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Trends and transitions in ledipasvir studies: A bibliometric assessment of a groundbreaking hepatitis C virus treatment

Kauthar Alshalla[1], Mohammed Al-Rasheed[2], Maryam Mahmoud[3], Alaa Azhari[4], Mahmoud kandeel[5*]

[1,2,5]*Department of Biomedical Sciences, College of Veterinary Medicine, King Faisal University, 31982 Al-Ahsa, Saudi Arabia.*
[3]*Faculty of Medicine, Delta University for Science and Technology, Gamasa 11152, Egypt.*
[4]*Faculty of Medicine, Khartoum University, Khartoum 11111, Sudan.*

Corresponding author: Mahmoud kandeel (*Email: mkandeel@kfu.edu.sa*)

Abstract

This study aimed to conduct a comprehensive bibliometric analysis of global research on ledipasvir from 2014 to May 2025, focusing on trends in research output, citation impact, authorship patterns, and thematic evolution. A bibliometric analysis was performed using 419 scientific articles from 199 sources indexed in Scopus. Data were extracted based on publication year, authorship, citations, keywords, and institutional affiliations. Visualization tools such as VOSviewer and Bibliometrix were employed to analyze co-authorship networks, keyword co-occurrence, and thematic trends. Inclusion criteria prioritized peer-reviewed English articles with complete bibliographic metadata. The analysis revealed a peak in publication output in 2018 (92 articles), followed by a gradual decline. The United States, Egypt, and Japan emerged as leading contributors, with Gilead Sciences and academic institutions like Cairo University playing pivotal roles. High citation rates (average of 39.57 citations per document) underscored the drug's ongoing relevance. Keyword analysis highlighted a shift from early clinical and pharmacokinetic studies to topics such as adherence, liver transplantation, and COVID-19 implications. International collaboration was robust, with 21.48% of publications involving multi-country teams. Ledipasvir research has evolved significantly, reflecting its foundational role in HCV treatment. Despite declining publication numbers, the drug's scientific impact remains strong, driven by international collaboration and diverse thematic exploration. Future research should focus on comparative efficacy, long-term outcomes, and resistance mechanisms to further inform clinical practice.

Keywords: Bibliometric, HCV, Hepatitis C Virus, Ledipasvir, Treatment.

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1. Introduction

Ledipasvir is a direct-acting antiviral drug that is used in conjunction with other treatments, especially sofosbuvir, to treat chronic hepatitis C virus (HCV) [1]. It inhibits the non-structural protein 5A (NS5A) [2, 3], which is required for viral RNA replication and HCV virion assembly [4]. The particular mechanism of action is unknown, but it has been proposed that it can prevent NS5A hyperphosphorylation [5]. The latter is required to generate viral protein [6].

Ledipasvir was effective against HCV genotypes 1a [7], 1b 4a [8], and 5a, but less so against genotypes 2a and 3a [9, 10],, which have a strong barrier to drug resistance [11, 12]. Furthermore, treatment with Ledipasvir is associated with low adverse effects [13, 14], which together with its reduced major side effects and short length of medication [15].

The present study aims to evaluate global research trends on ledipasvir, a direct-acting antiviral used for the treatment of chronic hepatitis C virus (HCV) infection. This is achieved through the identification of significant scientific advancements, emerging concerns, and collaboration networks in the field, which are explored by analyzing publication patterns, keyword co-occurrence, topic evolution, as well as contributions from countries, institutions, and journals. The current analysis also sheds light on how ledipasvir research has evolved over time, identifying areas for further investigation, principally regarding its actual applications with a focus on patient treatment outcomes.

2. Method

2.1. Study Design

This study provides a bibliometric analysis that evaluates global research on ledipasvir from 2014 to 2025. We conducted scientific research on publication counts, annual growth rates, citation metrics, co-authorship patterns, keyword co-occurrences, trend analyses, theme maps, and co-authorship networks as previously described [16].

2.2. Data Collection

Data for this bibliometric analysis were gathered from indexed scientific publications from 2014 to 2025. The search query included (((TITLE(Ledipasvir))) and (Exclude (SRCTYPE, "Undefined")) and (Exclude (Affil country,"Undefined")) and (Exclude (PREFNAMEAUID, "Undefined")) and (Exclude (SUBJAREA,"Undefined")) and (LIMIT-TO (DOCTYPE, "ar")) and (LIMIT-TO (LANGUAGE, "English"))). The bibliographic metadata were extracted based on publication year, source title, authorship, keywords, citations, document type, institutional affiliations, international collaboration, author impact (H-index, m-index), and keyword trends.

2.3. Inclusion Criteria

Articles were included if they contained the following: 1) The articles primarily discussed ledipasvir. 2) were primarily peer-reviewed Scopus-indexed articles. 3) provided complete bibliographic information. 4) Publications should be in English. On the other hand, the exclusion criteria included non-research publications such as editorials or letters, articles published in languages other than English, and any documents lacking essential metadata, including authorship details, institutional affiliations, or country of origin, which were eliminated.

2.4. Data Analysis

The obtained bibliographic data were examined using bibliometric approaches to estimate research trends, productivity, collaboration patterns, and the scientific impact of ledipasvir from 2014 to 2025. Descriptive statistics included annual publishing output, citation counts, and average citations per document. Authorship metrics included the number of authors, co-authorship per document, and h-index. We studied collaboration patterns using co-authorship networks, focusing on single-country publications (SCP) versus multi-country publications (MCP). Furthermore, we identified core journals that publish ledipasvir research and assessed their respective contributions to the field.

2.5. Visualization of Data

The trends were portrayed by time-series graphs and geographic distributions using maps with collaboration network overlays. The thematic study used keyword co-occurrence networks, with node size representing term frequency and edge thickness indicating co-occurrence strength.

2.6. Software and Tools

The bibliometric investigation was carried out with sophisticated software tools intended for scientific mapping and data visualization. Microsoft Excel was used for organizing the data and conducting initial analyses; VOSviewer helped visualize bibliometric networks such as author collaborations and keyword co-occurrences [17], and Bibliometrix, an R package, provided a more in-depth bibliometric analysis, including citation metrics and journal impact evaluations [18].

3. Results

The present bibliometric results showed significant trends in ledipasvir research from 2014 to 2025, with 419 documents published in 199 sources and an annual growth rate of -13.07%. Despite this, the documents are mostly mature, with an average age of 6.75 years, and possess significant influence, as indicated by an average of 39.57 citations per document and a high level of collaboration of 2,864 co-authors per paper and 21.48% international co-authorship. Additionally, the extensiveness of topics is reflected in over 3,021 Keywords Plus entries and nearly 621 author keywords. Additional details are shown in Table 1.

Table 1.
Main information of the present search results.

Description	Results
Main information about the data	
Timespan	2014:2025
Sources	199
Documents	419
Annual Growth Rate %	-13.07
Document Average Age	6.75
Average citations per doc	39.57
References	9580
Document contents	
Keywords Plus (ID)	3021
Author's Keywords (DE)	621
Authors	
Authors	2864
Authors of single-authored docs	6
Authors collaboration	
Single-authored docs	6
Co-Authors per Doc	9.75
International co-authorships %	21.48
Document types	
Article	419

3.1. Annual Scientific Production

The annual production of ledipasvir-related articles increased from a modest 14 in 2014 to a peak of 92 in 2018. The first years (2014-2015) saw consistent but limited output, with production remaining below 45 articles per year. Most notably, a considerable acceleration occurred after 2015, with article production increasing drastically to 25 (2015), 57 (2016), 76 (2017), and 92 (2018). After 2018, a rapid fall occurred, which continued at a slower but consistent rate until it reached 43 by 2019. From 2020 to 2021, production plateaued at roughly 33-34 items before falling further in 2022 to 2023 and continuing to decline until 2024. By 2024, scientific production dropped to fewer than 7 publications, the lowest level since 2014, indicating reduced research effort (Figure 1).

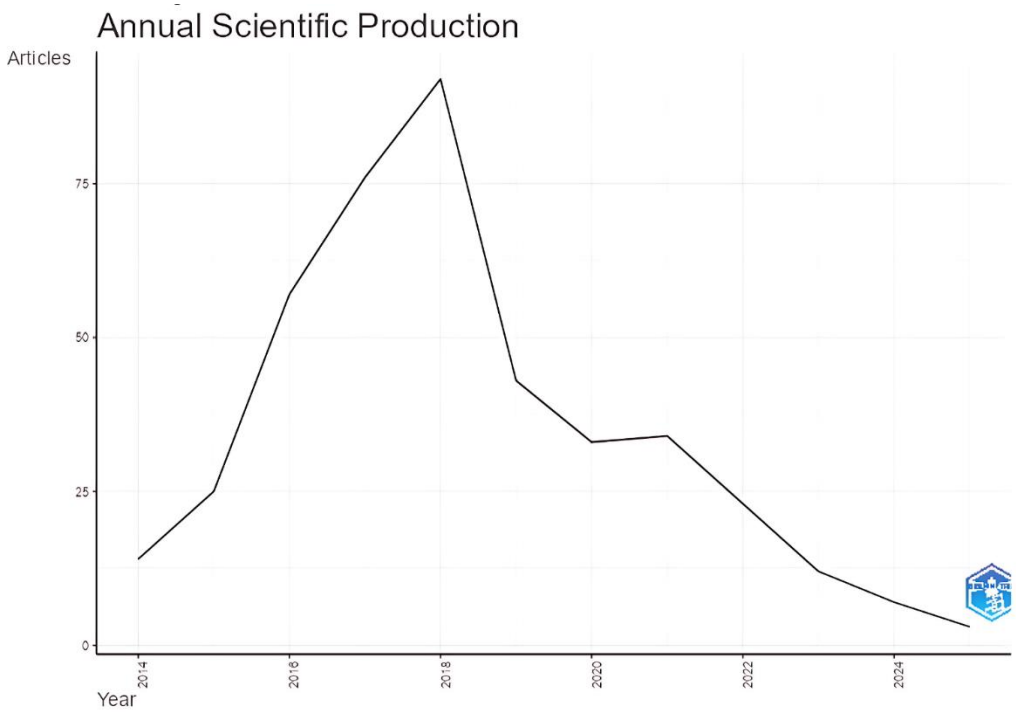

Figure 1.
Annual Scientific Production.

3.2. Publication Sources and Journal Impact

The academic publications publishing ledipasvir-related research revealed that the Journal of Viral Hepatitis and Hepatology were the most prominent sources, with 19 and 18 papers, respectively. These journals, together with Clinical

Infectious Diseases (11 papers) and Alimentary Pharmacology & Therapeutics (10 articles), emphasize the clinical and therapeutic aspects of ledipasvir research, particularly in hepatitis C treatment. The inclusion of PLOS ONE (9 articles), Spectrochimica Acta (9 articles), Antiviral Therapy and Hepatology Research (7 articles), and Microchemical Journal (7 articles) implies specialized analytical or pharmacological investigations on ledipasvir (Figure 2).

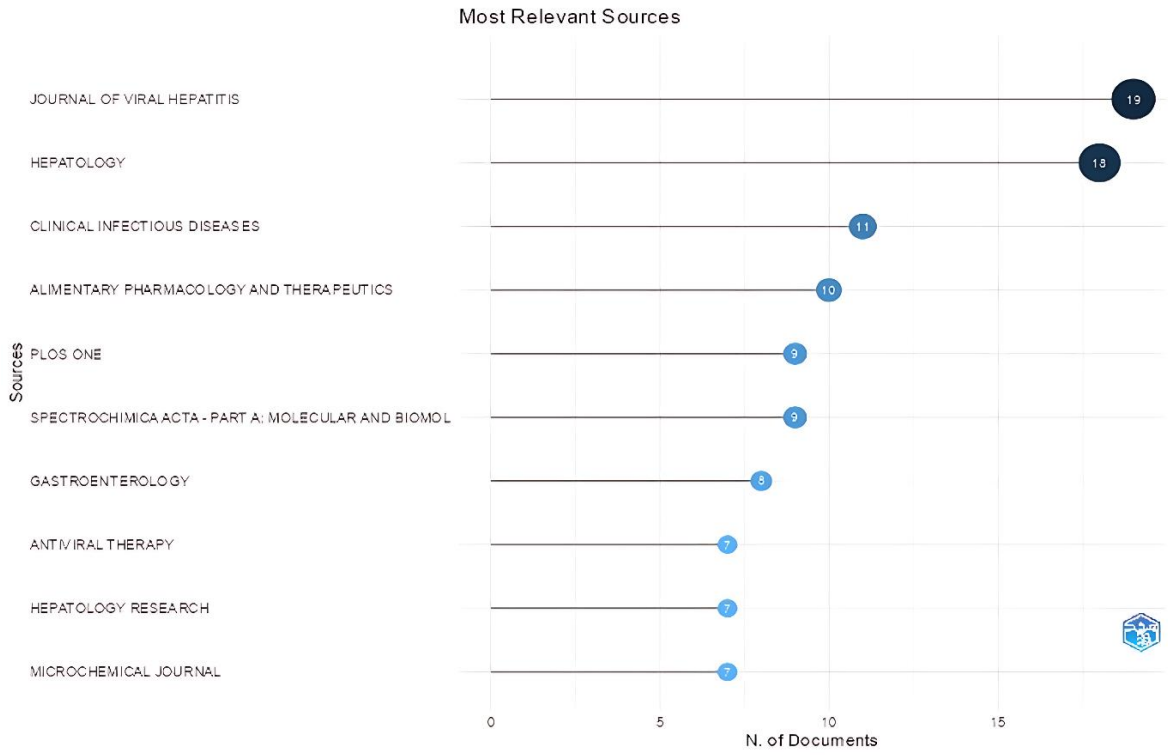

Figure 2.
Publication Sources and Journal Impact.

3.3. Author Impact and Research Leadership

McHutchison JG has the greatest H-index (26) with 8,017 total citations, suggesting a strong scholarly impact. He is followed by Pang PS (23) with 7,795 citations and Brainard DM (21) with 1,523 citations, all of whom have significant academic influence. Other authors, such as Mo H (16) with 3,123 citations and Dvory-Sobol and Youngssi ZM (14 each) (Figure 3).

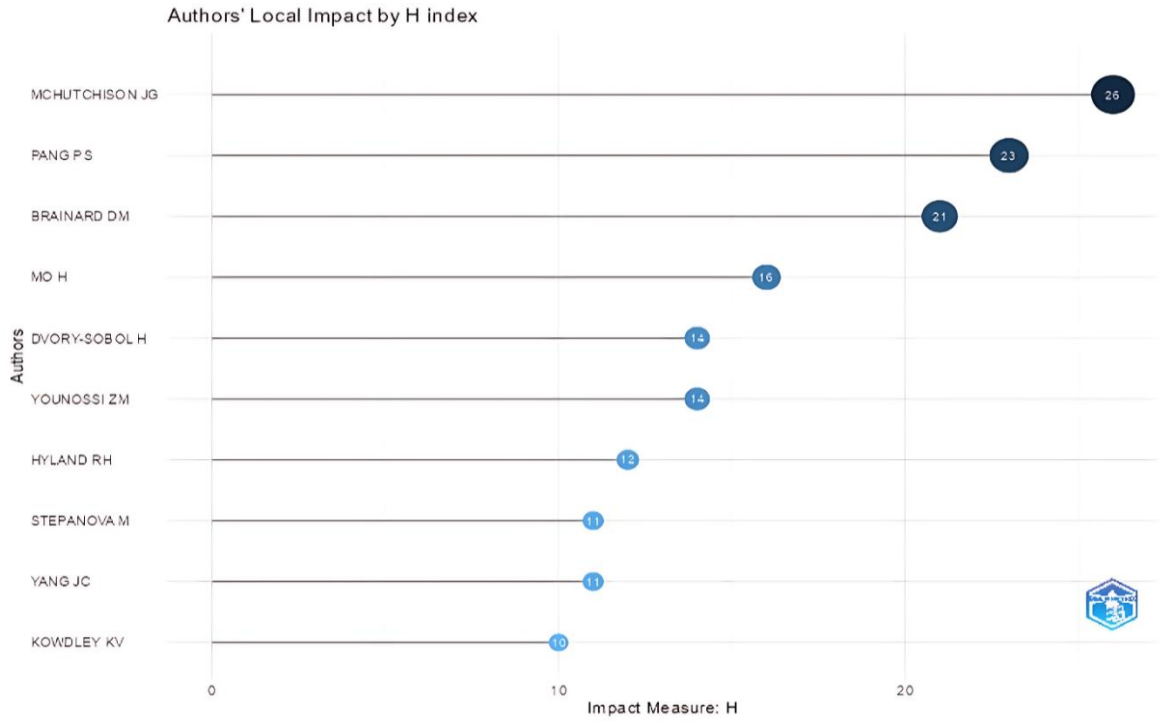

Figure 3.
Authors' Local Impact by H index.

3.4. Institutional and Geographic Distribution of Research

Gilead Sciences, the developer of ledipasvir, is the most prominent, with 248 publications. Academic institutions such as Cairo University (58), Osaka University Graduate School of Medicine (45), and Chiba University (34) demonstrate worldwide contributions, notably from countries with high hepatitis C prevalence (e.g., Egypt) or advanced medical research programs (e.g., Japan). The presence of Assiut University reinforces the emphasis on hepatitis C treatment in endemic locations. Institutions in the United States, such as the University of Maryland and the University of Florida, exhibit strong research activity in North America (Figure 4).

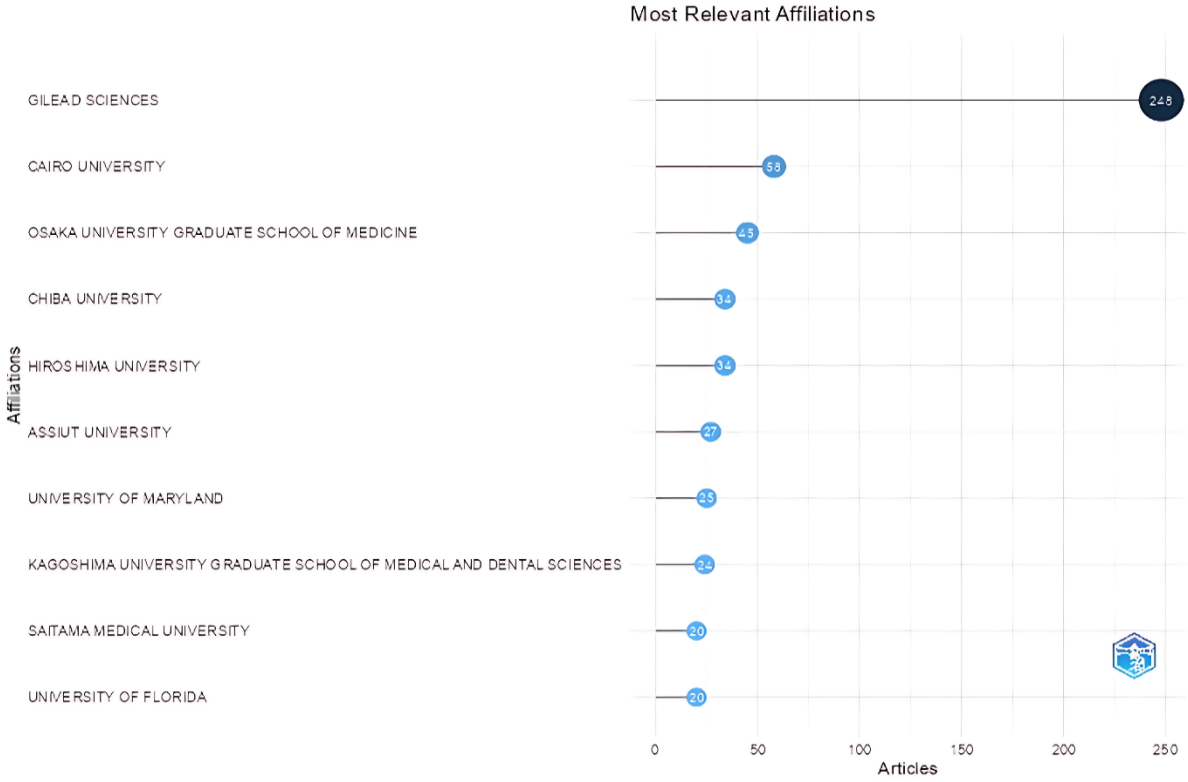

Figure 4.
Most Relevant Affiliations.

3.5. Corresponding Author Countries

When considering the countries of corresponding authors, the United States leads with 135 papers, followed by Egypt (65 articles) and Japan (41 articles). The inclusion of MCP% indicates that research on ledipasvir involves international collaborations. Collaboration patterns reflect significant differences in international participation; high-income countries such as New Zealand, the United States, and Germany have strong international collaboration percentages (MCP%) (Figure 5).

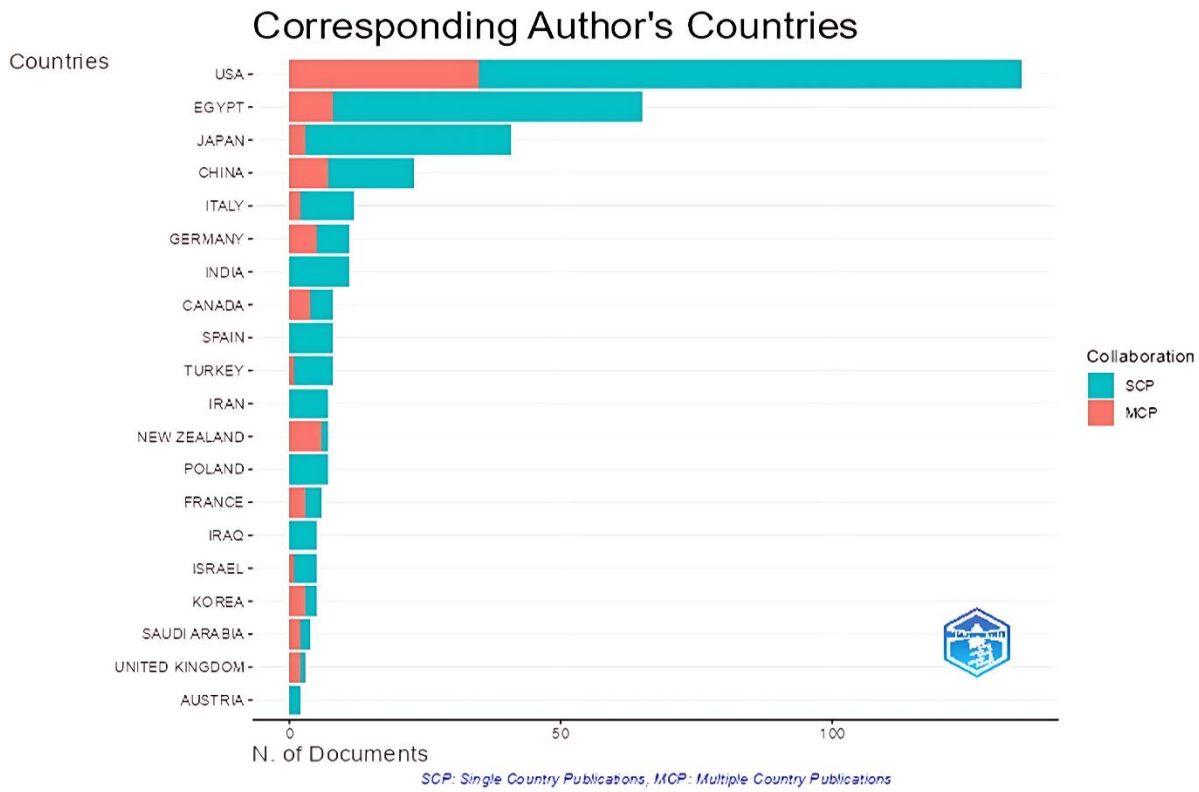

Figure 5.
Corresponding author countries.

3.6. Country Scientific Production

The regional distribution of scientific production emphasizes the United States' supremacy, followed by Japan and Egypt. Notably, numerous endemic regions make significant research contributions, including China, Turkey, Italy, and India (Figure 6).

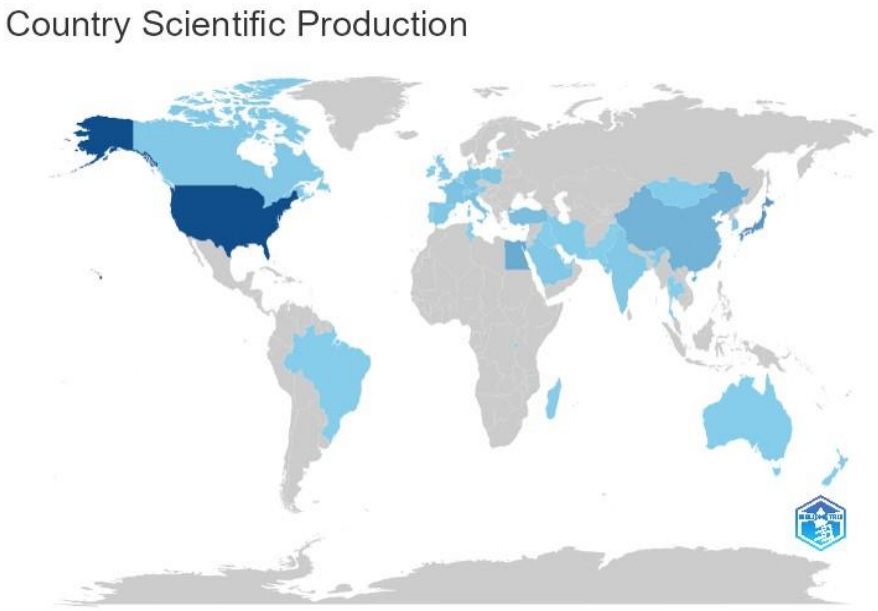

Figure 6.
Country Scientific Production.

3.7. Citation Impact and Research Trends

The analysis of citation metrics reveals significant research milestones and evolving thematic priorities in ledipasvir research. As presented in Table 2 & Figure 7, the most cited publication is AFDHAL N [19] & AFDHAL N [20], accumulating 1533 and 1214 citations, respectively, with an extraordinary citation rate of 127.75 and 101.16 per year, reflecting intense scholarly interest in ledipasvir's potential antiviral applications. The third most cited work, Kowdley et al. [21] with 1049 citations, represents foundational research in the field [22]. Further details are shown in Table 2 & Figure 7.

Table 2.
Most Global Cited studies. TC: total citations, DOI: Digital Object Identifier.

Paper	DOI	Total Citations	TC per Year	Normalized TC
Afdhal et al. [19], NEW ENGL J MED	10.1056/NEJMoa1402454	1533	127.75	4.22979898
Afdhal et al. [20], NEW ENGL J MED-a	10.1056/NEJMoa1316366	1214	101.166667	3.34962554
Kowdley et al. [21], NEW ENGL J MED	10.1056/NEJMoa1402355	1049	87.4166667	2.89436342
Charlton et al. [23], GASTROENTEROLOGY	10.1053/j.gastro.2015.05.010	707	64.2727273	5.36093418
Lawitz et al. [24], LANCET	10.1016/S0140-6736(13)62121-2	486	40.5	1.34095388
Naggie et al. [25], NEW ENGL J MED	10.1056/NEJMoa1501315	417	37.9090909	3.16196542
Manns et al. [26], LANCET INFECT DIS	10.1016/S1473-3099(16)00052-9	399	39.9	7.68085106
Chen et al. [27], F1000 RES	10.12688/f1000research.22457.2	365	60.8333333	14.4597839
Mizokami et al. [28], LANCET INFECT DIS	10.1016/S1473-3099(15)70099-X	317	28.8181818	2.40370033
Chhatwal [29], ANN INTERN MED	10.7326/M14-1336	309	28.0909091	2.34303913

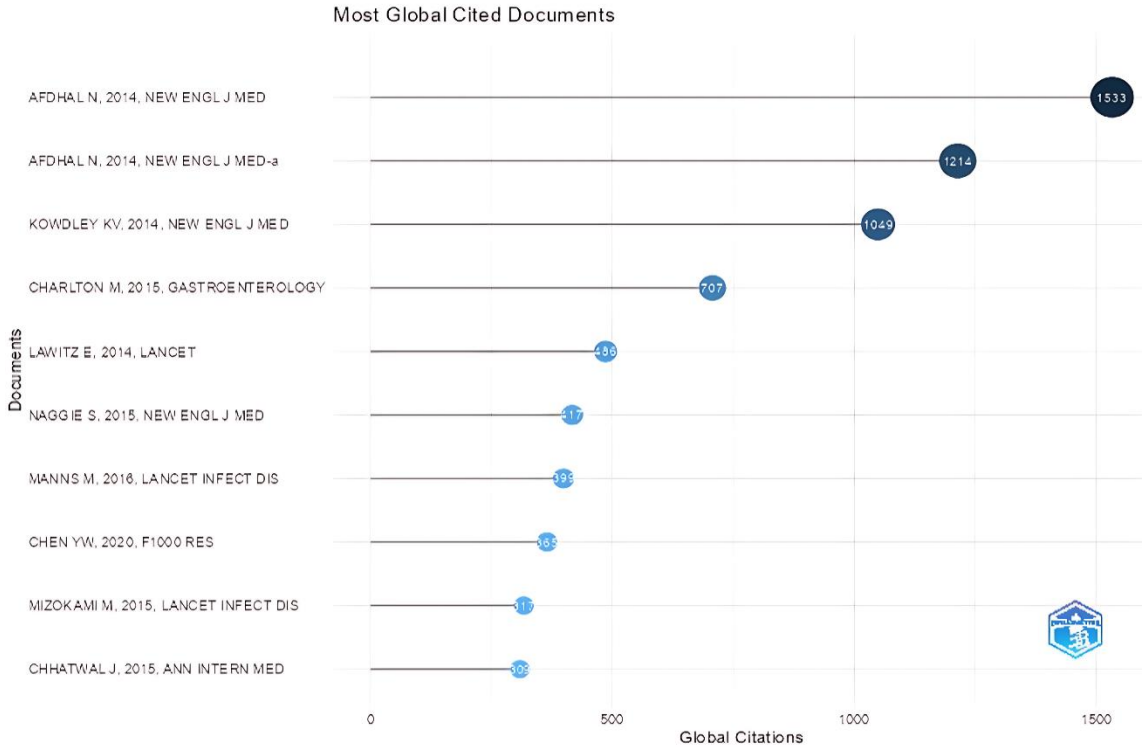

Figure 7.
Citation Impact and Research Trends.

3.8. Keyword Co-Occurrence Analysis

The central blue cluster highlights pharmacokinetics and analytical methods involving ledipasvir and related compounds like ledipasvir, HPLC, plasma, pharmacokinetics, daclatasvir, and simeprevir, emphasizing drug monitoring and bioavailability studies. The green cluster revolves around the clinical application of ledipasvir in managing HCV, cirrhosis, and liver transplantation. The red and orange clusters address combination therapies (e.g., ledipasvir/sofosbuvir with ribavirin), co-infection with HIV, drug-drug interactions, and population-specific concerns such as treatment in adolescents or Egyptian patients. Meanwhile, the yellow cluster focuses on genotype-specific treatment strategies and patient adherence, and the light blue cluster supports the analytical framework with terms related to plasma drug quantification (Figure 8).

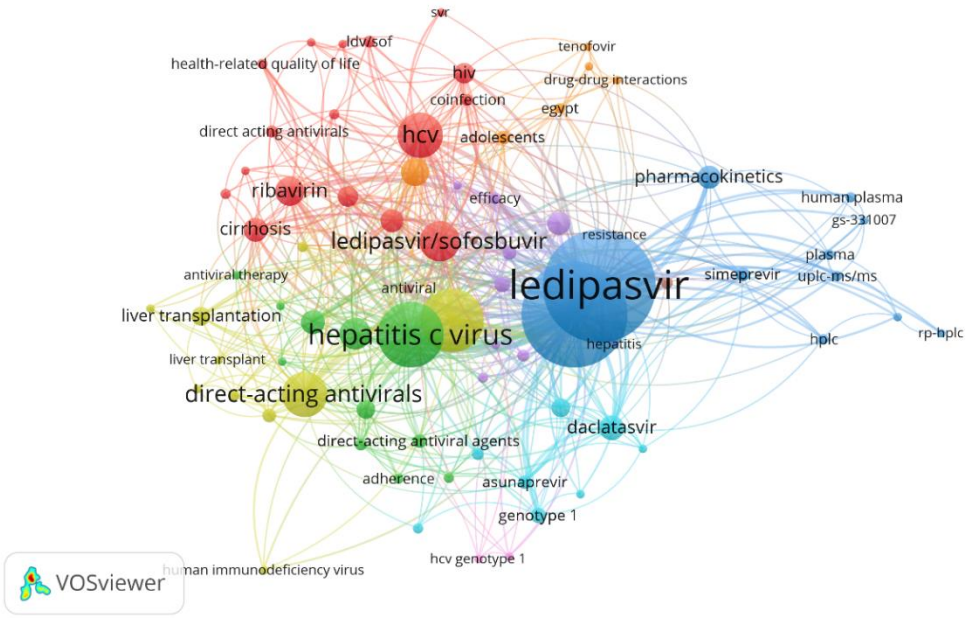

Figure 8.
Most frequent Words.

3.9. Trend Topics

The trend topic visualization reveals the evolving research focus related to ledipasvir and associated Hepatitis C treatments over the past decade. Early studies (2014–2016) emphasized foundational pharmacological aspects such as "pharmacokinetics," "administration and dosage," and "phase 2 clinical trials," reflecting initial drug development and regulatory phases. From 2016 onward, there was a noticeable shift toward clinical applications and population-specific outcomes, with frequent terms like "ribavirin," "sofosbuvir," "middle-aged," "male," "female," and "child," indicating trials across diverse demographics. Later years introduced public health and virology-related topics such as "COVID-19," "real-time polymerase chain reaction," and "blood transfusion," suggesting expanding intersections with other viral conditions and comorbidities. More recent terms like "silymarin" and "rat" point to renewed interest in preclinical and adjunctive therapeutic research (Figure 9).

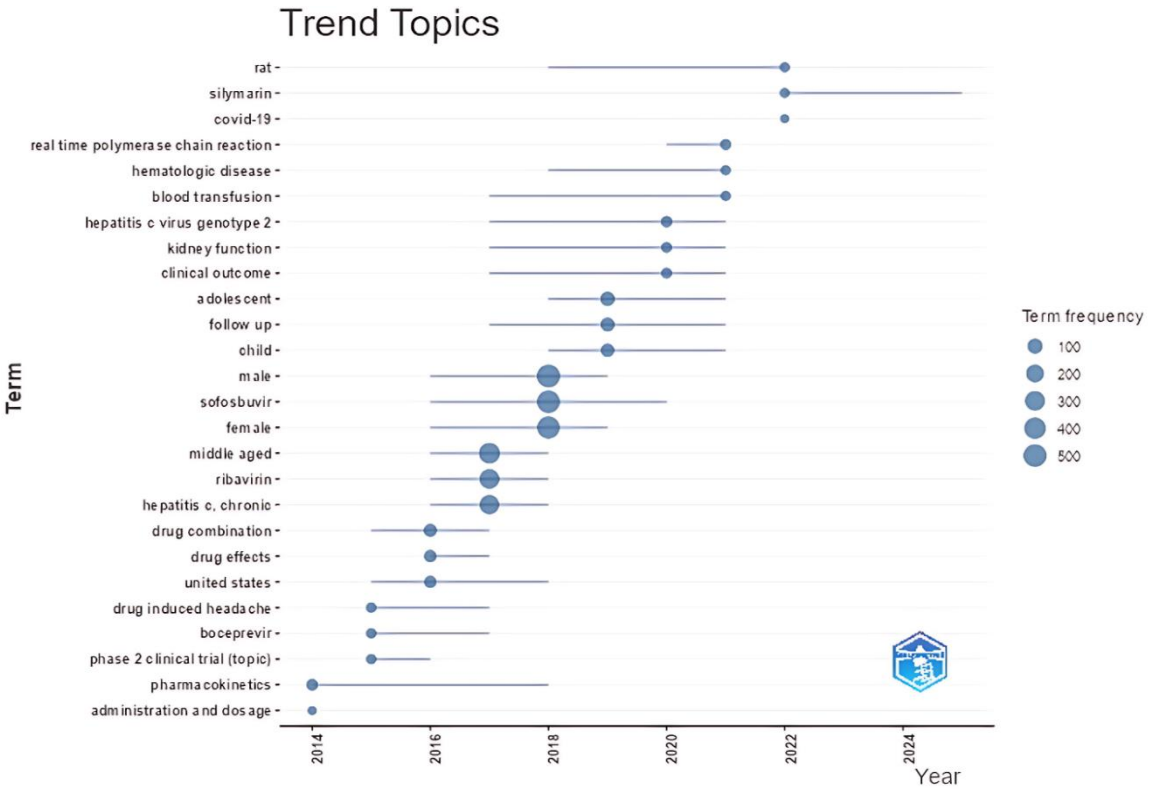

Figure 9.
Trend Topics over years.

3.10. Countries, Institutes and Relevant Keywords

The United States emerged as the leading country in ledipasvir-related publications, followed by Japan, Egypt, and Korea. On an institutional level, Gilead Sciences, the company that developed ledipasvir, is the largest contributor, followed by top academic institutions such as Osaka University, Hiroshima University, Chiba University, and the University of Maryland. These institutes are closely associated with major scientific keywords, including ledipasvir, sofosbuvir, hepatitis C virus, chronic hepatitis, direct-acting antivirals, and persistent virological response. There is also a significant contribution from Egyptian universities such as Cairo University, Assiut University, and Tanta University, emphasizing regional collaboration on liver disease research (Figure 10).

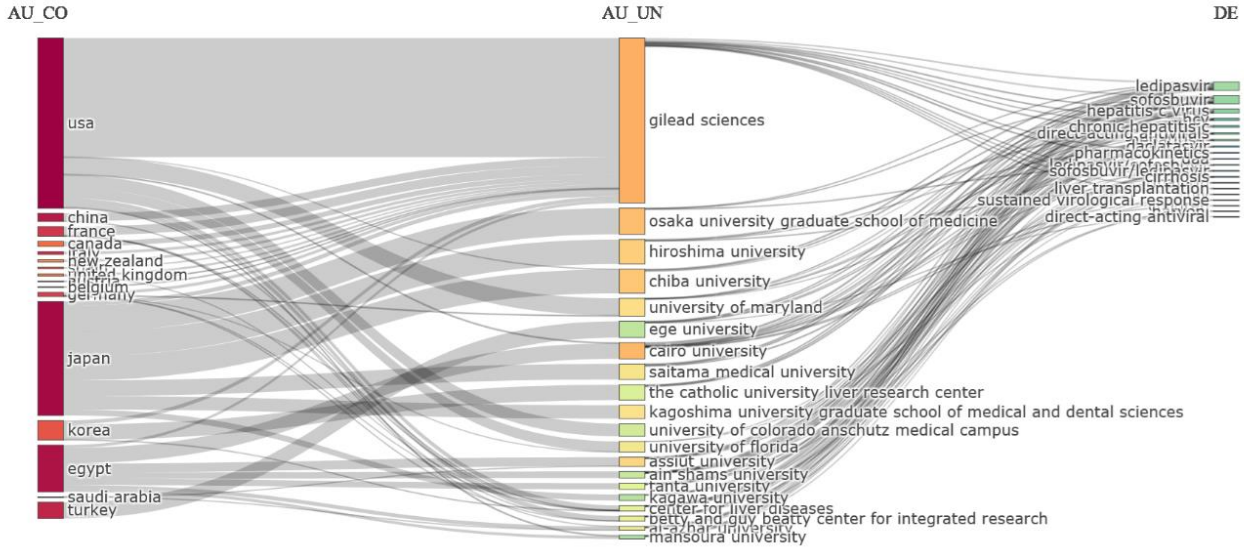

Figure 10.
Relationship between country (AU-CO), university (AU-UN), and keywords (DE).

3.11. Institutions, Scientific Journals, and Keywords

The linkages between academic institutions or organizations (AU_UN), scientific publications (SO), and major research words or drugs (DE) in the field of hepatitis C research of ledipasvir research showed that; Gilead Sciences and a number of Japanese universities, including Kagoshima University and Osaka University Graduate School of Medicine, make significant contributions. These organizations publish in journals on a regular basis, including Hepatology, Journal of Viral Hepatitis, and Hepatology Research. Sofosbuvir, ledipasvir, hepatitis C virus, and direct-acting antivirals are the most often researched topics and therapeutic drugs (Figure 11).

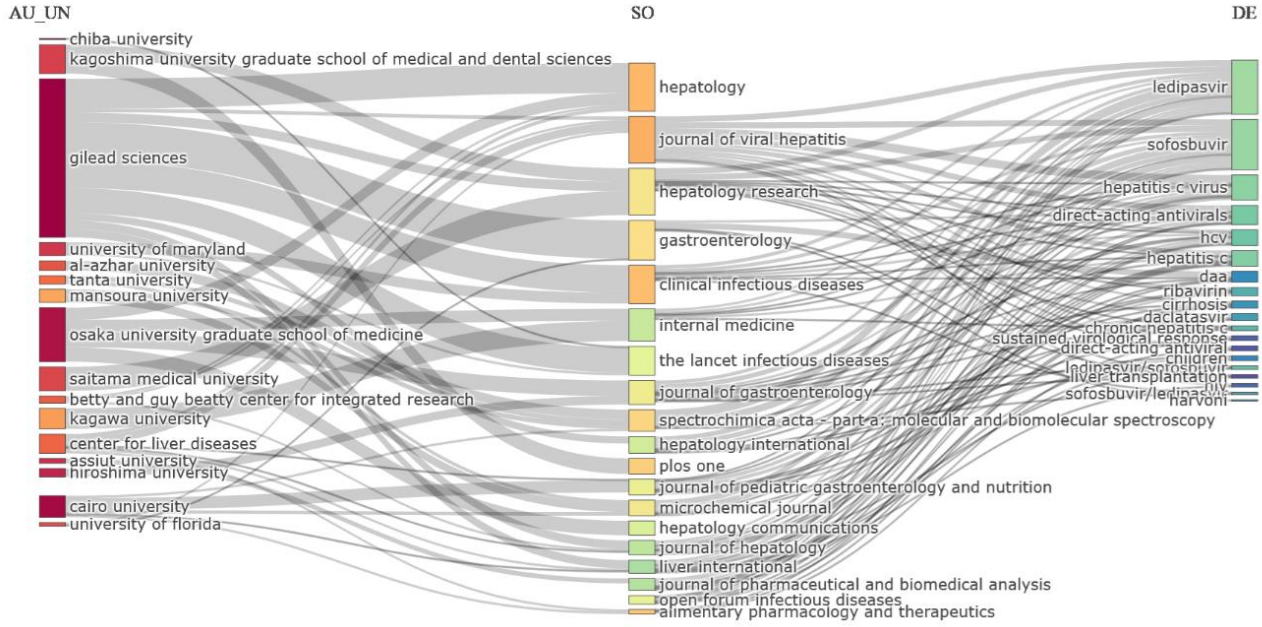

Figure 11.
Institutions, scientific journals, and keywords.

3.12. Thematic Map

The dynamic visualization divides the themes into four quadrants: motor themes, specialty topics, emerging or decreasing themes, and basic themes. Motor themes (top right) include drug safety, treatment duration, fatigue, and demographic phrases such as human, male, and humans, emphasizing their central and mature position in clinical research on Hepatitis C treatments. Niche themes (top left): Terms such as reproducibility, chromatography, high-pressure liquid chromatography, and reproducibility of results appear here, indicating specialized yet isolated research areas. Emerging or declining themes (bottom left) include chemistry, drug stability, spectrophotometry, and high-performance liquid chromatography, indicating more technical or out-of-date approaches. Basic themes (bottom right): Daclatasvir, limit of quantification, and unidentified drug are listed, indicating their importance in the area but a lack of specialist development (Figure 12).

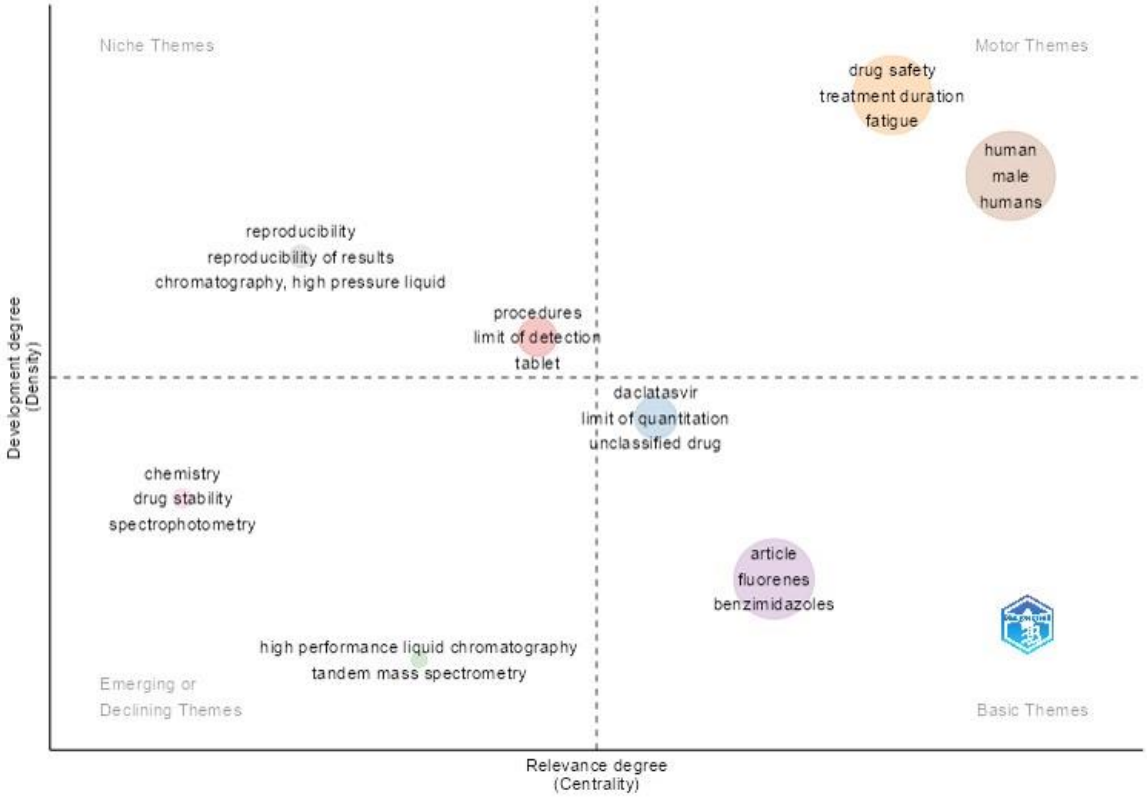

Figure 12.
Thematic Map.

3.13. Keyword Overlay Visualization

The overlay visualization shows a clear historical progression of key phrases associated with antiviral therapy in ledipasvir research, with colors representing the time evolution of publications, revealing how research objectives changed between 2017 and 2020. During 2017-2018, represented by blue/green coloration, dominant terms such as direct-acting antivirals, ledipasvir/sofosbuvir, and hepatitis C virus are observed. By 2018-2019 (the changeover to yellow/green coloration), words like pharmacokinetics, human plasma, and drug-drug interactions are included. The most current phase (2019-2020, yellow coloration) features terms like COVID-19, real-world, and quality of life (Figure 13).

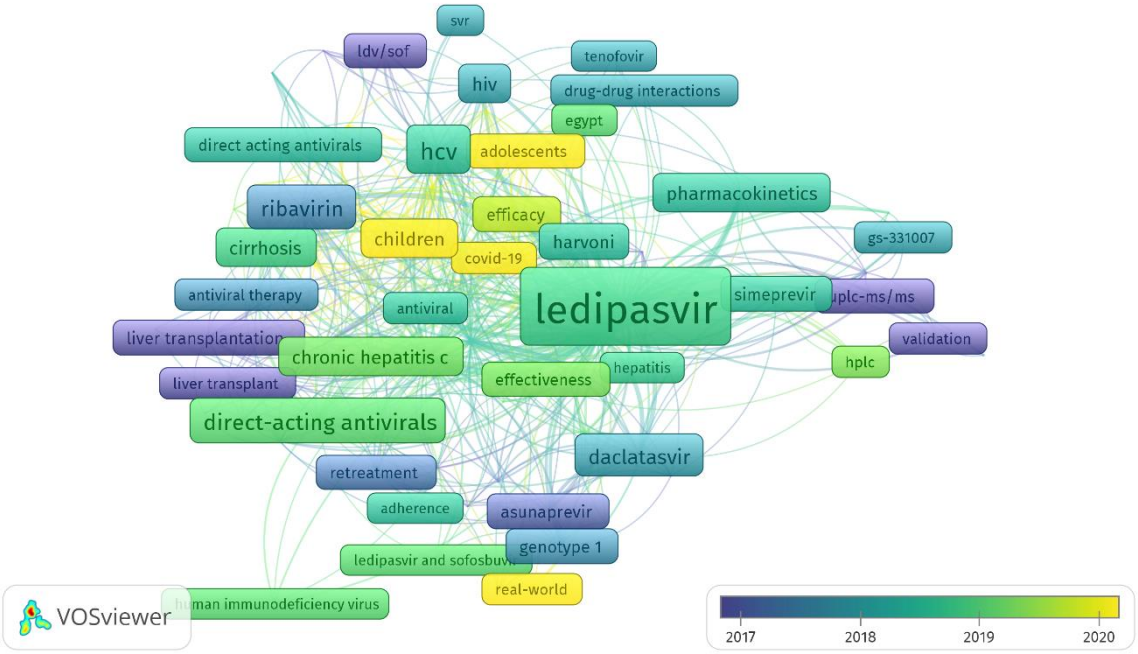

Figure 13.
Overlay Visualization of Keyword Co-occurrence in ledipasvir Research.

3.14. Collaboration Map

The United States exhibits the darkest shade and the densest network of collaboration lines, indicating that it is the primary focus of research activity. Numerous connections extend from the United States to countries in Europe (especially the UK, Germany, France, and Italy), Asia (particularly China and Japan), and Australia (Figure 14).

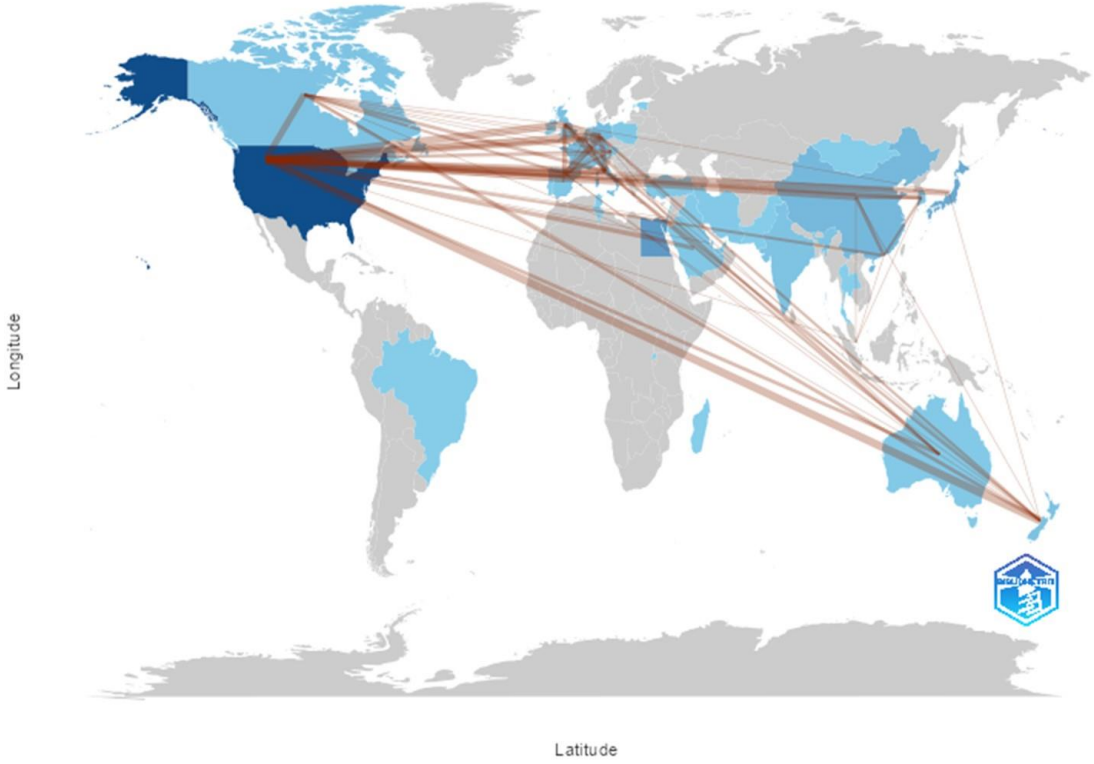

Figure 14.
Collaboration map.

4. Discussion

The bibliometric analysis of ledipasvir-related research from 2014 to May 2025 provides valuable insights into the evolution and global distribution of knowledge surrounding this direct-acting antiviral. The early increase in papers

demonstrates broad scientific and clinical interest, particularly in its application to treat HCV. The peak in 2018, followed by a slow decline, indicates that, while the drug received significant early attention, research focus has shifted to newer therapeutic agents or combinations. Despite this decline, the high average citation rate (39.57 citations per document) demonstrates the ongoing relevance and importance of early foundational works.

The multidisciplinary character of ledipasvir research is demonstrated by its publishing in a variety of journals, including the Journal of Viral Hepatitis [30], Hepatology [31] and PLOS ONE [32], demonstrating both clinical and multidisciplinary interest. Institutions like Gilead Sciences demonstrate the importance of research and development sections in drug discovery, especially in cooperation with academic departments [33, 34]. The predominance of institutions from the United States [35], Egypt [36] and Japan [37, 38] indicates both disease burden and research capacity, with Egypt's large participation reflecting the country's historically high HCV incidence [39].

Keyword analysis shows that research has shifted from a focus on pharmacokinetics and therapeutic efficacy to broader themes, including adherence, liver transplantation, and even COVID-19 implications [40, 41].

Despite a declining trend in publication volume, the sustained international collaboration and thematic richness suggest that ledipasvir remains a key reference point in antiviral research. This is especially true in areas with chronic hepatitis C difficulties, where it remains an important component of public health strategies. The bibliometric data thus provide a thorough summary of the scientific trajectory while also highlighting opportunities for future research, such as comparative pharmacological effectiveness, long-term effects, and resistance mechanisms.

5. Conclusion

This bibliometric analysis provides a complete picture of the global research landscape for ledipasvir from 2014 to 2025. The findings show a clear evolution in scientific interest, with a dramatic increase in publications over the first few years after the drug's debut, followed by a gradual fall as the field matured. Despite a decrease in publication numbers in recent years, ledipasvir research is still prominent, as indicated by high citation rates and ongoing worldwide collaboration. Key contributors, including renowned authors, institutions, and countries, have had a substantial impact on the development and understanding of ledipasvir, notably in the context of hepatitis C treatment. The drug's growing significance in antiviral therapy is highlighted by its many study areas, which include clinical efficacy, pharmacokinetics, co-infections, and emerging topics such as COVID-19.

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