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A Bibliometric Analysis of Acyclovir's Nobel Legacy in Treating Billions of Humans and Animals Infected with Herpes Viruses

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ABSTRACT

Acyclovir, a cornerstone antiviral agent since the 1980s, has played a vital role in treating herpes virus infections. Its widespread use and ongoing relevance have generated substantial research interest across multiple disciplines and regions. This study aimed to analyze global trends, thematic evolution, and collaborative networks in acyclovir research from 1979 to April 2025, offering a comprehensive overview of scientific output, influential contributors, and emerging research directions. A bibliometric analysis was conducted using the Scopus database, retrieving 2,949 English-language publications containing "acyclovir". Analytical tools including VOSviewer and Bibliometrix, were employed to assess publication trends, author and institutional impact, keyword evolution, and international collaboration networks. The highest annual output occurred in 1982 (118 publications), with consistent activity maintained between 2020–2024. The United States led in publication output (259 articles), followed by India (201). Key institutions included the University of Washington and Rega Institute. Thematic analysis revealed an evolution from early mechanistic studies to current focus areas such as nanotechnology and drug delivery. Thematic analysis of acyclovir research revealed a clear evolution across distinct keyword clusters, beginning with foundational pharmacological and virological studies. Over time, the focus expanded to encompass clinical applications, followed by a recent shift toward pharmaceutical innovation and advanced drug delivery strategies. Acyclovir research exhibits a dynamic and collaborative global landscape. While the USA remains dominant, the emergence of new contributors from the Global South signals a shift toward greater inclusivity. Evolving themes emphasize technological innovation and resistance management, offering direction for future investigations and policy-making to enhance access and therapeutic efficacy.

Keywords: Acyclovir, Bibliometric analysis, Antiviral therapy, Herpes simplex virus, Varicella-zoster virus, Research trends.

INTRODUCTION

Acyclovir, a synthetic nucleoside analog introduced in the 1980s, has fundamentally transformed antiviral therapy, particularly for infections caused by herpes simplex virus (HSV) and varicella-zoster virus (VZV) (Pisitpayat et al. 2021; Taylor and Gerriets 2025). By selectively inhibiting viral DNA polymerase, acyclovir disrupts viral replication, offering effective treatment for conditions such as genital herpes, herpes encephalitis, shingles, and chickenpox (Kłysik et al. 2020). Acyclovir`s impact is profound, with HSV affecting over 3.7 billion individuals globally, according to the World Health Organization (Oleszko et al. 2025) and VZV posing significant risks, particularly in immunocompromised populations (Oleszko et al. 2025). The drug's development, which earned Gertrude B. Elion and George H. Hitchings a Nobel Prize in Physiology or Medicine in 1988, marked a

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milestone in antiviral research, establishing acyclovir as a cornerstone of clinical practice (Wei et al. 2021; Núñez Valdés et al. 2022).

Since its introduction, acyclovir has been celebrated for its efficacy, safety, and affordability, making it a first-line therapy in diverse clinical settings (O'Brien and Campoli-Richards 1989). It is administered orally, intravenously, or topically, providing flexibility for managing acute infections and preventing recurrences in chronic conditions (Wei et al. 2021; Mirzaei et al. 2024). Its role extends beyond HSV and VZV, with research investigating its potential against other viruses, such as the Epstein-Barr virus (Majewska and Mlynarczyk-Bonikowska 2022; Thomas et al. 2024). However, challenges persist, including the emergence of acyclovir-resistant viral strains (Schalkwijk et al. 2022) and the need for improved delivery systems to enhance bioavailability (Hassan et al. 2016). These issues have spurred extensive research into acyclovir's pharmacokinetics, resistance mechanisms, and novel formulations, such as prodrugs like valacyclovir (Warner et al. 2025).

The global burden of herpesviruses underscores the importance of sustained research into acyclovir. Genital herpes, caused by HSV-2, contributes to significant morbidity and increases HIV transmission risk (Looker et al. 2017), while VZV-related shingles can lead to debilitating postherpetic neuralgia in older adults (Johnson and McElhaney 2009). Additionally, acyclovir's role in pediatric and neonatal populations, where HSV infections can be life-threatening, highlights its broad clinical relevance (Harris and Holmes 2017). In addition, acyclovir showed important applications in veterinary medicine, through treatment of equine herpesvirus 3 (Toishi et al. 2020), canine papillomatosis (Uwagie-Ero et al. 2017) and feline herpesvirus 1 (Ozkanlar et al. 2023).

This study aims to map the global landscape of acyclovir research by analyzing publication trends, thematic shifts and collaborative networks. Its objectives are: (1) to identify geographical patterns in research output, pinpointing leading contributors; (2) to examine the evolution of research themes, such as resistance and novel applications, through keyword and citation analysis; and (3) to assess collaborative networks among researchers, institutions and countries, highlighting opportunities for partnership.

MATERIALS AND METHODS

Study design

This study employed a bibliometric analysis approach to evaluate the global research of acyclovir from its initial development till April 2025. The bibliometric methodology was selected to quantitatively assess publication patterns, identify key contributors and institutional networks, evaluate citation impact, and analyze thematic evolution within the acyclovir research domain.

Data collection

The Scopus database was utilized as the primary data source due to its comprehensive indexing of peer-reviewed literature in biomedical and pharmaceutical sciences. The search strategy employed "Acyclovir" as the primary search term and was conducted in Scopus on April 12, 2025. It covered literature published from 1979 through April 2025. The search was restricted to the title field and limited to articles (DOCTYPE, "ar"), excluding records with undefined author names or affiliations (EXCLUDE (PREFNAMEAUID, "Undefined") and EXCLUDE (AFFILCOUNTRY, "Undefined")), and included only publications in English. The exact search query used was: TITLE (acyclovir) and (LIMIT-TO (DOCTYPE, "ar")) and (EXCLUDE (PREFNAMEAUID, "Undefined")) and (EXCLUDE (AFFILCOUNTRY, "Undefined")) and (LIMIT-TO (LANGUAGE, "English")).

Inclusion criteria

Documents were included based on English-language publications indexed in Scopus between 1979 and April 12, 2025, containing "Acyclovir" as a keyword or in the title/abstract. All document types were included to ensure comprehensive representation of the research landscape.

Data analysis

Chronological analysis identified temporal patterns of scientific production. Source analysis determined the primary publication venues for acyclovir research. Author-level metrics included h-index, g-index, m-index, and total citation counts to identify influential researchers. Institutional productivity was assessed through affiliation data, while geographical distribution distinguished between total scientific production and corresponding authorship. Collaboration networks were mapped through co-authorship analysis. Citation metrics identified influential works. Research themes were analyzed through keyword frequency, temporal trends, co-occurrence networks, and thematic mapping.

Visualization of data

Visualization techniques included line graphs for chronological trends, bar charts for source distribution and institutional productivity, bubble charts for author impact, world maps for geographical distribution, network visualizations for collaboration patterns, strategic diagrams for theme categorization, co-occurrence networks for keyword relationships, three-field plots for connecting countries, institutions, and research topics, and timeline visualizations for keyword evolution.

Software and tools

The analysis was facilitated by multiple software tools: Microsoft Excel was utilized for data organization and preliminary analysis; VOS viewer enabled the visualization of bibliometric networks, such as author collaborations and keyword co-occurrences (van Eck and Waltman 2010) and Bibliometrix, an R package, offered a deeper bibliometric evaluation, including citation metrics and journal impact assessments (Darvish 2020).

RESULTS

Our study utilizes the Scopus database to analyze English-language sources from 1979 to April 12, 2025. It focuses on the keyword "Acyclovir," with data extracted on April 12, 2025. A total of 2,949 records were identified, screened, and included for bibliometric analysis, with no records removed (Fig. 1).

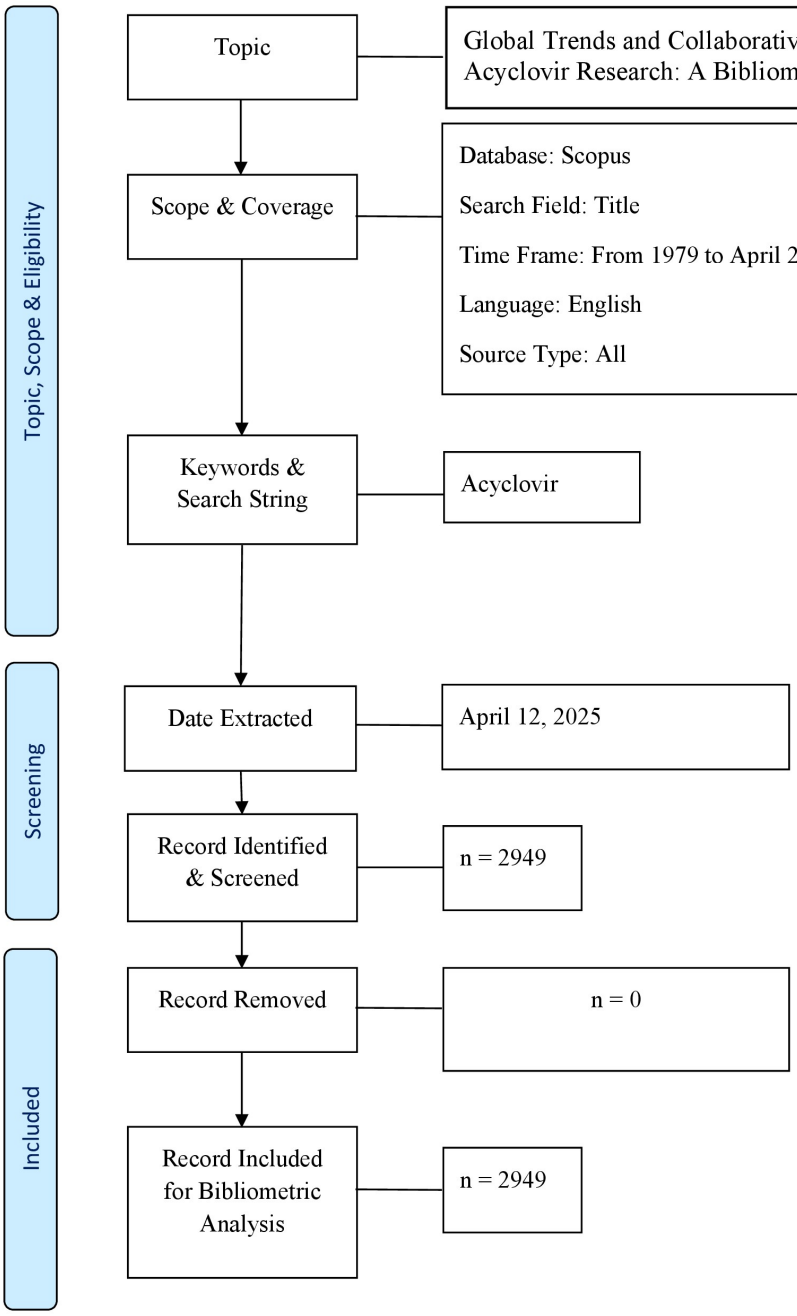

Fig. 1: Screening details of our study.

Chronological scientific production trends

The early years (1979-1981) witnessed modest publication numbers (4, 22, and 40 articles respectively), followed by a remarkable surge in 1982 with 118 publications—the highest annual output recorded during the entire study period. Throughout the 1980s and early 1990s, publication rates remained high, reflecting the continued clinical exploration of this breakthrough antiviral. The mid-2000s showed a temporary decline (with only 37-39 publications in 2004-2006), but research interest rebounded by the late 2000s. Recent years (2020-2024) have a maintained publication rates around 61-77 papers annually (Fig. 2).

Leading journals and publication sources

Our analysis reveals that "Antimicrobial Agents and Chemotherapy" leads with 110 publications, establishing itself as the primary platform for acyclovir research. The "Journal of Infectious Diseases" (87 publications) and "The American Journal of Medicine" (82 publications). "Antiviral Research" has contributed 81 publications, emphasizing the drug's importance in broader antiviral therapy discussions. Notably, the representation of prestigious medical journals like "New England Journal of Medicine" (24 publications) and "Annals of Internal Medicine" (23 publications) underscores acyclovir's impact on general medical practice beyond specialized fields. The distribution across pharmaceutical journals ("International Journal of Pharmaceutics" with 49 publications) reflects the multidisciplinary nature of acyclovir research, spanning drug formulations, clinical applications, and infectious disease management (Fig. 3).

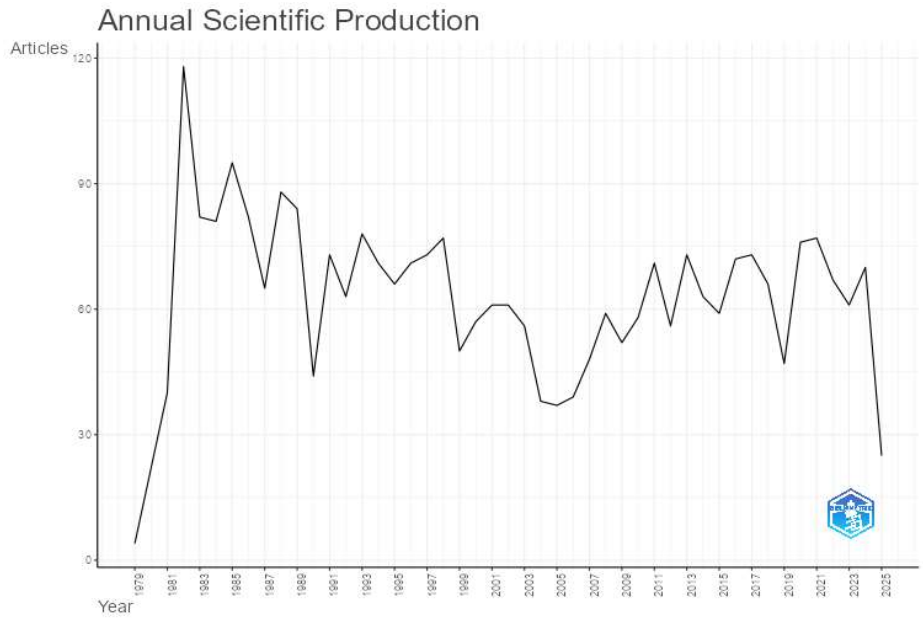

Fig. 2: Annual Scientific Production.

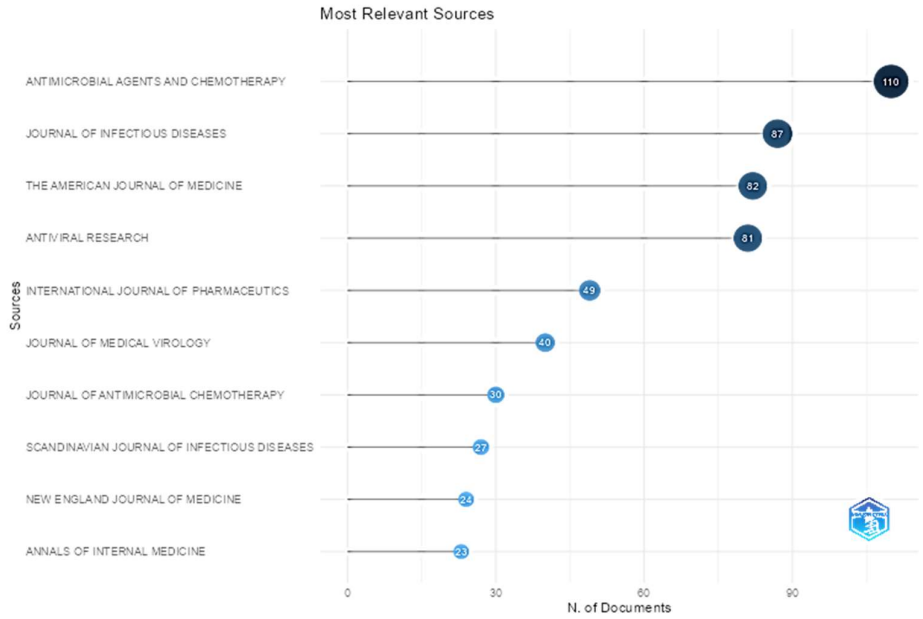

Fig. 3: Most relevant sources from which data is collected.

Geographical distribution of research

The geographical distribution analysis shows that the United States dominates acyclovir research (Fig. 4). India ranks second, followed by China and Japan. The data of countries of the corresponding authors reveals that the USA leads in publication output with 259 articles (8.78%), followed by India (6.82%), China (3.73%) and Japan (2.81%) (Fig. 5). In the first four countries—USA, India, China, and Japan—there is a contrast between domestic and international research collaboration patterns as reflected by their SCP and MCP values. The USA leads with SCP (83.78%) and MCP (16.22%). While India exhibits high levels of domestic research activity, with 92.54% of their articles being SCP, countries like Canada and Italy demonstrate strong international collaboration, reflected by their MCP rates of 25.64% and 25%, respectively. France and Brazil also show moderate collaboration levels (around 15–17%).

International collaboration networks in acyclovir research

The data reveals significant international collaboration networks that have shaped acyclovir research globally, with the United States functioning as the central hub in this research ecosystem, maintaining strong collaborative ties with numerous countries. The strongest USA collaboration link is with the United Kingdom (28 collaborative papers), followed by Canada (24 papers), and Belgium (12 papers). The United Kingdom similarly demonstrates extensive collaborative reach, particularly with European partners like France (15 papers) and Belgium (10 papers). Meanwhile, emerging patterns show India's growing international presence, with strong ties to Saudi Arabia (11 collaborative papers) and South Africa (4 papers). Several regional collaboration clusters are evident, such as between Egypt and Saudi Arabia (8 papers) and between Pakistan and Saudi Arabia (8 papers) (Fig. 6).

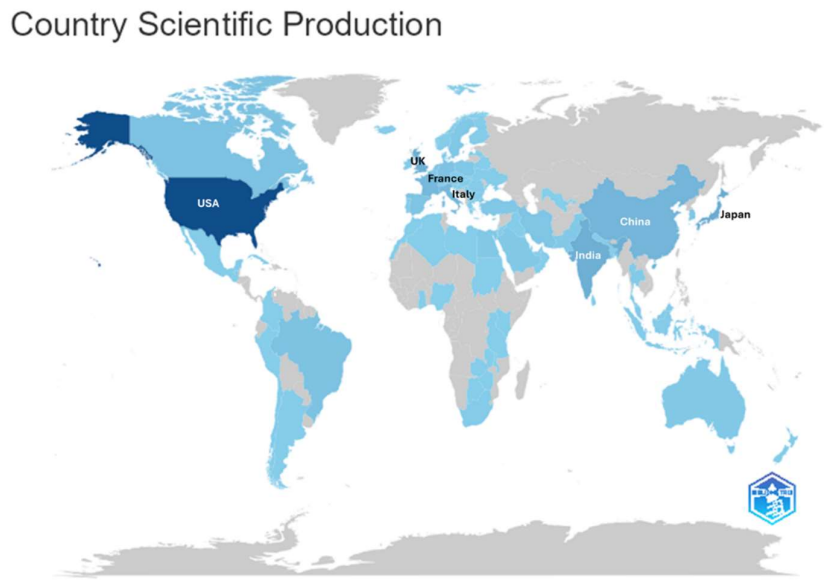

Fig. 4: Country scientific production labelled with the highest producing countries.

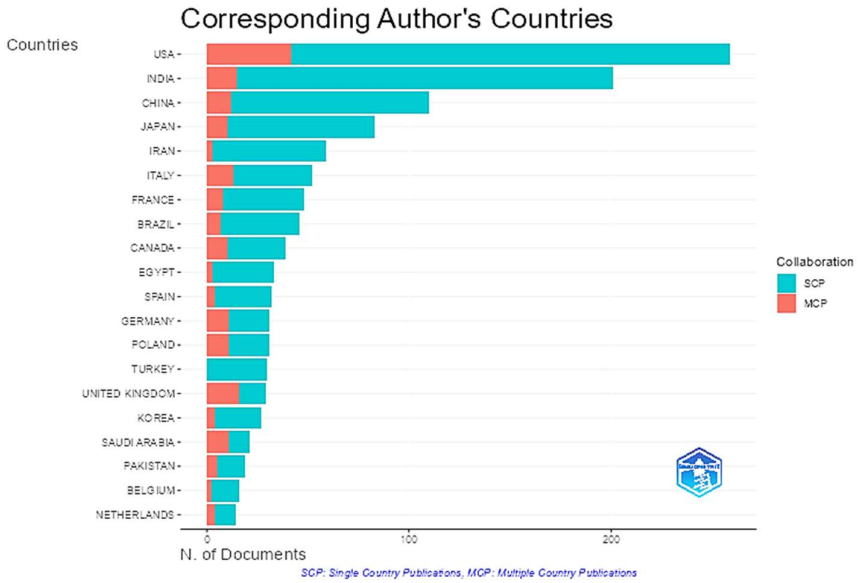

Fig. 5: Corresponding Authors Countries.

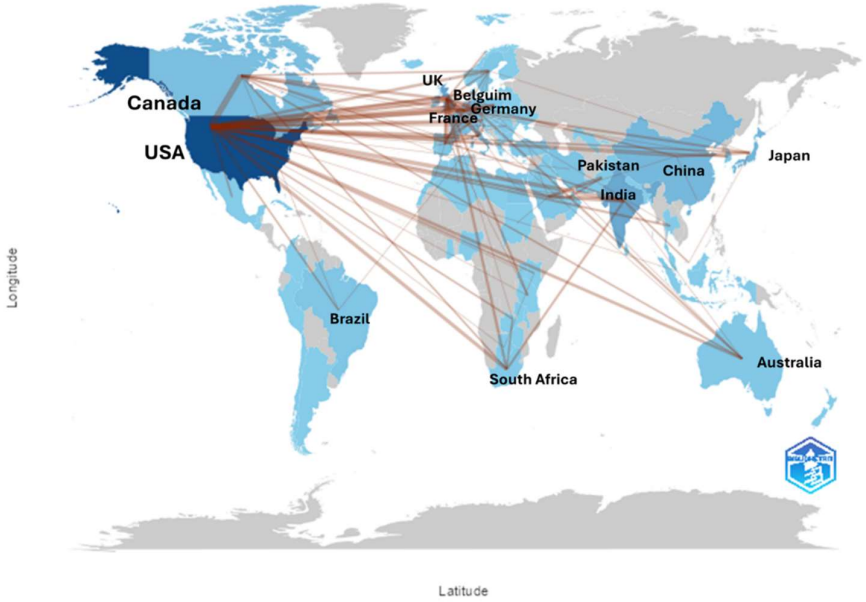

Fig. 6: Collaboration World Map.

Citation impact and research influence

Citation analysis reveals fascinating patterns regarding the most influential works in acyclovir research. The highest cited paper is Whitley RJ's 1986 publication in the New England Journal of Medicine, encompassing 742 citations (Whitley et al. 1986). Interestingly, more recent papers achieve higher annual citation rates, such as Sullivan FM's 2007 publication (30.79 citations per year) (Sullivan et al. 2007) and Celum C's 2010 work (28.31 citations per year) (Celum et al. 2010), suggesting accelerating interest in newer applications of acyclovir (Table 1).

Evolution of research keywords and conceptual framework

The keyword analysis confirms "acyclovir" as the dominant keyword with 1,093 occurrences, followed by "herpes simplex virus" (125 occurrences), reflecting the drug's primary indication (Fig. 7). The chronological analysis of keywords reveals fascinating research trajectory shifts. Early research (1980s-1990s) focused on fundamental aspects like "chemotherapy," "ELISA," and "vidarabine," establishing basic understanding of acyclovir's mechanisms and comparison with existing antivirals. By the mid-1990s, clinical application keywords emerged strongly, including "AIDS," "renal transplantation," and "varicella," reflecting acyclovir's expanding therapeutic applications. The 2000s showed an increased emphasis on specific viruses and conditions, with "herpes simplex virus type 1," "cytomegalovirus," and "genital herpes" gaining prominence. Most recent research (2015-2025) has shifted dramatically toward pharmaceutical development aspects, with keywords like "nanoparticles," "drug delivery," "controlled release," and "molecular docking" dominating the landscape (Fig. 8).

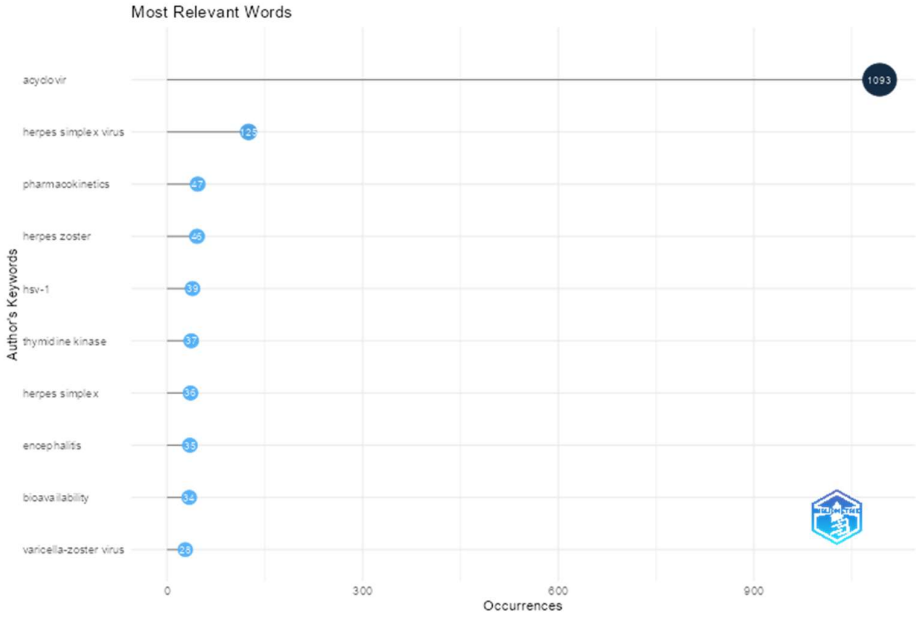

Fig. 7: Most frequent keywords.

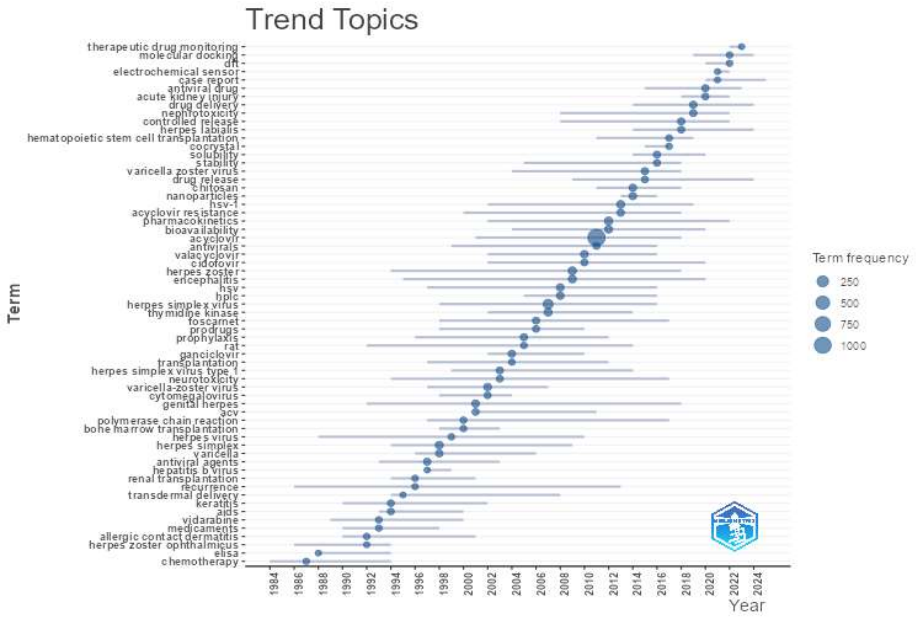

Fig. 8: Trend topics by years.

Visual representation of research patterns and collaborations

The collaborative network in acyclovir research links countries and institutions with key research topics, showcasing the USA and Japan as major contributors. Institutions like the University of Washington and Jichi Medical University focus on topics such as "acyclovir," "herpes simplex virus," and "pharmacokinetics," emphasizing antiviral applications. Other nations, including the Belguim and Canada, exhibit significant ties with the Rega Institute and University of Toronto, reflecting a global effort (Fig. 9).

Key institutions like the University of Washington and Rega Institute for Medical Research connect to prominent sources such as Antiviral Research and Antimicrobial Agents and Chemotherapy, linking to core areas like "acyclovir" and "pharmacokinetics." Other institutions, including the University of Alabama and King Saud University, contribute to diverse topics like "drug delivery" and "nanoparticles," underscoring the interdisciplinary collaboration across global academic and clinical platforms (Fig. 10).

Table 1: The most cited papers

Paper	DOI	Total Citations	TC per Year	Normalized TC
WHITLEY RJ, 1986, NEW ENGL J MED	10.1056/NEJM198601163140303	742	18.55	20.93016856
BEUTNER KR, 1995, ANTIMICROB AGENTS CHEMOTHER	10.1128/AAC.39.7.1546	596	19.22580645	17.01384083
SULLIVAN FM, 2007, NEW ENGL J MED	10.1056/NEJMoa072006	585	30.78947368	12.85714286
KIMBERLIN DW, 2001, PEDIATRICS-a	10.1542/peds.108.2.230	490	19.6	9.796787938
SKÖLDENBERG B, 1984, LANCET	10.1016/S0140-6736(84)92623-0	487	11.5952381	10.15105507
BALFOUR HH, 1989, NEW ENGL J MED	10.1056/NEJM198905253202105	461	12.45945946	10.51425468
KIMBERLIN DW, 2001, PEDIATRICS	10.1542/peds.108.2.223	456	18.24	9.117010816
CELUM C, 2010, NEW ENGL J MED	10.1056/NEJMoa0904849	453	28.3125	13.48767967
SARAL R, 1981, NEW ENGL J MED	10.1056/NEJM198107093050202	450	10	8.995502249
WOOD MJ, 1994, NEW ENGL J MED	10.1056/NEJM199403313301304	417	13.03125	8.34470124

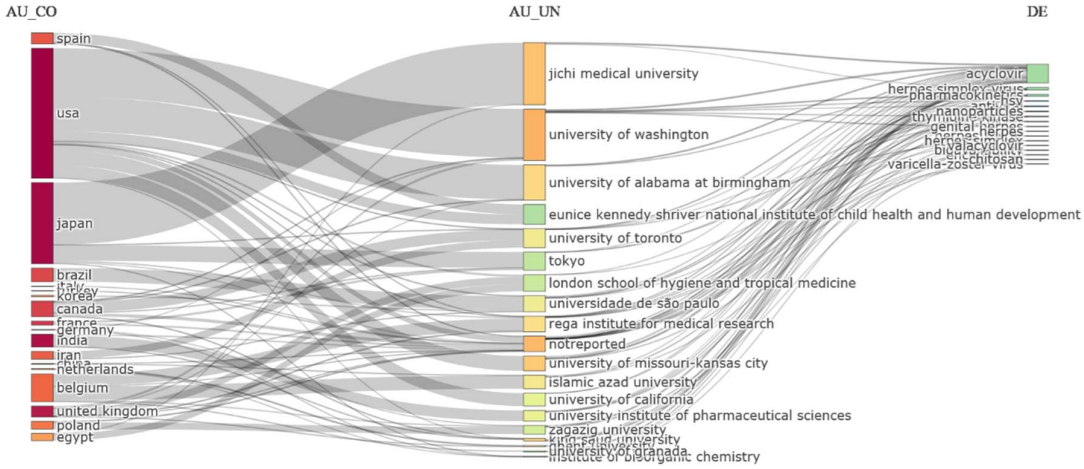

Fig. 9: Relationship between countries (AU_CO) and institutions (AU_UN) with key research topics (DE).

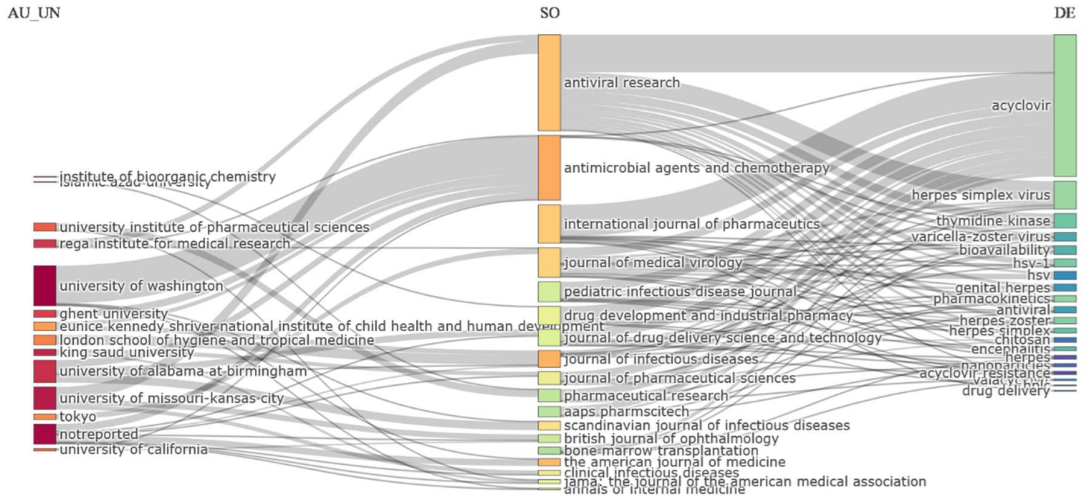

Fig. 10: Relationship among institutions (AU_UN), sources (SO), and research topics (DE).

Research themes are categorized based on development density and relevance, with "acyclovir," "pharmacokinetics," and "bioavailability" as highly relevant and developed areas. "Herpes simplex virus," "HSV-1," and "thymidine kinase" form foundational topics, while "herpes zoster," "encephalitis," and "varicella-zoster virus" show high development but lower relevance. "Nanoparticles" suggests a shifting focus, and "antiviral drug" remains a less central niche theme, reflecting the evolving research landscape driving acyclovir studies (Fig. 11).

Visualization of keyword co-occurrence in acyclovir research

The diagram (Fig. 12), created using VOSviewer, presents a co-occurrence network of keywords in acyclovir research, grouped into five color-coded clusters. The central yellow cluster, dominated by "acyclovir," connects to pharmacological aspects like "drug comparison," "antiviral therapy," "chemotherapy," and "oral drug administration." The red cluster focuses on pharmaceutical aspects, including "drug delivery system," "drug formulation," and "nanoparticles." The blue cluster emphasizes experimental virology studies, with "herpes simplex virus," "HSV-1," "drug resistance," "Vero cells," and "thymidine kinase" as key terms. The green cluster highlights clinical outcomes and epidemiological aspects like "encephalitis," "chickenpox," "treatment outcome," "retrospective study," "prevention" and "adverse drug reaction." This network illustrates the multidisciplinary scope of acyclovir research.

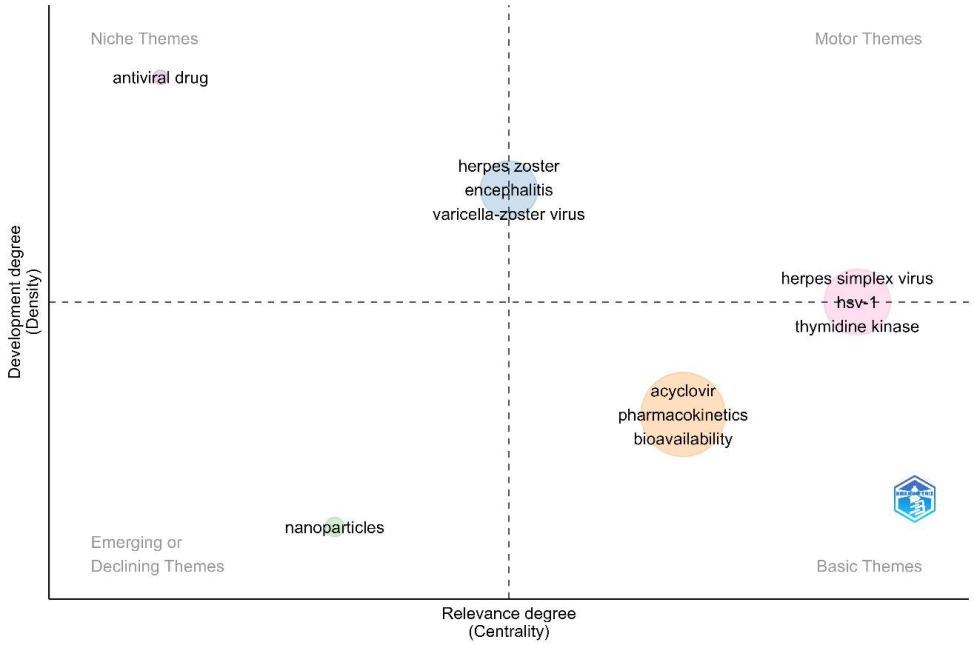

Fig. 11: Categorizing acyclovir research themes based on development density and relevance degree.

Fig. 12: Overlay visualization of keyword co-occurrence in acyclovir research.

DISCUSSION

Our analysis of 2,949 Scopus-indexed publications reveals a dynamic research landscape. The peak of 118 publications in 1982 reflects the research steering actions following acyclovir's introduction as a groundbreaking therapy for HSV and VZV. Sustained output through the 1980s–1990s (70–90 papers annually) underscores its role in managing conditions affecting over 3.7 billion people globally (Oleszko et al. 2025). A mid-2000s dip (37–39 papers in 2005–2006) likely arised from market saturation of first-generation antivirals, while the resurgence and steady 60–76 papers annually from 2020–2024 highlight ongoing challenges like resistance and innovative delivery systems (Hassan et al. 2016; Schalkwijk et al. 2022). The United States leads with 259 corresponding author articles, driven by strong funding and institutions like the University of Washington (102 articles). India's rise (201 articles) reflects its generic drug industry and high disease burden (Saksena et al. 2024).

Thematic shifts show early focus on mechanisms (1980s), clinical applications (1990s), and recent emphasis on nanoparticles and drug delivery (2015–2025). Collaboration networks center on the USA, with strong ties to the UK and Canada, while emerging hubs like India–Saudi Arabia signal growing Global South contributions. High-impact journals (Antimicrobial Agents and Chemotherapy, 110 papers) and citations (e.g., Whitley et al. 1986, 742 citations) affirm acyclovir's clinical significance. These trends are likely driven by global health needs, technological advancements, and collaborative research structures.

The evolution of acyclovir research aligns with Rogers' Diffusion of Innovation theory, which posits that innovations spread through stages of adoption, driven by key actors and networks (Rogers 2004). Acyclovir's rapid uptake in the 1980s, reflected in the 1982 publication peak, marks its early adoption by innovators like Corey L. and De Clercq E. Recent focus on nanotechnology suggests a mature phase, where late adopters refine the innovation (Hassan et al. 2016). Collaborative networks, particularly USA-led, act as diffusion channels, accelerating global research.

Our findings clearly reflect how the field is adapting to global health demands. The USA's dominance reflects its research infrastructure, but India's ascent signals a shift toward inclusivity, vital for addressing access disparities in high-burden regions (Johnston et al. 2024). Thematic shifts toward nanotechnology and resistance strategies indicate a forward-looking field adapting to challenges like the resistance rate in immunocompromised patients (Majewska and Mlynarczyk-Bonikowska 2022; Schalkwijk et al. 2022). Collaboration networks suggest a strong global community, yet gaps in low-resource regions highlight untapped potential. For researchers, these insights identify high-impact areas (e.g., drug delivery) and collaborators (e.g., University of Washington). Clinicians benefit from understanding resistance patterns and novel formulations, enhancing patient care. Policymakers can prioritize funding for emerging hubs to ensure equitable access, particularly in the Global South, where acyclovir's affordability is critical.

This study's strengths lie in its comprehensive scope, analyzing 2,949 publications over 46 years. The use of Scopus ensures high-quality data, and our multi-faceted approach—covering chronology, geography, themes, and collaborations—provides a comprehensive view. However, limitations exist. Reliance on Scopus may exclude non-English or regional journals, potentially underrepresenting contributions from non-Western countries. The English-language filter and article-only focus might miss reviews or non-English studies, limiting breadth.

This study reveals acyclovir's vibrant research landscape, driven by global collaboration and innovation. We recommend promoting partnerships with emerging hubs like India and Saudi Arabia to enhance access and innovation. Funding should prioritize nanotechnology and resistance research to address clinical challenges. Journals should encourage publications from underrepresented regions to diversify the field.

Conclusion

This bibliometric analysis comprehensively maps the global evolution of acyclovir research from 1979 to April 2025, highlighting key contributors, thematic shifts, and collaborative networks. Thematic progression from early mechanistic studies to recent innovations in drug delivery and nanotechnology reflects the field's responsiveness to clinical and technological challenges. High-impact publications, robust institutional outputs, and expanding global partnerships affirm acyclovir's enduring relevance in antiviral therapy. Promoting inclusivity and supporting underrepresented regions will be essential for sustaining innovation and equitable access in future antiviral research.

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Data Availability: Data can be requested from the corresponding author upon reasonable request

Ethics Statement: "Not applicable".

Author's Contribution: Conceptualization (MA, SA, IA, YAA, MA, MM, AA, KB, MK); Data curation (MA); Formal analysis (SA, IA); Investigation (MA, MM, AA, KB, MK); Methodology (MA, SA, IA, YAA, MA, MM, AA, KB, MK); Project administration (IA); Resources (MK); Software (MK); Writing - original draft (MK); Writing - review and editing. (MA, SA, IA, YAA, MA, MM, AA, KB).

Generative AI Statement: The authors declare that no Gen AI/DeepSeek was used in the writing/creation of this

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