Research Article

Anti-Neuroinflammatory Therapies in Epilepsy: A Bibliometric Analysis

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Abstract

Background: Neuroinflammation's role in epilepsy has heightened interest in immune-mediated therapies. Epilepsy, affecting a substantial global population, has a 30% treatment resistance rate. Alternative therapies have shown promise. Neuroinflammation triggers seizures via cytokine production, exacerbated by the lack of antagonistic systems. Effective epilepsy management requires understanding its physiological and pathological causes.

Method: Articles from the SCOPUS database (1994-2024) were reviewed using MeSH terms "Inflammation," "Epilepsy," and "Treatment" or "Therapies." From 2821 initial articles, 717 were selected based on specific filters. After exclusions, 673 articles were analyzed using Bibliometrix and VOS viewer software, covering 302 journals and 3179 authors.

Discussion: Inflammation catalyzes epilepsy when regulatory mechanisms fail. A compromised blood-brain barrier allows inflammatory substances into the brain, with astrocytes and microglia playing crucial roles. Initial research emphasized astrocytes, but later studies highlighted microglia's significant contribution. Understanding these mechanisms underpins anti-inflammatory treatments. Recent trends indicate a shift in focus, with 68.5% of related articles published in the last four years, exploring the roles of glia, the blood-brain barrier, and proinflammatory cytokines. The relationship between neuroinflammation and neurodegenerative diseases has also been studied.

Results: Most publications were in 2019, with 461 of 673 articles (68.5%) published in the last four years across 302 journals, averaging 38.3 citations per article. International collaborations accounted for 25%, with the United States leading in article production.

Conclusion: Neuroinflammation in epilepsy has gained significance, with international collaboration crucial for advancing research and treatment. This study highlights the importance of exploring new biomarkers and targeted therapies like miRNA manipulation to improve epilepsy treatment. Innovative research suggests potential revolutionary methods to enhance patients' quality of life, emphasizing the need for multidisciplinary collaboration.

Keywords: Neuroinflammation; Epilepsy; Therapeutic targets; Anakinra; Ketogenic diet; MicroRNAs; Gene therapies; Drug-resistant epilepsy

Introduction

The potential epileptogenic role of neuroinflammation has enhanced interest in therapies that primarily target immune-mediated processes [1]. It is commonly accepted that epilepsy is a widespread disorder that affects a large part of the world population. Although a lot of effort has been spent on getting to know its origin and development, resistance to treatment still represents rather a serious barrier in about 30% of cases [2,3]. Other modalities of therapy, such as nutritional therapy [4] and surgery [5], have been investigated as adjunct approaches to pharmaceutical therapy and have shown promising potential in improving prognosis of the disease. Moreover, several processes have been postulated to act as triggering factors and initiators of epileptic seizure activity. Among these mechanisms, glutamate, and GABA production imbalance has been one of the most recognized [6]. However, it is important to point out that the neuroinflammation process, specifically referring to the central nervous system, also exerts significant influence. It triggers epileptic seizures through the production of innumerable cytokines. This may occur either after an acute traumatic event [7] or as a result of the constant production of inflammatory substances by other neurological disorders [8]. Moreover, the lack of systems that antagonize neuroinflammation is involved in this mechanism. Furthermore, undeniable data show a direct relationship between higher levels of cytokines in the cerebrospinal fluid and the length and intensity of seizures [9]. Good management of epilepsy necessitates a full understanding of the physiological and pathological causes linked to it.

Bibliometrics analysis is an approach mostly used by academicians to measure research productivity by analyzing scientific material publication, for example, a research article, book, conference proceeding, among others. It helps to quantify the research activity within a certain field [10]. Using a Bibliometric Analysis [BA], one is able to find the emerging tendencies of the journal, analyze the performance of the article, detect the collaborative pattern, and find information on constituents like author description, co-authorship, and citations received. It also helps analyze the intellectual structure of a particular area from the available literature. The trend for using BA has significantly increased with several articles written on its usages [11].

As stated in the introduction, Mexican scientists in the medical area have mostly neglected BA. has generated significant interest in several regions worldwide, prompting developed nations across North America, Europe, Asia, and Oceania, as well as less sophisticated economies in South America and Africa, to assess the significance of their scientific contributions to the global body of knowledge. We seek to motivate additional Mexican researchers to collaborate with us in analyzing our scientific contributions [12].

Anti-neuroinflammatory therapies have proven promising in both experimental and clinical investigations [13–16]. The importance of these bibliometric studies is so extreme, which is why it is a kind of mapping of medical literature. Quantitative measures are taken to understand the effects of scientific production over time, to determine important areas of study, and to discover aspects that contribute to improved impact in the future publications [17]. It was the clear and obvious objective of this study to achieve objectivity in global research. The purpose is not to make a negative value judgment of the publications found in the given journals. Instead, its purpose is to point out the potential benefits of this approach in pointing to the areas of research opportunities which will assist in the development of anti-neuroinflammatory therapies for epilepsy.

Method

The data were elicited from articles in scientific journals. We selected articles written by using the MeSH phrases "Inflammation," "Epilepsy," and "Treatment" or "Therapies.", which involved establishing inclusion and exclusion criteria to ensure the relevance and quality of the selected research. The criteria included consideration of publication type. Primary research articles, systematic reviews, and book chapters: A filter was applied to include only studies published in English between 1994 and 2024. Studies that examine the efficacy of anti-neuroinflammatory treatments in the context of epilepsy.

To accomplish this objective, a Study Database was generated in the CSV format to ascertain their identification using the Scopus database. We implement exclusion. Standards or guidelines are used to evaluate or assess something. Publication Type Opinions, Correspondence, Summaries of Research conducted on animals, and scientific papers that have not yet undergone peer review. Upon thorough examination of our database, we found duplicate studies that were recognized electronically prior to the review, as well as studies that did not clearly pertain to the topic of neuroinflammation in epilepsy. Subsequently, our selection procedure discovered 3927 records from the Scopus database. A total of 47 redundant records were eliminated. A preliminary screening was conducted to evaluate the titles and affiliations, yielding 717 studies that included the keyword " neuroinflammation ".

After reviewing our criteria, we rejected 501 titles that did not meet the inclusion requirements. In addition, we excluded 117 letters from the editor, 45 abstracts, and 339 animal studies. Consequently, a thorough examination encompassing, 3379 complete texts was performed. Among these, 2994 were articles, 314 were reviews, and 71 were book chapters. The Final Inclusion ultimately comprised 673 papers, including 302 literature articles, for analysis.

After applying these filters, we had 673 articles to be examined by the GNU University of Naples Federico II software, Bibliometrix, and the GNU Leiden University software, VOS viewer. There are wide tables with graphics that will cover from 1999 to 2024 and include data from 302 journals and 3,179 authors; Only 25 articles were written individually by a single author. In the main, the articles were performed with co-authors from other countries.

Results

Essential data were extracted from the provided papers covering the period from 1999 to 2024. The choice to implement the subject in 1999 was influenced by the publication of a significant paper, specifically, a case report on Rasmussen's encephalitis **(Figure 2)**. This study used biomarkers and Positron Emission Tomography (PET) to identify increased microglial activity. Although it does not propose a specific therapy method, it lays the necessary groundwork for future research in this area. Most of the evaluated publications were published in 2019, marking a pivotal moment in the progress of this topic. Of the 673 articles evaluated, 461 were published within the last four years, constituting 68.5% of the total publications. The 673 papers mentioned above are distributed across 302
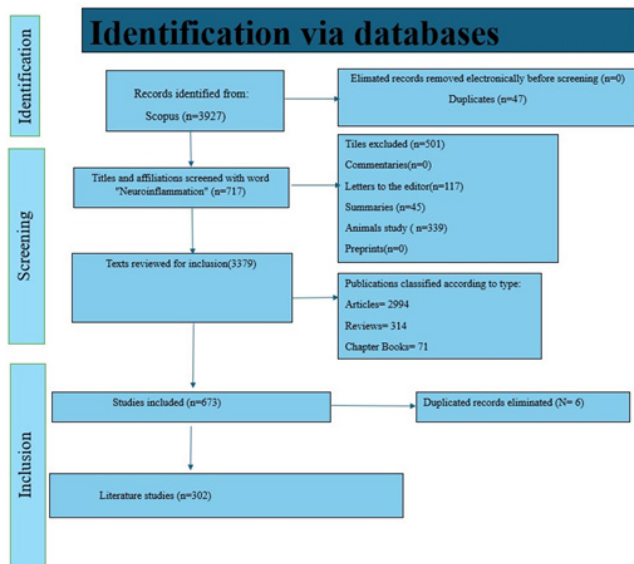
Figure 1: Flow Diagram. Determining the approach for developing a search strategy.
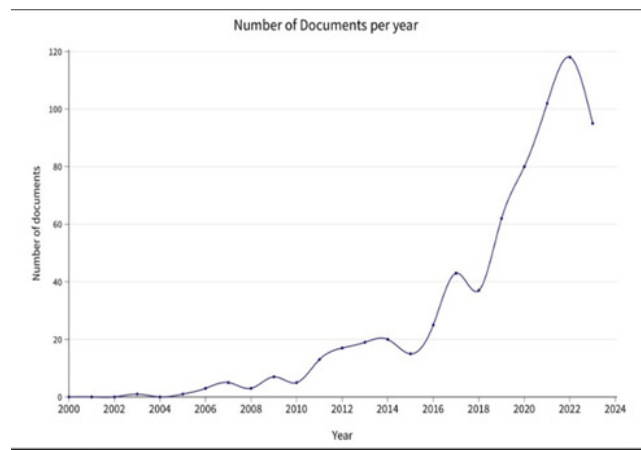

Figure 2: Evolution of the number of documents published per year from 2019 to 2023.

journals, with an average of 38.3 citations per paper. Table 1 contains data on the 1,727 unique keywords found in the articles. These articles were written by 3,179 authors. However, the number of articles with only one author were small, with a median of six authors per article. The collected data provide vital knowledge on the feasibility of collaboration, revealing the number of possible collaborators for future studies.

Of all the collaborations, only 25% have been international, indicating that most publications resulted from collaborations with scholars from the same country. Notably, the United States is the leading country in terms of producing the largest number of bibliometric research papers, followed by Italy coming in a close second. However, despite their substantial participation in the sector, countries such as China and India exhibit a restricted impact, as illustrated in Figure 3. This indicates a possible connection between their limited involvement in international cooperation and influence.

In the realm of research, it is crucial to consider that the significance of citations outweighs the number of published articles. Although the United States, Italy, and China continue to hold their positions in the Top 3, an analysis of the median number of citations per article shows a significant association between these two factors. Under this specific paradigm, the Netherlands, Canada, and the United States stand out for their

elevated citation rates, whereas China and India have averages of fewer than 20 citations per piece. These findings indicate that, while Chinese and Indian research output is large, its effect and relevance may be relatively limited compared to that of other countries. Collaboration networks between countries have a considerable effect on the influence of countries on publications.

Figure 3 clearly illustrates the United States as the primary center for collaboration with countries from different locations throughout the world. In contrast, countries such as India and China are located on the periphery and predominantly participate in partnerships with countries in their immediate geographical vicinity. Latin American countries are situated in the northeastern upper-right quadrant of the picture, where their minimal cooperation with other countries, including those within the same region, is clearly noticeable.

United States, Italy, China, and United Kingdom stood out as the major centers of collaboration, which had strong connections with other countries in the network. The colors indicate different regional clusters of collaboration.

Of the 302 journals included in the database, the International Journal of Molecular Sciences published the highest number of articles [23] and had the highest impact factor in the field
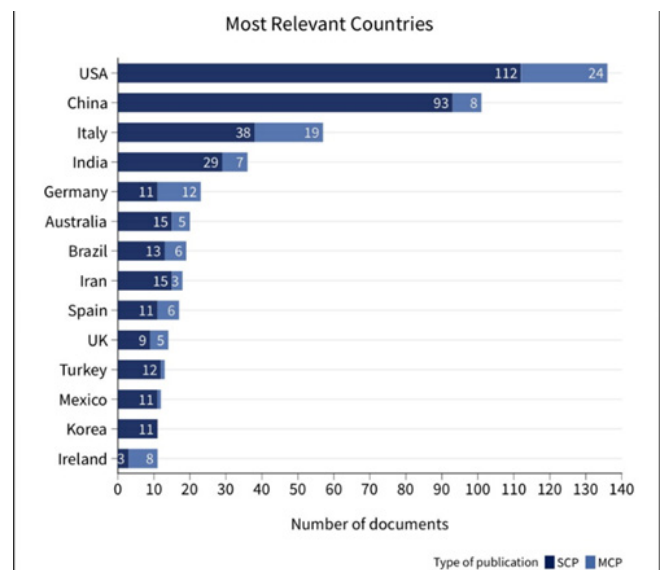

Figure 3: Countries with the highest number of articles published. The graph distinguishes between publications from a single country [SCP] and collaborative publications between multiple countries [MCP].
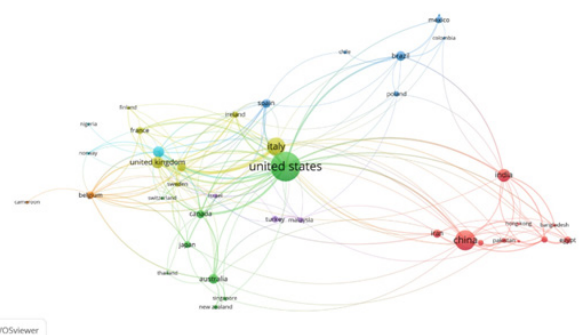

Figure 4: International collaboration map based Vosviewer on research paper co-authorships. Country nodes and their sizes indicate the number of publications, while links show how countries are collaborating with each other.

of antineuroinflammatory therapies for epilepsy. The following are the Neurobiology of Disease and Epilepsy, with 21 and 20 articles, respectively **(Figure 6)**.

Table 1: Main information ab\out articles included.

Description	Results
Time span	1999-2023
Sources	302
Documents	673
Average citations per documents	38.3
Authors	
Total number of authors	3179
Author´s keywords	1727
Documents	
Single-authored documents	25
Authors per documents	6.13
International co-authorship %	24.96

It is important to note that these journals do not specifically focus on neuroinflammation. Among the top 10 journals [Figure 5], the Journal of Neuroinflammation had the greatest impact factor of 9.3. This journal primarily focuses on neuro-inflammation. It is important to note that among the top ten journals with the highest number of published articles on this topic, only eight had an impact factor exceeding 5.

These findings indicate that considerable attention has been paid to the use of anti-neuroinflammatory treatments for epilepsy. Some authors have stood out over time among the numerous publications on this subject. Annamaria Vezzani, an Italian writer, published five essays on this subject in 2019, making her a very notable author in this field.

The combined total number of citations for these studies was 115. Over the past decade, Vezzani has consistently generated scholarly publications. Her 2019 work, titled "Neuroinflammatory pathways as therapeutic targets and biomarkers in epilepsy," has significantly influenced scholarly research on this subject. Other authors who have made noteworthy contributions to the growing interest in neuroinflammation in epilepsy include Teresa Ravizza and Silvia Baloto. These scholars, like

Table 2: The 10 Most Cited Documents Worldwide.

| Rank CC	Author	Journal	Type of Publication	Title	TC	CY	Y
1	Vargas DL	Annals of Neurology	Article	Neurogial Actvation and Neurointtammation in the Brain of Patients with Autism	1568	82.53	2005
2	Obermeier	Nature Medicine	Review	Development, Maintenance and Disruption of the Blood-Brain Barrier	1512	137.45	2013
3	Polderman KH	Critical Care Medicine	Review	Mechanism of Action, Physiological Effects, and Complications of Hypothermia	840	56.00	2009
4	Devinsky O	Trends in Neurosciences	Review	Glia and Epilepsy; Excitability and Inflammation	572	52.00	2013
5	Vazzani A	Neuropharmacology	Review	Neuromodulatory properties of inflammatory Cytokines and their Impact on Neurona! Excitability	415	46.11	2015
6	Rempe RG	Journal of Cerebral Blood Flow and Metabolism	Review	Matrix Metalloproteinases in the Brain and Blood-Brain Barrier: Versatile Breakers and Markers	387	48.38	2016
7	Vezzani A	Nature Reviews Neurology	Review	Neuroinflammatory Pathways as Treatment Targets and Biomarkers in Epilepsy	385	77.00	2019
8	Lima Giacobbo B	Molecular Neurobiology	Review	Brain-Derived Neurotrophic Factor in Brain Disorders; Focus on Neuroinflammation	370	74.00	2019
9	MacFabe DF	Behavioural Brain Research	Article	Neurobíological Effects of Intraventricular Propionic Acid in Rats; Possible Role of Short Chain Fatty Acids on the Pathogenesis and Characteristics of Autism Spectrum Disorders	336	19.76	2007
10	Jiménez F.	Neuroscience and Biobehavional Reviews	Review	Clinical Triáis of N-Acetylcysteine in Psychiatry and Neurology; A Systematic Review	320	35.56	2015
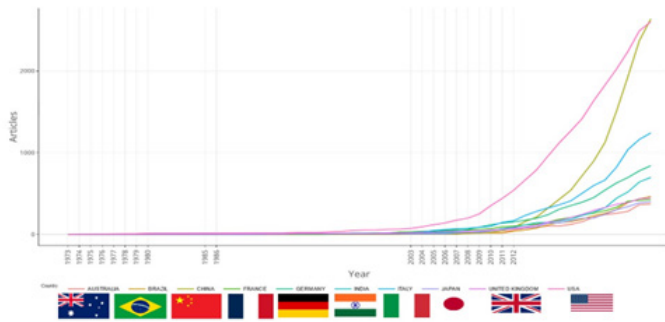
Figure 5: United States, Italy, China, and United Kingdom stood out as the major centers of collaboration, which had strong connections with other countries in the network. The colors indicate different regional clusters of collaboration.
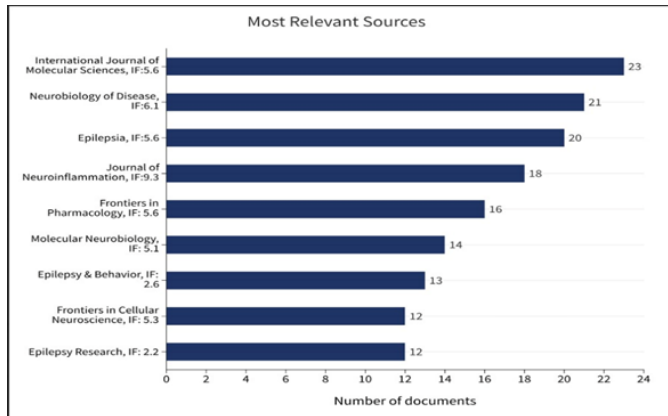

Figure 6: Journals with the highest number of articles published along with their impact factor.

Vezzani, were part of an Italian team that brought about significant changes in the field of neuroscience in 2019 **(Figure 7)**.

Globally, the top ten most frequently cited publications have several common characteristics. Among the 10 publications, 8 were review articles, while the remaining 2 were original articles. Publications with the largest number of citations in records are not only focused on epilepsy. The objective of this study was to elucidate the pathophysiological mechanisms of neuroinflammatory activation, particularly the involvement of neuroglial activation, in individuals diagnosed with autism. The article was published in 2005 and has an average of 82.53 citations each year. It is noteworthy that the article with the second highest number of citations also had the highest average number of citations per year, totaling 137.45 citations annually. This paper, published in Nature Medicine, explores the importance of blood-brain barrier disruption as a crucial mechanism in the advancement of many neurological illnesses, specifically epilepsy. This article highlights that systemic inflammation can disturb the equilibrium of the brain's internal environment, allowing the entry of ions and chemicals that may trigger epileptic activity into the central nervous system through the blood-brain barrier **(Table 2)**.

An effective approach to uncovering the relationships between major concepts in a certain field is to identify the most commonly used keywords. The persistent correlation between neuroinflammation and its relevance over time was remarkable. The most commonly used terms from 2015 to 2018 were kainic acid, glia, drug resistance, astrocytes, blood-brain barrier, multiple sclerosis, Parkinson's disease, neurodegeneration, epileptogenesis, status epilepticus, and mTOR. Since 2019, there has been a discernible surge in the number of papers and citations. At this juncture, the author's choice of keywords be-

comes more precise. The most frequently used terms were biomarkers, hmgb1, oxidative stress, mitochondrial dysfunction, depression, ketogenic diet, anakinra, nrf2, inflammasome, and microrna **(Figure 8)**.

Discussion

Inflammation is not a direct etiological element of epilepsy, as it is a non-specific physiological reaction of the organism to any type of aggression elicited by specific causes. The immune system includes mechanisms that counteract inflammation and ultimately terminate the inflammatory process. However, the lack of regulation of this mechanism and the reduction in regulatory mechanisms act as catalysts and sustainers of the epileptogenic process [18]. The entry of several substances that cause inflammation across a weakened barrier that separates blood from the brain is an important first step in initiating inflammation in the brain [19]. Astrocytes and microglia, which are glial cells, play crucial roles in sustaining this condition. Initially, astrocytes were considered the main cell type implicated. Nevertheless, subsequent research has emphasized the substantial contribution of microglia in a similar situation [20]. While these notions may be seen as basic, they are essential as they establish the basis for understanding the reasoning behind anti-inflammatory treatments. Although epilepsy is the second most prevalent neurological illness worldwide, research endeavors in this field are predominantly concentrated in a few nations, mirroring the patterns observed in other fields of study. Although the United States has the largest number of articles and citations, Italian authors have become leaders in global studies of neuroinflammation in epilepsy. The efforts of economically deprived nations, coincidentally the regions with the highest prevalence of epilepsy, present a significant potential
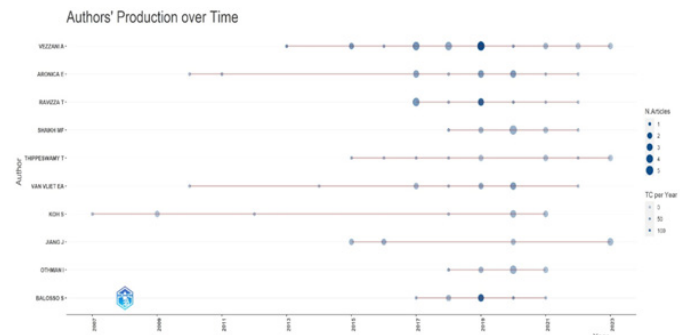

Figure 7: Author's production over time. The size of the circles represents a higher number of publications, while the shade of the circle represents the number of citations received.
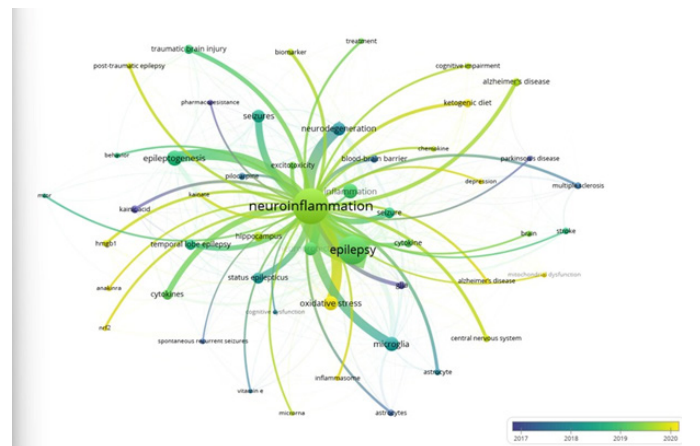

Figure 8: Author's keywords map. Nodes and their sizes indicate the number of times they are used, while links show how they are related to each other. While yellow represents the most recent keywords, blues represents the oldest.

to develop scientific collaboration networks and generate new ideas [21]. This would lead to the creation of global networks and foster collaboration among countries that are not necessarily in proximity. China is a notable example because it produces a significant amount of research; however, its articles have a relatively low impact. The importance of international collaboration lies in its ability to provide new perspectives on particular topics. The diagnostic and therapeutic approaches utilized for investigating epilepsy vary throughout distinct places of the world. Moreover, participating in global collaborations allows researchers to obtain specialized resources and take advantage of financing prospects that are currently not accessible within a certain jurisdiction [21].

Neuroinflammation is a highly intriguing issue for researchers and studies in this area are expected to have a substantial influence on many neurological diseases. Confirmation of this phenomenon is evident when considering that the Journal of Neuroinflammation, which has an impact factor of 9.3, ranks in the top 10 search results, surpassing journals such as the International Journal of Molecular Sciences [I.F. 5.6], and Neurobiology of Disease [I.F.] 6.1], and epilepsy [I.F. 5.6].

To provide a scientific framework, it is important to connect recent discoveries in the field of epilepsy and neuroinflammation with current trends and their corresponding effects [22]. It is important to highlight that the dominant topics in this discipline have undergone substantial changes over the last two decades. However, the high occurrence of 68.5% of the articles being published in the last four years led us to divide the authors' keywords into two separate groups: those used before 2019 and those used after 2019. Previous studies on treatments for neuroinflammation in epilepsy have mainly focused on the role of glia, blood-brain barrier, and astrocytes in the development of neuroinflammation [23,24]. Several studies have shown that elevated levels of proinflammatory cytokines IL-1, IL-6, and TNF-α in the CSF cerebrospinal fluid fluid are linked to a higher occurrence of status epilepticus and a greater proportion of epilepsies that do not respond to treatment [25,26]. Nine to 2019, research has mostly focused on exploring the relationship between neuroinflammation, which initiates the onset of epilepsy, and neurological illnesses such as Parkinson's disease and multiple sclerosis [27–29]. Neurodegenerative illnesses involve the buildup of α-synuclein, which can harm the mitochondria. This damage leads to an uneven distribution of ions across the cell membranes of neurons [30]. This discrepancy leads to an elevation in intracellular calcium and proinflammatory cytokine levels, which can result in impairment of the blood-brain barrier and aberrant neuronal overactivity [31]. In the realm of fundamental science, many experimental models have been used to investigate epilepsy, including chemical, electrical, and genetic methodologies. Of these options, chemical models, specifically the pilocarpine model, are the most frequently used [32,33]. However, the kainic acid model has been widely used in therapeutic approaches because it is highly reproducible, easily accessible, and shows minimal variability across the specimens used. In addition, kainic acid acts as a stimulant of AMPA and kainate receptors, resulting in damage caused by excessive Ca2+ activity and triggering a significant inflammatory reaction [34].

Since 2019, substantial modifications have been made to rules pertaining to the investigation of neuroinflammation in epilepsy. The authors' keywords currently adopt a more exact strategy, concentrating on therapeutic targets that encompass the control of individual proteins, such as HMGB1 and NRF2. The primary therapeutic methods used in the last five years, as indicated by the authors' published keywords, can be classified as pharmacological. Among these, anakinra is the most frequently used pharmaceutical intervention. The likely cause of this is most likely related to its unique mechanism of action as an IL-1 receptor antagonist. Although its main use is for managing autoinflammatory disorders, such as rheumatoid arthritis, specific clinical studies have shown positive results in treating epilepsy [35–38]. IL-1 exerts its effects through multiple mechanisms, such as stimulating microglia, changing ionic permeability to allow sodium and calcium to enter neurons, increasing neuronal excitability by triggering the release of glutamate, and the production of proinflammatory cytokines, such as IL-6 and TNF [39,40].

The ketogenic diet has garnered significant attention in both experimental and clinical research as an adjuvant therapy mainly because of its excellent tolerance [41]. Clinical studies have shown that the ketogenic diet has therapeutic effects in patients with various neurological diseases, including epilepsy. This is in contrast to other treatment approaches such as caloric restriction, the Mediterranean diet, and the low-glycemic index diet, which are not yet fully understood. However, the management of different inflammatory pathways is not exclusively dependent on this dietary intervention and additional clinical studies are necessary to assess its feasibility. However, there is currently a worldwide investigation of innovative gene therapies. Emerging therapeutics have focused on targeting certain microRNAs [miRNAs] to delay the onset of epilepsy. These specific therapies indicate that the manipulation of non-coding RNAs can regulate important signaling networks [42]. This process stimulates neuroinflammation, resulting in increased neuronal hyperexcitability.

Conclusion

The problem of cerebral inflammation associated with drug-resistant epilepsy has gained substantial global importance over the last five years. The global trend of concentrating publications in a limited number of countries highlights the necessity of international cooperation, especially with influential research nations such as the United States and Italy. Meticulous examination of the neurobiology of inflammation is particularly important for identifying new treatment targets. The crucial year for this notable progress was 2019, characterized by the transition from studying the causes of seizures to conducting targeted investigations on well-established treatment targets. The invaluable contributions of the Italian research team led by Annamaria Vezzani have made this progress possible.

Currently, anakinra is the most extensively studied pharmaceutical therapy, whereas a ketogenic diet is considered a complementary treatment. Studying and identifying miRNAs that show altered expression in particular types of epilepsy can offer valuable insights into the genetic pathways that cause these disorders. Despite notable advances, several possibilities remain in this domain. Investigating new biomarkers, such as nrf2, hmgb1, or indications of oxidative stress and mitochondrial dysfunction, has the potential to uncover targets for therapy in clinical research aimed at modifying the condition. Unfortunately, the adoption of these therapies in low-income nations is still distant, underscoring unequal access to sophisticated treatments in various parts of the world.

Therefore, through an overall review of many anti-neuroinflammatory therapies for epilepsy, one can appreciate the huge and contemporary potential that is beyond imagination in developing innovative and revolutionary methods to improve treatment. These novel findings suggest not only the vast scope for improvement through increased efficacy in therapy against epileptic disorders but also the importance of following novel and promising strategies to alleviate neuroinflammation. these advanced approaches enable revolutionary improvements in the treatment of epilepsy, with bright rays of hope for an enhanced quality of life for patients suffering from this incapacitating condition. It is therefore quite evident now that groundbreaking research and its application in such strategies go a long way toward determining new landscapes in the treatment of epilepsy, getting closer to a much brighter, healthier future for everyone who is affected by these neurological disorders.

Such innovative research lays the groundwork for new directions, and there are indications that the addition of these newer therapies to existing regimens may provide a paradigm shift with major improvements in patient outcomes. Medical professionals may draw a new path toward a future with much less or even no epilepsy burden by utilizing the knowledge gained from these analyses. With the prospect of such transformation in mind, it is now important that scientific and medical communities come together to strive to drive the momentum home. The evidence in the study assembled is, thus, a little spark of hope for millions of people worldwide suffering from epilepsy. This finding brings new hope and fresh motivation to the researcher as well as to their patients for devising a successful anti-neuroinflammatory therapy. For this to be possible, recognition of the critical need for continued exploration and innovation in treatment may be what will spur a paradigm shift with regard to epilepsy treatment into a new era of personalized, targeted therapeutics that more comprehensively deal with its root causes. This groundbreaking strategy was implemented using a multifaceted approach. Collaboration with experts in neurology, immunology, and pharmacology is key to developing comprehensive and holistic single-treatment frameworks. Pulling in specialists from different disciplines will create the synergy necessary to exercise the real potential of these new therapies.

Data Availability Statement: Original CSV files from each database along with the final list of papers in Excel can be provided by the corresponding author upon reasonable request.

Conflict of Interest: The authors declare no conflict of interest.

Informed Consent Statement: Not applicable.

Institutional Review Statement: Not applicable.

Research Involving Animals: Not applicable.

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