-centered pharmacological program rather than a single-receptor effect. CHRM1/M1 muscarinic receptor blockade remains a central and well-supported mechanism because it can release OPCs from differentiation constraints and promote maturation into oligodendrocytes (Yamazaki and Ohno 2025). Nevertheless, the recent research also implicates ERK activation, Gsta4/4-HNE signaling, H3K9 histone methylation, and NMDA receptor-rich OPC states as contributors to the pro-remyelinating phenotype (Yamazaki and Ohno 2025) (Fig. 10). This broader mechanism helps explain why bibliometric hotspots have expanded from receptor pharmacology to myelination, synaptic integrity, cognitive outcomes, and neuroinflammatory modulation.

A related translational implication is that remyelination should not be viewed only as a histological endpoint. Chen et al. (2023) extended clemastine's pharmacological relevance to the level of neuronal health and functional network performance, reporting improved chronic microelectrode recording signal detectability, multi-unit activity, interlaminar connectivity, oligodendrocyte density, myelination, and excitatory/inhibitory neuronal survival near implanted electrodes. Although this model should not dominate the therapeutic narrative, it supports the concept that myelin integrity may contribute to axonal metabolic support, neuronal survival, and network function.

Clemastine also exhibits significant anti-inflammatory and anti-apoptotic properties (Meng et al. 2021; Zhi et al. 2021; Zou et al. 2025; Zuo et al. 2023). It reduces levels of pro-inflammatory cytokines like TNF-α and IL-1β by inhibiting the p38 MAPK/NLRP3/IL-1β pathway in microglia (Wu et al. 2021; Xie et al. 2020). This dual role—promoting repair while suppressing inflammation—is a recurring theme in high-impact clemastine literature (Jiang et al. 2023; Sabir et al. 2023; Zhu et al. 2023b).

- Emerging frontiers and future outlook

The bibliometric transition toward remyelination research should be interpreted alongside pharmacological barriers that constrain repurposing. Table 3 summarizes the main translational risks and development opportunities that emerge from the evidence map and recent mechanistic literature.

Table 3
Pharmacological and translational barriers of clemastine repurposing

Barrier	Pharmacological basis	Current evidence	Implication
Sedation	BBB penetration plus H1 antagonism	Know first-generation antihistamine effect	Limits dose escalation and long-term tolerability
Anticholinergic burden	Muscarinic receptor antagonism, including M1/M3-related effects	The same receptor class implicated in OPC differentiation may contribute to adverse effects	Therapeutic window and receptor selectivity require careful evaluation
Disease-stage dependence	OPC availability, lesion chronicity, and inflammatory context	Clinical signal in optic neuropathy contrasts with concerns in progressive disease settings	Patient selection and disease-stage stratification are essential
Timing and duration dependence	OPC state and repair window may change across lesion stages	Preclinical models suggest different outcomes depending on treatment timing and duration	Trial design should specify timing, duration, and lesion biology
Endpoint uncertainty	VEP, MRI myelin markers, and disability measure different biological levels	ReBUILD and MWF studies support remyelination signals but not definitive disability modification	Biomarker-guided trials need clinically meaningful endpoints
CNS PK/PD uncertainty	Plasma exposure may not reflect CNS target engagement	Human CNS exposure-response data remain limited	PK/PD modeling and target-engagement biomarkers are needed
Repurposed drug limitation	Old, non-selective receptor profile	Multiple pharmacological targets and adverse-effect liabilities	Selective brain-penetrant M1 antagonists or combination strategies may offer cleaner development paths

The latest research frontiers, identified through burst detection, emphasize combination therapies and advanced PK/PD modeling (Hildebrandt et al. 1975; Sodeifian et al. 2021; Urbina et al. 2021).

1. 1. Synergy strategies: The CCMR-Two trial is testing metformin plus clemastine as a strategy to restore responsiveness of senescent OPCs to pro-differentiation cues (Riboni-Verri et al. 2025). This direction is important because remyelination may depend not only on receptor pharmacology, but also on OPC state, lesion age, metabolic context, and treatment timing.
2. 2. Next-generation selectivity: To reduce sedation, anticholinergic burden, and other off-target liabilities of first-generation antihistamine pharmacology, research is shifting toward more selective and brain-penetrant M1 antagonists such as PIPE-307 (Ali et al. 2021; Osanai et al. 2022; Poon et al.

2024; Rosko et al. 2023; Yamazaki and Ohno 2025). These agents may clarify whether the remyelination signal can be separated from clemastine's broader receptor profile.

3. 3. High-resolution biomarkers: Specialized MRI myelin metrics, LC-MS/MS-based exposure assessment, and longitudinal functional endpoints will be essential for distinguishing pharmacodynamic remyelination signals from non-specific symptomatic or anti-inflammatory effects (Caverzasi et al. 2023; Odell et al. 2024).
4. 4. Species and developmental-stage translation: Rodent and other preclinical models remain valuable, but species differences, developmental-stage effects, and disease-stage dependence require careful interpretation. Human myelinated brain organoids and biomarker-enriched clinical designs may help bridge the gap between OPC biology and patient-level outcomes (Green et al. 2017; Lange et al. 2025; Liu et al. 2016; Moghaddasi et al. 2020).

Limitations

While this study provides a systematic overview, several limitations must be acknowledged. First, data were retrieved from WoSCC and PubMed and were restricted to English-language articles and reviews, which may underrepresent non-English studies, regulatory reports, trial protocols, or multidisciplinary engineering and neurotechnology literature. Second, citation metrics are time-dependent; recent studies from 2024–2025, including work on selective M1 antagonists, organoid models, and translational safety, may not yet have accumulated citations proportional to their future influence. Third, the neuropharmacological evidence map was an interpretive classification designed to connect bibliometric patterns with pharmacological questions; it does not replace a systematic review or meta-analysis of efficacy and safety. Finally, bibliometric signals identify research momentum and knowledge structure, but they cannot determine clinical efficacy, CNS target engagement, optimal dosing, or disease-stage-specific benefit.

Conclusion

This bibliometric analysis supports clemastine fumarate as a clear example of pharmacological repositioning in neuropharmacology, though not yet a fully validated remyelinating therapy. The literature has evolved from historical H1-antihistamine use and CNS sedation toward OPC-centered remyelination mechanisms, preclinical white-matter repair, early clinical remyelination signals, and emerging functional interpretations linking myelin integrity with neuronal and network performance. At the same time, the translational path remains constrained by sedation, anticholinergic burden, uncertain CNS PK/PD relationships, timing and disease-stage dependence, species differences, and endpoint uncertainty. Future research should therefore prioritize biomarker-guided trials, explicit patient-selection strategies, CNS target-engagement assessment, careful dosing and duration studies, and comparison with next-generation selective remyelinating pharmacology. In this form, clemastine research is best viewed as a drug-repurposing roadmap that connects bibliometric evolution with pharmacological mechanism and cautious translational development.

Declarations

Ethics approval and consent to participate

This bibliometric study did not involve human participants, human data, or animals; therefore, ethics approval and consent to participate were not required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Funding

This research was funded by the Science and Technology Plan Projects of Shanghai Science and Technology Commission (No. 25SF1908200), and the Fundamental Research Funds for the Central Universities of Shanghai Jiao Tong University (No. YG2023LC15).

Data availability

All source data for this work or generated in this study are available from the corresponding author upon reasonable request.

Author Contribution

Y.L. contributed to conceptualization, formal analysis, data curation, and writing of the original draft. S.W. and H.L. contributed to validation, methodology. G.L. performed data curation. Q.M. contributed to writing, review, and editing. Z.X. contributed to project administration, supervision, and funding acquisition. All authors agreed on the submission and are responsible for all aspects of the work. The authors declare that all data were generated in-house and that no paper mill was used.

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Figures

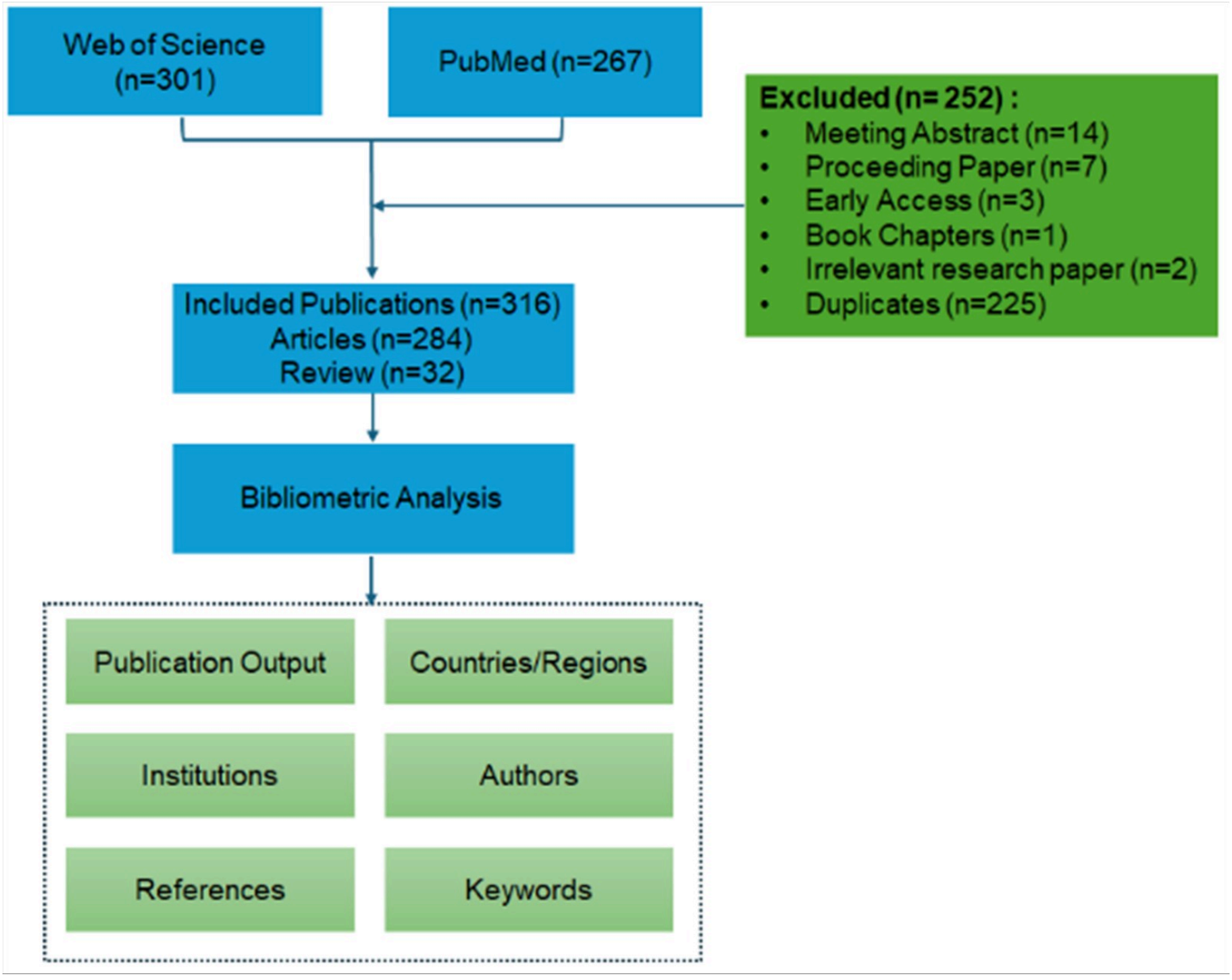


Figure 1

Flowchart of data extraction, processing and bibliometric analysis

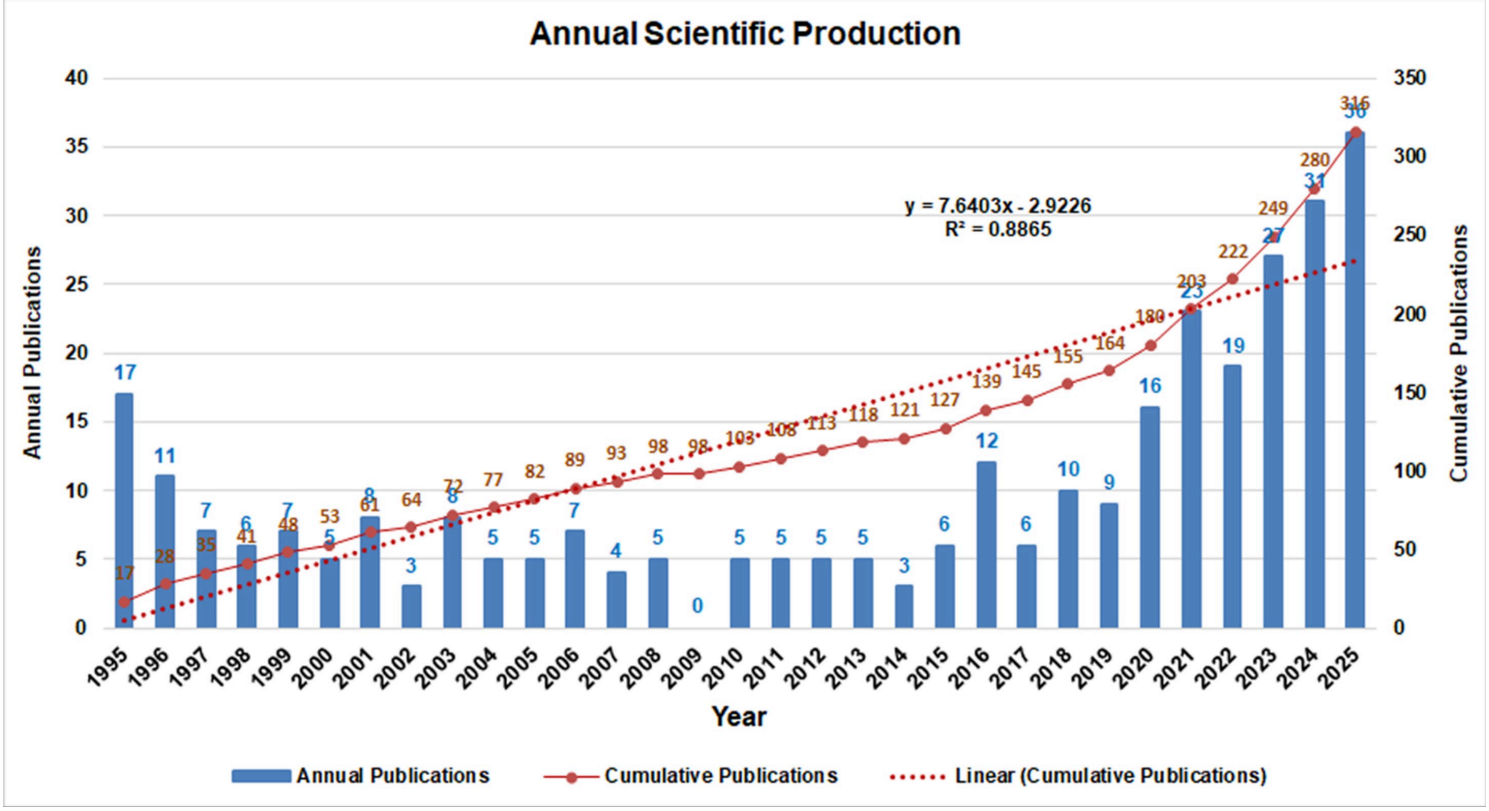


Figure 2

Trends in the number of annual and cumulative publications from 1995 to 2025 (The bar chart (left y-axis) illustrates annual publication counts, while the red line (right y-axis) represents cumulative publications)

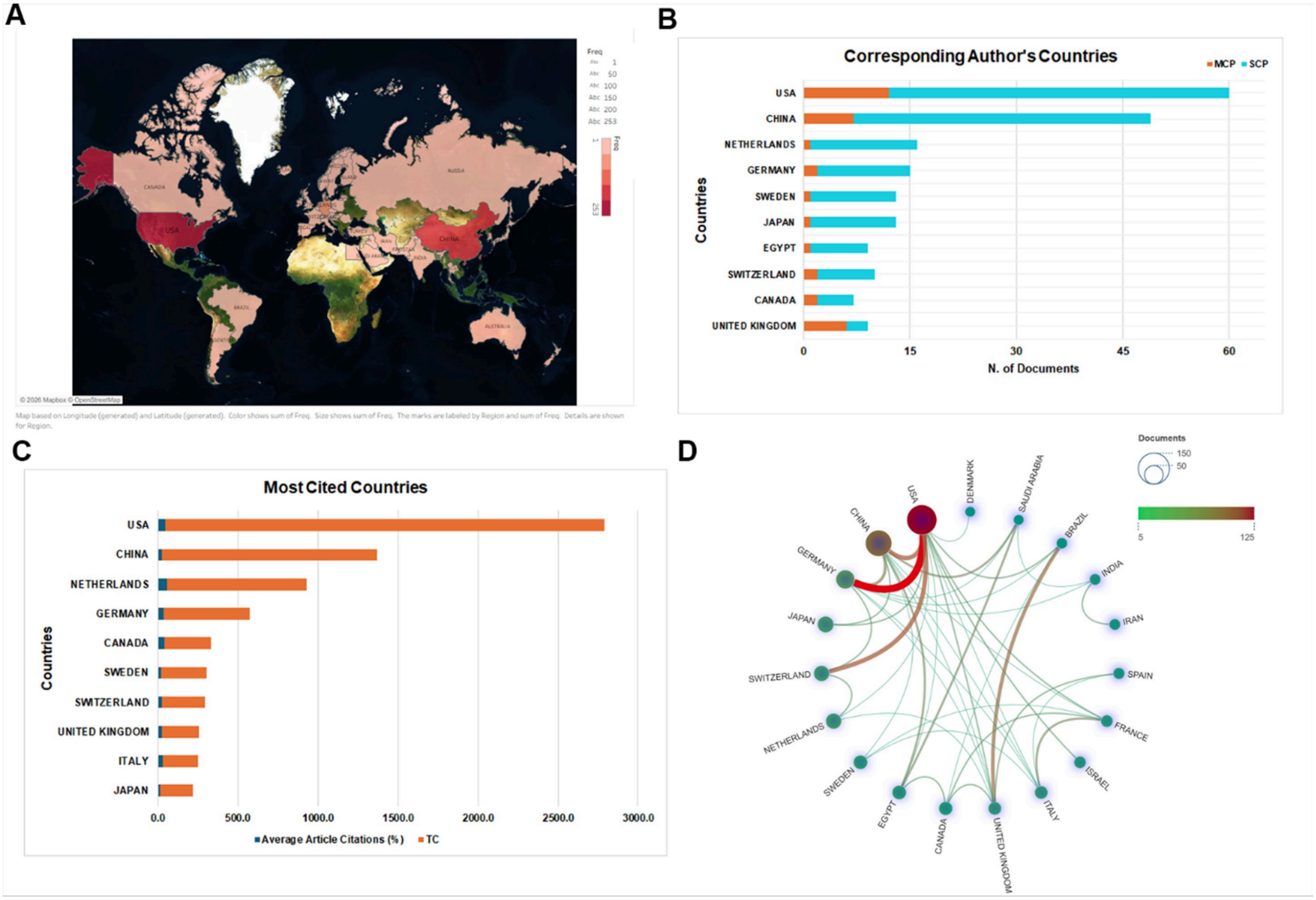


Figure 3

A Geographic distribution of publications by country/region based on publication count. **B** The number of documents by corresponding author's country (Light blue bar: Single country publications; orange bar: Multiple country publications). **C** The top 10 most productive countries from 1995 to 2025 (Orange bar: Total citation; Blue bar: Average article citations). **D** Collaboration analysis among different countries/regions. The node size represents publication volume, and link thickness indicates collaboration strength

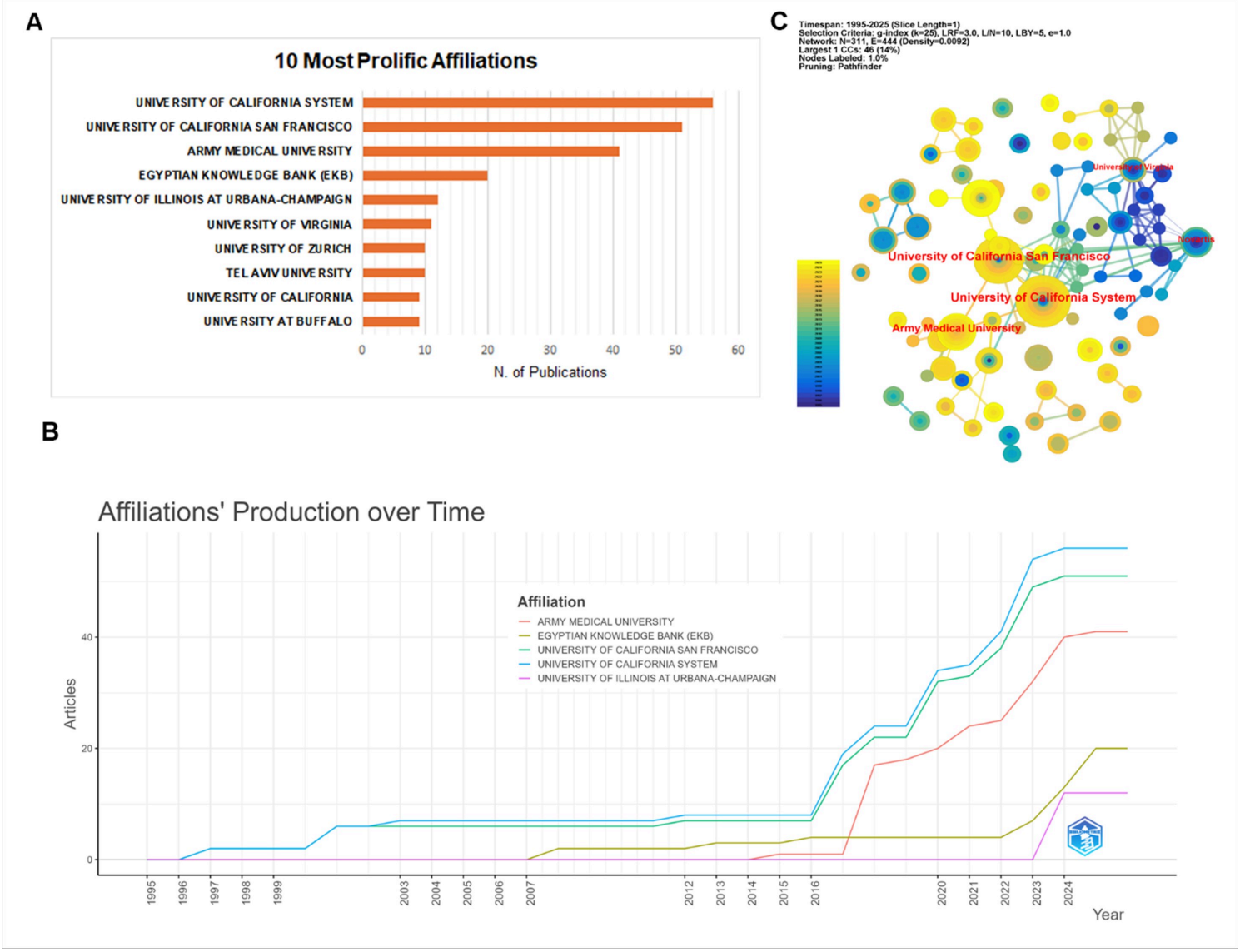


Figure 4

Institutional productivity and collaboration in clemastine research. A The top 10 institutions with the largest number of publications. **B** Temporal production trends of the five leading affiliations from 1995 to 2025. **C** Visualization map of institutional collaboration generated by CiteSpace. Node size represents publication volume, and links indicate collaborative relationships.

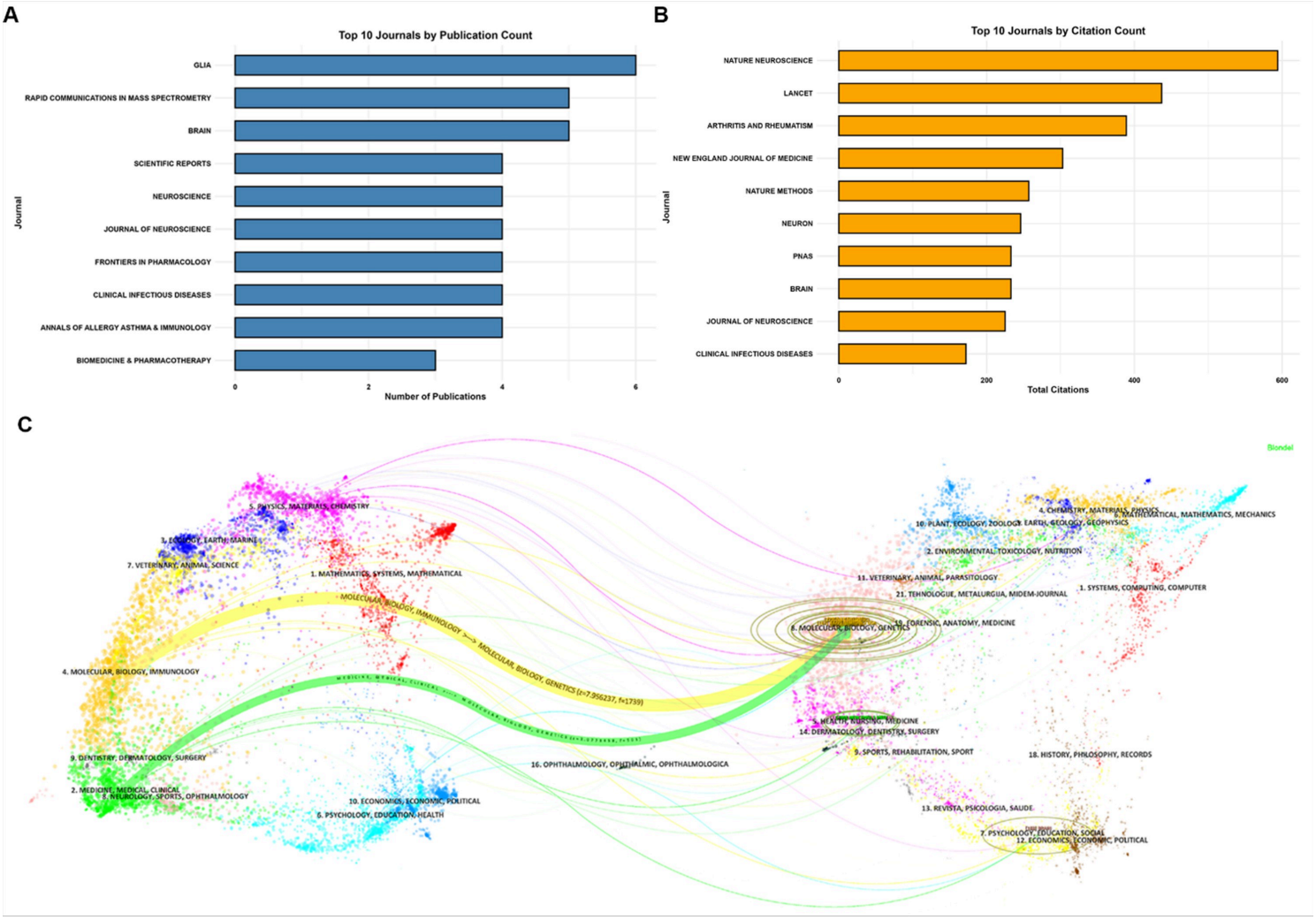


Figure 5

A The top 10 journals with the largest number of publications. **B** The top 10 journals ranked by total citations. C Dual-map overlay of journals generated by CiteSpace. The left side represents citing journals and the right side represents cited journals. Curved ribbons indicate citation direction and strength; central hub (6. Molecular Biology, Genetics) highlights a key interdisciplinary nexus. Colors denote subject categories (e.g., green: medicine; yellow: molecular biology).



Figure 6

Author productivity and local impact. A Authors' production over time. Each row represents an author, and each bubble indicates publications in a given year. Bubble size reflects the number of articles, while color intensity represents total citations per year (TC per Year). **B** Authors' local impact by H-index. Bubble size corresponds to the author's H-index within the dataset, highlighting the most influential contributors in this research field.

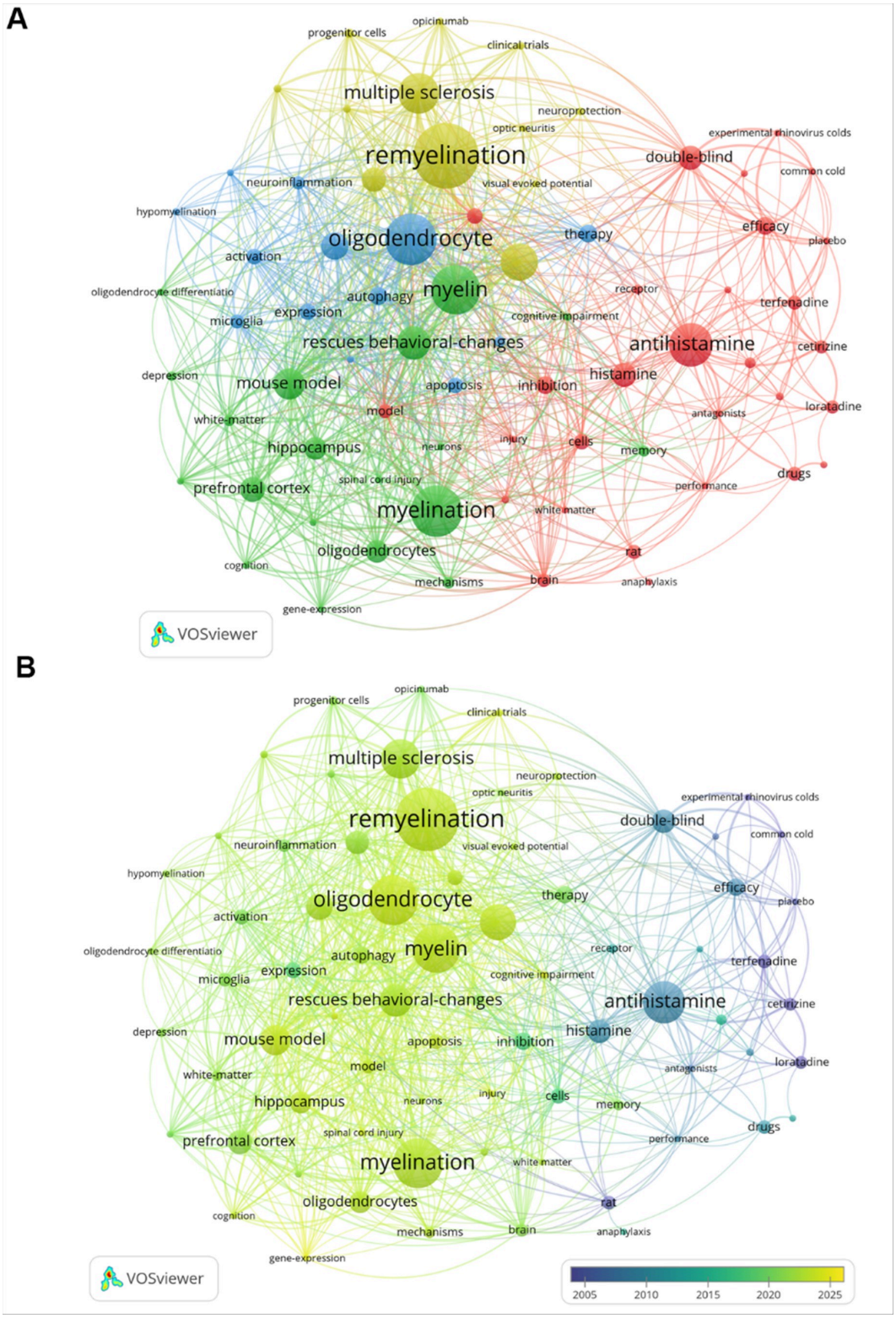


Figure 7

Keyword co-occurrence and temporal evolution analysis. A VOSviewer keyword co-occurrence network. Node size indicates keyword frequency, link thickness reflects co-occurrence strength, and colors represent thematic clusters. **B** Overlay visualization of keyword evolution over time. Node color indicates the average publication year, from earlier terms in blue to recent terms in yellow.

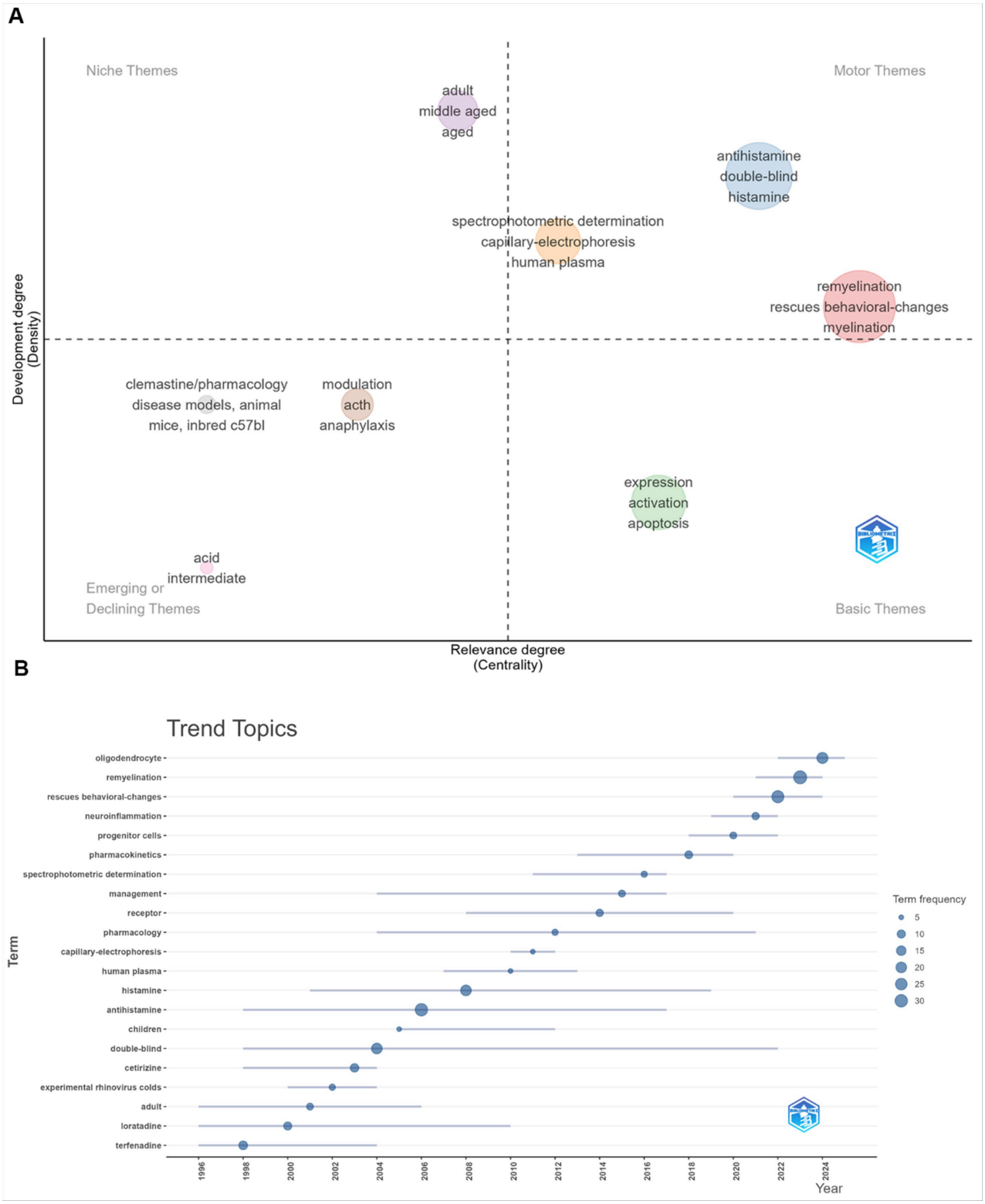
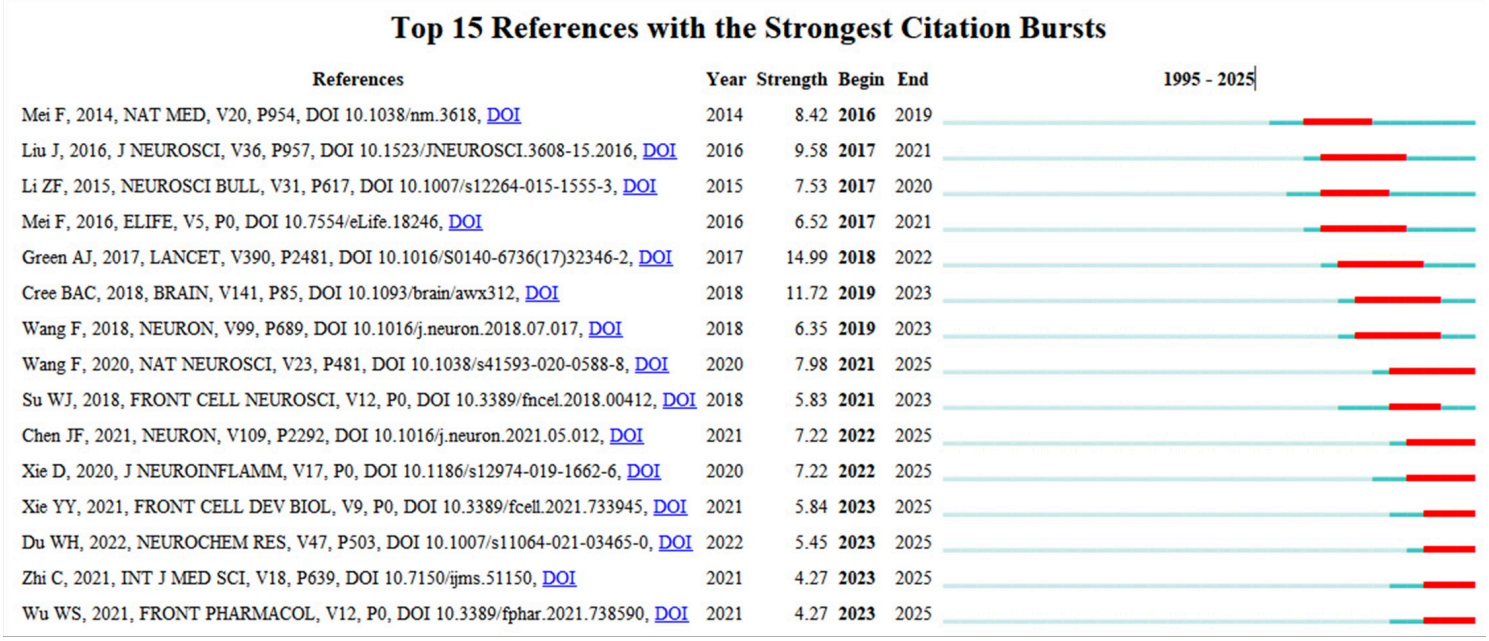


Figure 8

Thematic structure and trend topics in clemastine research. A The strategic diagram of keyword clusters classified into four quadrants based on centrality (relevance degree, x-axis) and density (development degree, y-axis). The Motor Themes (upper-right quadrant) features high-occurrence terms with strong centrality; occupy basic (lower-right) and motor (upper-right) quadrants indicate foundational and driving roles in the field; the niche themes (upper-left quadrant) are specialized with high density but

low centrality. **B** Trend topic analysis showing the temporal distribution of high-frequency keywords. Bubble size represents term frequency, and horizontal lines indicate the active period of each term.



Top 15 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	1995 - 2025
Mei F, 2014, NAT MED, V20, P954, DOI 10.1038/nm.3618, DOI	2014	8.42	**2016**	2019	
Liu J, 2016, J NEUROSCI, V36, P957, DOI 10.1523/JNEUROSCI.3608-15.2016, DOI	2016	9.58	**2017**	2021	
Li ZF, 2015, NEUROSCI BULL, V31, P617, DOI 10.1007/s12264-015-1555-3, DOI	2015	7.53	**2017**	2020	
Mei F, 2016, ELIFE, V5, P0, DOI 10.7554/eLife.18246, DOI	2016	6.52	**2017**	2021	
Green AJ, 2017, LANCET, V390, P2481, DOI 10.1016/S0140-6736(17)32346-2, DOI	2017	14.99	**2018**	2022	
Cree BAC, 2018, BRAIN, V141, P85, DOI 10.1093/brain/awx312, DOI	2018	11.72	**2019**	2023	
Wang F, 2018, NEURON, V99, P689, DOI 10.1016/j.neuron.2018.07.017, DOI	2018	6.35	**2019**	2023	
Wang F, 2020, NAT NEUROSCI, V23, P481, DOI 10.1038/s41593-020-0588-8, DOI	2020	7.98	**2021**	2025	
Su WJ, 2018, FRONT CELL NEUROSCI, V12, P0, DOI 10.3389/fncel.2018.00412, DOI	2018	5.83	**2021**	2023	
Chen JF, 2021, NEURON, V109, P2292, DOI 10.1016/j.neuron.2021.05.012, DOI	2021	7.22	**2022**	2025	
Xie D, 2020, J NEUROINFLAMM, V17, P0, DOI 10.1186/s12974-019-1662-6, DOI	2020	7.22	**2022**	2025	
Xie YY, 2021, FRONT CELL DEV BIOL, V9, P0, DOI 10.3389/fcell.2021.733945, DOI	2021	5.84	**2023**	2025	
Du WH, 2022, NEUROCHEM RES, V47, P503, DOI 10.1007/s11064-021-03465-0, DOI	2022	5.45	**2023**	2025	
Zhi C, 2021, INT J MED SCI, V18, P639, DOI 10.7150/ijms.51150, DOI	2021	4.27	**2023**	2025	
Wu WS, 2021, FRONT PHARMACOL, V12, P0, DOI 10.3389/fphar.2021.738590, DOI	2021	4.27	**2023**	2025	

Figure 9

References with the strongest citation bursts in clemastine research. Burst status of the top 15 references with the strongest citation bursts from 1995 to 2025. Red bars indicate periods of intense citation activity, reflecting influential studies that shaped the field.

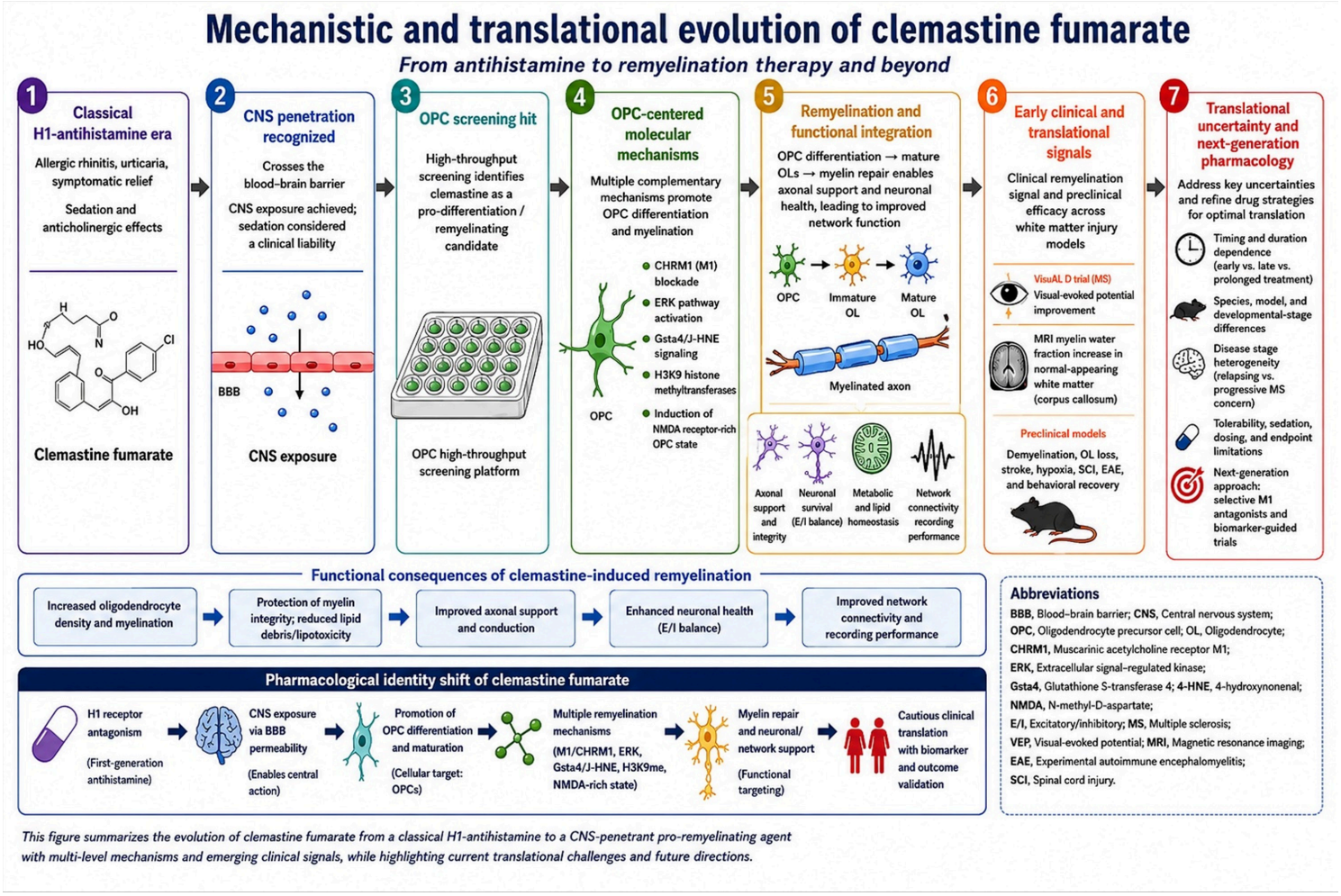


Figure 10

Mechanistic and translational evolution of clemastine fumarate. This schematic summarizes the pharmacological repositioning of clemastine fumarate from a classical first-generation H1-antihistamine to a CNS-penetrant pro-remyelinating candidate. The image was generated using ChatGPT's image-generation tool based on prompts and scientific instructions provided by the authors, followed by author review and conceptual refinement.