Trop J Nat Prod Res, May 2025; 9(5): 2244 - 2251 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Global Multidisciplinary Collaboration in Therapeutic *Cannabis* Research, Regulatory and Pharmaceutical Challenges

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ARTICLE INFO

Article history:
Received 09 February 2025
Revised 08 April 2025
Accepted 10 April 2025
Published online 01 June 2025

ABSTRACT

This bibliometric analysis examines the development of research in *cannabis* therapeutic. This research has seen explosive growth from 1972 to 2024, with 2022 documents published across 819 sources. This rapid expansion underscores the increasing global interest in understanding *cannabis*' therapeutic potentials. This vast body of work is richly interconnected, citing over 122124 references, and is characterized by 17624 "Keywords Plus" and 4607 author keywords, revealing the multidimensional nature of the research topics. Medical *cannabis* research draws from a diverse pool of 8706 researchers. The collaborative spirit is strong, with an average of 5.13 co-authors per document and 19.14% of these partnerships spanning international borders. Notable contributions to the field include works by Vincenzo Di Marzo and Daniele Piomelli, as well as highly cited articles like "The endocannabinoid system as an emerging target of pharmacotherapy" by Pacher *et al*., which has garnered 1775 citations. These studies are foundational, exploring critical areas like the endocannabinoid systems, treatment of neuropathic pain, and the pharmacological and clinical impacts of *cannabis*. However, the field faces significant gaps that warrant further investigation. There is a pressing need for more randomized controlled trials, longitudinal studies, and comprehensive research on drug-*cannabis* interactions. Addressing these gaps through rigorous clinical studies, interdisciplinary research, and supportive policies is crucial for advancing the field. Medical *cannabis* research is dynamic and rapidly evolving, with substantial contributions that continue to shape scientific and therapeutic landscapes. The combined efforts of researchers worldwide, supported by robust international collaborations, are key to unlocking the full potential of *cannabis* as a therapeutic agent.

Keywords: Therapeutic *Cannabis*, Bibliometric Analysis, Cannabinoids, Clinical Trials, Pharmacology, Neurology.

Introduction

Research on therapeutic *cannabis* has significantly expanded over the past decades, driven by growing interest in its medical applications.[1-3] Cannabinoids, the active compounds in *cannabis*, exhibit therapeutic potential in treating various diseases, leading to a notable increase in scientific publications in this field.[4,5] Anecdotal evidence and preliminary studies motivated the exploration of the beneficial effects of therapeutic *cannabis*, prompting researchers to deepen their investigations.[2,6]

The increase in clinical trials and experimental studies has led to a better understanding of cannabinoids' mechanisms of action and their effects on the human body.[7] Additionally, evolving legislation in many countries allowing the use of *cannabis* for medical purposes has also fostered research and the development of new treatments.[2,3] Financial support from research institutions and government agencies has been crucial for the progress of these studies.[2,5]

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Citation: Benomar A, Fekrouni M, Moutawalli A, Elhoudaibi S, Chakkor S, Mojemmi B. Global Multidisciplinary Collaboration in Therapeutic *Cannabis* Research, Regulatory and Pharmaceutical Challenges. Trop J Nat Prod Res. 2025; 9(5): 2244 – 2251 https://doi.org/10.26538/tjnpr/v9i5.52

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

However, a notable gap in the research lies in the particular nature of electrode reactions and pharmaceutical and structural development studies. These areas are not always published due to patents and intellectual property.[5,7] Formulation development is still a young field, and the available data are often limited as researchers and companies protect their innovations for intellectual property reasons.[2,5,8] This situation can limit the amount of accessible information and slow progress in the field of therapeutic *cannabis*.[1,8]

Furthermore, it is important to note that plant-based products are not harmonized between Europe and the United States. European regulations discuss traditional herbal medicines, well-established use, and full marketing authorization if the final product is purified and clinical trials are conducted.[9-11] In contrast, American regulations differ, complicating the comparison and application of research results between the two regions. This underscores the need for regulatory harmonization to facilitate the global development and acceptance of plant-based medicines.[3,12]

The primary objective of this study is to analyze the growth and trends in publications on therapeutic *cannabis*. Additionally, the study aimed to identify the main research themes, thematic clusters, contributions from authors, affiliations, and funding sponsors, as well as the implications of the results for the pharmaceutical applications and future research directions.

Materials and Methods

Research data

Comprehensive data were sourced from academic databases, focusing on articles published between 1972 and 2024. The search encompassed

terms such as "*cannabis*," "cannabinoid," "drug," "medicine," "phytomedicine," "pharmaceutic," "formulation," "manufacturing," and "regulatory".[13,14]

Document selection process

The selection protocol followed a structured four-stage process: Identification, Screening, Eligibility, and Inclusion (Figure 1). Initially, a total of 3029 articles were identified via the Scopus database. Upon initial screening, 3029 articles were retained based on the established inclusion criteria: the domain focus included Medicine (1448 articles) and Pharmacology, Toxicology, and Pharmaceutics (965 articles), with document types restricted to original articles (1296) and reviews (733). The analysis filtered only finalized publications, with language criteria limited to English (2020 articles) and French (12 articles). A thorough review of 2027 full texts was conducted, excluding seven due to incomplete or ambiguous information. This rigorous selection culminated in including 2022 texts in the final review, ensuring that only high-quality, pertinent documents informed the bibliometric analysis and enhanced the research reliability and rigour.

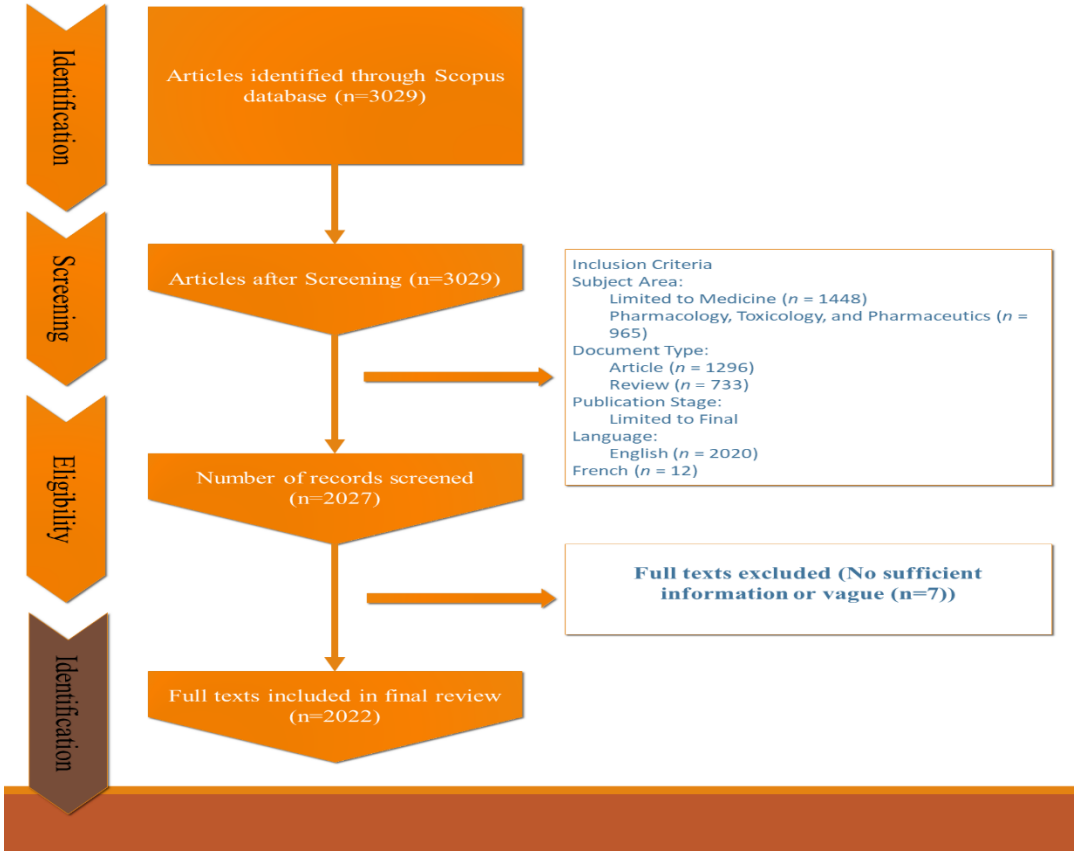

Figure 1: Flowchart of the document selection process

Visualization and analysis of bibliometric networks

The Bibliometrix R package (version 4.3.2, released in 2017) [1] was employed for the bibliometric network analysis, allowing for sophisticated calculations and visualizations. Through Bibliometrix, a descriptive statistics table was compiled, detailing the dataset's temporal evolution and diversity, capturing vital bibliometric metrics such as the total document count, annual growth rate, average citations per document, and degree of international collaboration.[14,15] The ten most-cited works were extracted from Scopus, highlighting foundational publications that have significantly contributed to the domain of -based pharmaceuticals and their formulations. These works were ranked according to total and average yearly citations, underscoring their sustained influence.[7,13]

Visualization efforts utilized VOSviewer (version 1.6.20, released October 31, 2023)[2], Bibliometrics, and Python (version 3.11, released October 24, 2022) to generate bibliometric maps illustrating keyword co-occurrence (Figures 2a and 2b), author collaboration networks, and reference co-citation patterns.[14,15] These visualizations crystallized research clusters that encapsulated key themes, emerging trends, and prominent contributors within the field. Integrating outputs from Bibliometrix and VOSviewer afforded a comprehensive view of the discipline's intellectual and collaborative landscape. This integrated approach provided an extensive overview of the field and ensured methodological robustness and visual clarity, facilitating enhanced understanding, dissemination, and practical application of the research outcomes.[7,15,16]

Results and Discussion

Basic statistics

The field of medical *cannabis* research has experienced significant growth, with a total of 2022 documents published between 1972 and 2024. These publications came from 819 different sources, reflecting the increasing interest in this topic. The annual growth rate of publications was 9.2%, indicating a steady increase in research in this field. The average age of the documents was 8.56 years, showing that studies in this area remain relevant and influential over an extended period. On the average, each document receives 44.32 citations, highlighting the importance and impact of the published works. The documents contained 122124 references, illustrating the richness of sources and previous research. Additionally, they were rich in keywords, with 17624 "Keywords Plus" and 4607 author keywords. Medical *cannabis* research involved 8706 researchers, with 206 having published solo-authored documents. Collaboration among authors was notable, with an average of 5.13 co-authors per document and 19.14% of collaborations representing international partnerships. The main types of documents were articles (1290) and reviews (732), reflecting the predominance of original studies and syntheses of existing knowledge.

Intellectual structure

The most prolific researchers in the field of medical *cannabis* research include Vincenzo Di Marzo and Daniele Piomelli, each having

published 11 documents.[17] These researchers have significantly contributed to advancing knowledge about *cannabis* and its therapeutic applications (Figure 3).[17] In terms of the geographical distribution of publications, the United States leads with 12420 documents, followed by the United Kingdom with 2236 documents and Canada with 2062 documents (Figure 4).[18] The main sponsors of medical *cannabis* research include the National Institutes of Health (NIH) in the United States, which support a wide range of research on *cannabis* and cannabinoids, as well as Canadian *cannabis* companies that are heavily involved in research sponsorship (Figure 5).[18,19] The main sources of documents include the journal "Drug and Alcohol Dependence," which published the most articles (705), and the "Journal of *Cannabis* Research," which offers a broad range of articles on *cannabis* (Figure 6). The most active affiliations are the University of California with 14 publications, the National Research Council of Italy with 12 publications, and the NIH with 12 publications. The top ten most cited articles in the field of medical *cannabis* cover various topics, mainly in pharmacology, medicine, neurology, and physiology (Figure 7). Among them, the article "The endocannabinoid system as an emerging target of pharmacotherapy" by Pacher *et al*., published in 2006 in Pharmacological Reviews, was the most cited with 1775 citations. This article explored the endocannabinoid system as a promising target for new pharmacotherapies. Another notable article is "EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision," published by Attal *et al*., which provided important guidelines for the treatment of neuropathic pain.[19] The analysis of authors shows significant multidisciplinary nature of medical *cannabis* research. Contributions came from various fields, including pharmacology, medicine, neurology, physiology, and botany. This diversity reflects the complexity of *cannabis* studies, requiring collaboration among different specialists for a comprehensive understanding (Table 1).[19,20]

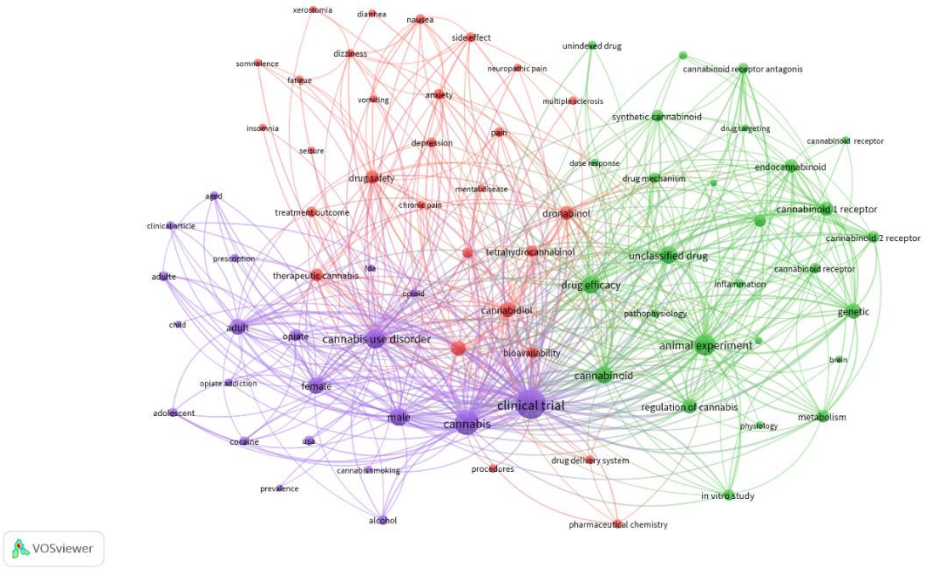

Figure 2a: The network map of author keywords co-occurrence. Each cluster is represented by a color. The size of the node is proportional to the number of occurrences of a keyword. The distance between nodes is proportional to the frequency of keyword co-occurrence.

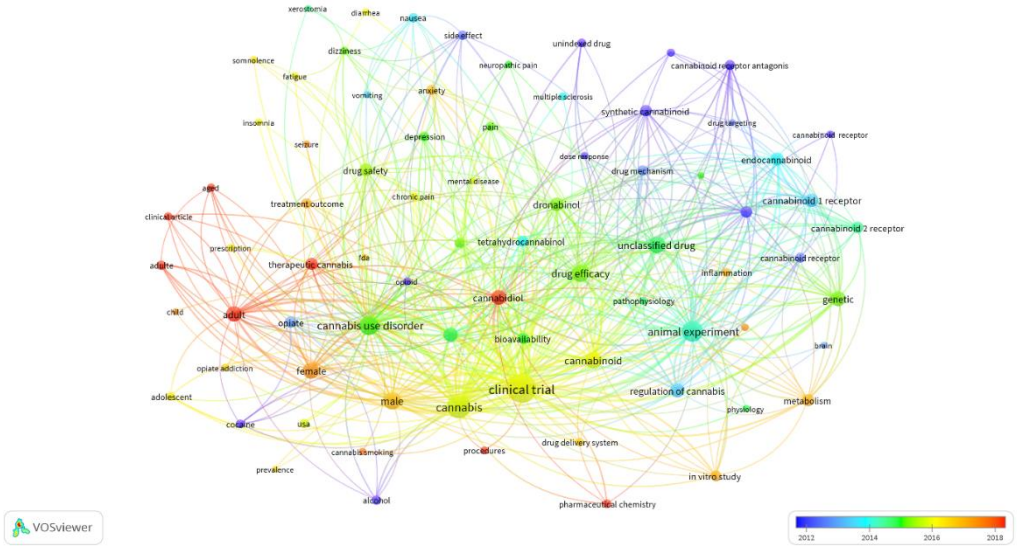

Figure 2b: The network map of author keyword co-occurrence indexed per publication year. The keywords were colored based on the average publication year.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

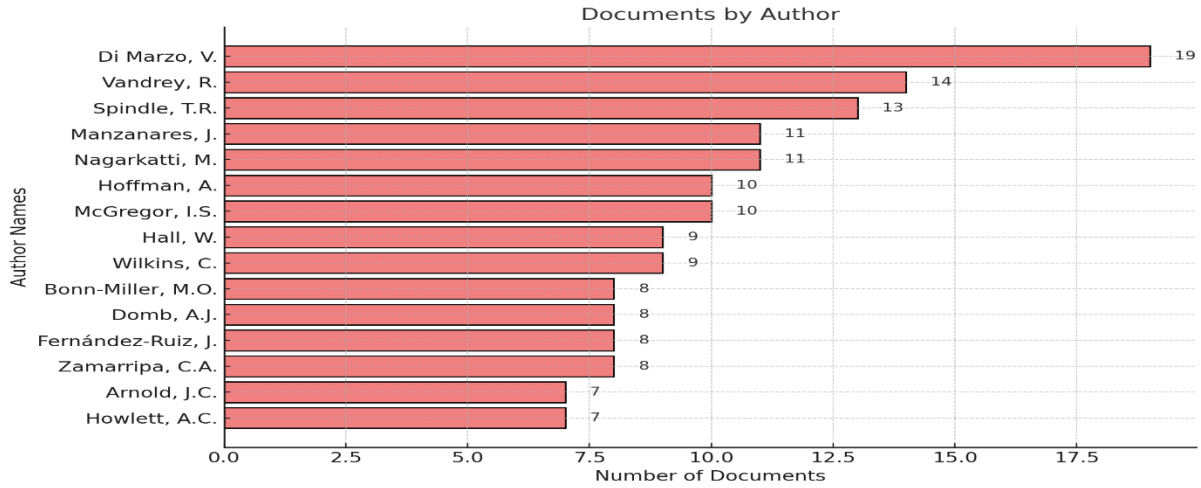

Figure 3: Number of Documents by Researchers

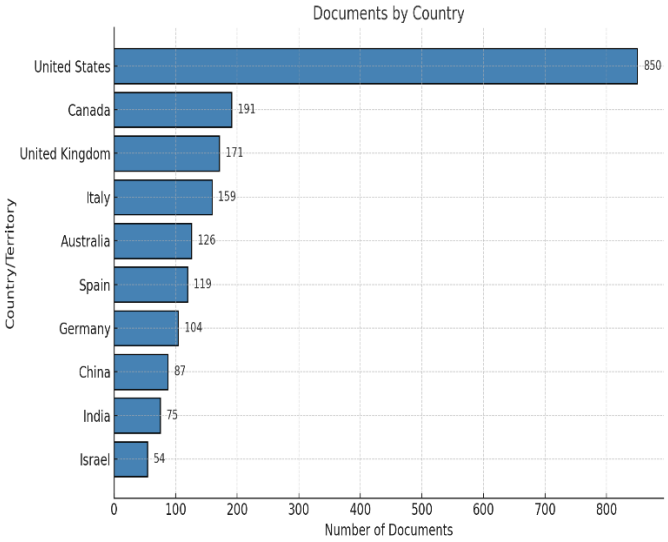

Figure 4: Number of Documents by Country

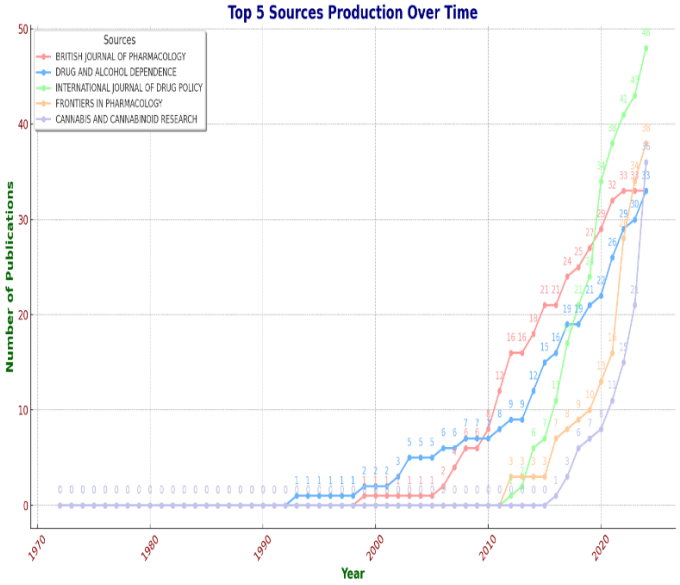

Figure 6: Top 5 Sources production over time

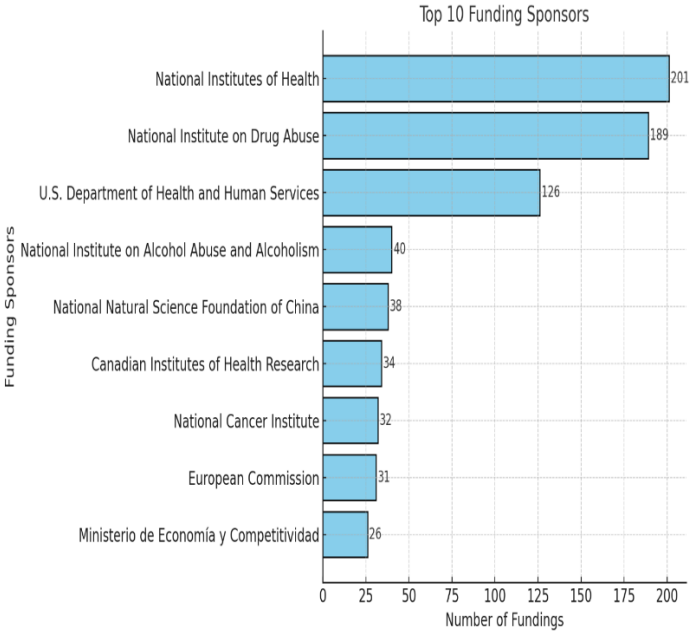

Figure 5: Top 10 Funding Sponsors

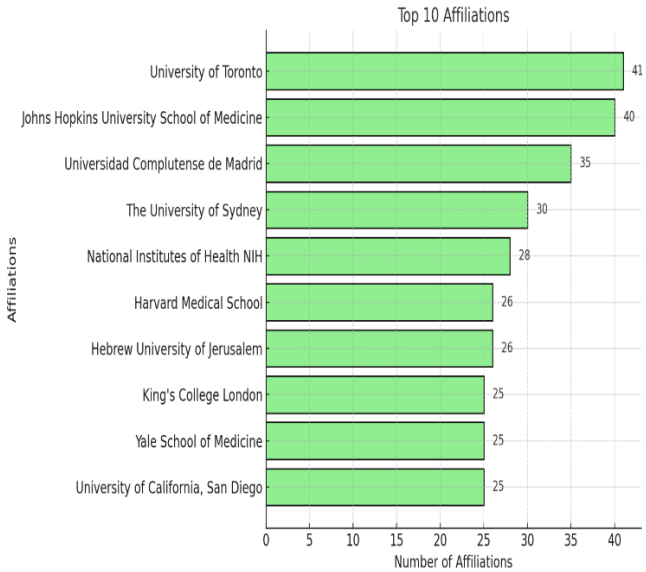

Figure 7: Top 10 Affiliations

Table 1: Top 10 Articles

Authors	Title	Year	Source	Number of Citations
Pacher P.; Bátkai S.; Kunos G.	The endocannabinoid system as an emerging target of pharmacotherapy	2006	Pharmacological Reviews	1775
Attal N.; Cruccu G.; Baron R.; Haanpää M.; Hansson P.; Jensen T.S.; Nurmikko T.	EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision	2010	European Journal of Neurology	1554
Russo E.B.	Taming THC: Potential *cannabis* synergy and phytocannabinoid-terpenoid entourage effects	2011	British Journal of Pharmacology	1141
Constantinescu C.S.; Farooqi N.; O'Brien K.; Gran B. Grotenhermen F.	Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS)	2011	British Journal of Pharmacology	1126
	Pharmacokinetics and pharmacodynamics of cannabinoids	2003	Clinical Pharmacokinetics	1115
Cota D.; Marsicano G.; Tschöp M.; Grübler Y.; Flachskamm C.; Schubert M.; Auer D.; Yassouridis A.; Thöne-Reineke C.; Ortmann S.; Tomassoni F.; Cervino C.; Nisoli E.; Linthorst A.C.E.; Pasquali R.; Lutz B.; Stalla G.K.; Pagotto U.	The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis	2003	Journal of Clinical Investigation	1075
Osei-Hyiaman D.; DePetrillo M.; Pacher P.; Liu J.; Radaeva S.; Bátkai S.; Harvey-White J.; Mackie K.; Offertáler L.; Wang L.; Kunos G.	Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity	2005	Journal of Clinical Investigation	1004
Cahill K.; Stevens S.; Perera R.; Lancaster T.	Pharmacological interventions for smoking cessation: An overview and network meta-analysis	2013	Cochrane Database of Systematic Reviews	982
Lee U.E.; Friedman S.L.	Mechanisms of hepatic fibrogenesis	2011	Best Practice and Research: Clinical Gastroenterology	812
Williamson E.M.	Synergy and other interactions in phytomedicines	2001	Phytomedicine	796

Social structure

Collaborations among researchers are crucial for the development of medical *cannabis* research (Figure 8). They allow different expertise and perspectives to be combined, enriching the quality of studies and fostering innovation.[21,22] For example, researchers in pharmacology, neurology, and clinical medicine can work together to explore the mechanisms of action of cannabinoids and their therapeutic applications.[16,18,21] This multidisciplinary approach is essential for addressing the complexities of *cannabis* effects on the human body and developing effective treatments. International collaborations play a key role in medical *cannabis* research, allowing knowledge and resource sharing on a global scale. Collaborations between the United States, Canada, and the United Kingdom illustrate how supportive policies and research investments can foster innovation (Figure 9).[22] These collaborations also facilitate the standardization of research protocols and regulations, which is crucial for harmonizing approaches and practices internationally.[16,18,20-22]

Conceptual structure and gap analysis

Research on medical *cannabis* focused on several key concepts and identified important gaps that require future studies to optimize the therapeutic use of *cannabis*.

Identified thematic clusters

The identified thematic clusters, represented by distinct colours, revealed the main research directions:

Clinical trials (Blue)

These studies evaluated the effectiveness and safety of medical *cannabis* in humans. Keywords such as "Clinical Trial," "Therapeutic *Cannabis*," and "Treatment Outcome" indicated that this research focused on clinical results and therapeutic applications of *cannabis*.[2] These studies are crucial for establishing solid evidence of the effectiveness of *cannabis* in treating various medical conditions, such as chronic pain, anxiety, and neurological disorders. They also help identify optimal dosages and potential side effects.[23,25]

In vitro and animal studies (Green)

This cluster included experimental studies conducted in laboratories and on animal models to explore the mechanisms of cannabinoids.[2,25] Keywords such as "*In Vitro* Study," "Animal Experiment," and "Neuroprotection" indicate that this research explores the mechanisms of action of cannabinoids and their protective effects on nerve cells.

These studies provided the fundamental information on how cannabinoids interact with biological systems, paving the way for new therapeutic applications. For example, neuroprotection is a particular area of interest for neurodegenerative diseases such as multiple sclerosis and Parkinson's disease.[12,23]

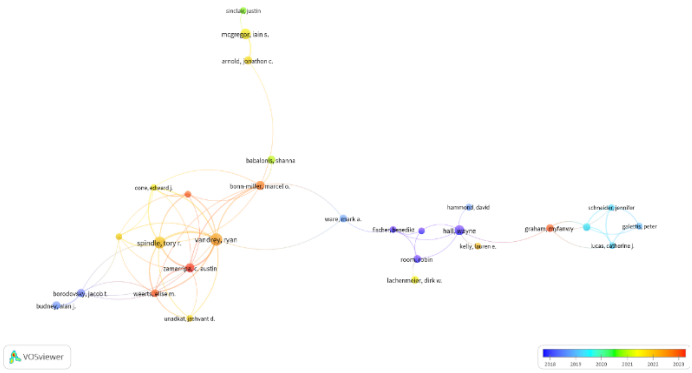

Figure 8: Map of the network of collaborations between individuals

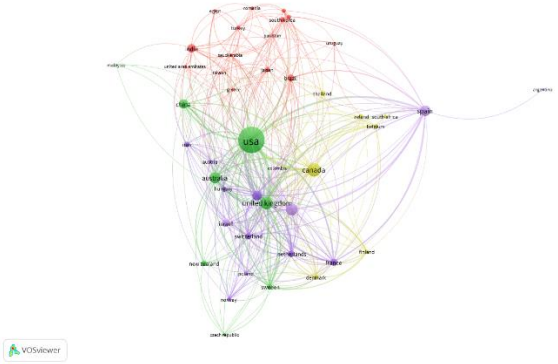

Figure 9: Map of the network of collaborations between countries

Addiction and symptom relief (Red)

This cluster groups researched on the effects of *cannabis* on addiction and symptom relief, such as anxiety and pain. Keywords such as "*Cannabis* Use Disorder," "Anxiety," and "Pain" showed that these studies focused on disorders related to *cannabis* use and the potential therapeutic effects of *cannabis* on specific symptoms. This research is essential for understanding how *cannabis* can be used to treat mood disorders, chronic pain, and other conditions while minimizing the risks of abuse and dependency.[25-27]

Pharmaceutical industry (Dark Yellow)

This cluster included studies on the development of *cannabis*-based drug formulations. Keywords such as "Drug Formulation," "Bioavailability," "Drug Delivery," "Cannabidiol," "*In Vitro* Studies," "Procedure (Process)," and "Pharmaceutical Chemistry" indicate that this research focused on creating effective, safe, and stable cannabinoid formulations for medical use.[28] Emerging trends in this cluster included terms such as "*Cannabis* Therapeutic," "Adult Ages," "Female Male," "Cannabidiol," "Pharmaceutical Chemistry," "*In Vitro* Studies," "Drug Delivery," "Inflammation," "Metabolism," "Seizure," and "Anxiety." These studies are crucial for transforming scientific discoveries into marketable pharmaceutical products and ensuring patients receive high-quality medications.[17,24,28]

The industrial aspect of therapeutic *cannabis* involves critical elements of drug formulation, drug delivery systems (DDS), and product stability. Drug formulation includes the development of specific cannabinoid formulations to optimize delivery and treatment efficacy, covering oral, transdermal, inhaled, and injectable forms.[26,27] Each administration method was designed to maximize cannabinoid absorption and bioavailability, ensuring optimal therapeutic efficacy. DDS technologies play a vital role in cannabinoid administration.[28] Modern DDS innovations include nanoparticles, controlled release systems, and implantable devices, which allow for more targeted and efficient cannabinoid delivery, enhancing therapeutic outcomes for patients. Product stability was another priority, involving stability studies to ensure therapeutic *cannabis* formulations maintain their efficacy and safety throughout their shelf life.[26,29] This included testing under various storage conditions, such as temperature, humidity, and light, to ensure products remain stable and effective until expiration. These three clusters illustrated a multidimensional approach to therapeutic *cannabis* research. Clinical trials provided evidence on human treatment efficacy and safety, while *in vitro* and animal studies help understand mechanisms of action and assess safety before clinical trials. Additionally, research on the pathophysiology of *cannabis* addiction and its symptom-relieving effects helps optimize treatments and minimize risks. The pharmaceutical industry's role was crucial in developing effective and safe formulations, and implementing innovative delivery systems to maximize the therapeutic benefits of *cannabis*. This integrated and regulated approach ensured the quality, safety, and efficacy of *cannabis*-based products in the market.[28,29]

Gap analysis

Underrepresentation of clinical studies

While preclinical and observational studies are abundant, there is a lack of large randomized controlled clinical trials to validate the therapeutic applications of *cannabis*. Further research is needed to establish solid evidence of the efficacy and safety of cannabinoids for various medical conditions.[12,30]

Lack of longitudinal data

Most current studies focused on the short-term effects of medical *cannabis*, leaving a gap in understanding the long-term effects. Longitudinal studies are crucial to assess the long-term consequences of therapeutic *cannabis* use, including potential risks of dependency and other adverse effects.

Drug-Cannabis interactions

Interactions between *cannabis* and other medications are still under-studied, limiting our understanding of the risks and benefits of concomitant use of cannabinoids and other pharmacological treatments. Additional research on drug-*cannabis* interactions is needed to ensure the safety of patients using combined treatments.[17,24]

Future directions

Rigorous clinical studies

It is essential to increase the number and quality of randomized controlled clinical trials to provide solid evidence for the efficacy and safety of therapeutic *cannabis* applications. Establishing standardized and rigorous research protocols will help obtain comparable and reliable results.[25,30]

Interdisciplinary research

Promoting collaboration among researchers from different fields, such as pharmacology, neurology, clinical medicine, and physiology, is crucial for addressing the complexities of *cannabis* effects. Interdisciplinary approaches will integrate various perspectives and develop more comprehensive therapeutic solutions.[18,25,30]

Supportive policies

Strengthening investments and policies supporting research on medical *cannabis* is necessary to encourage innovation and advance knowledge in this field. Governments and research institutions must create a supportive environment that facilitates international collaboration and knowledge exchange.[12,17,24]

Conclusion

The analysis highlights significant contributions by key researchers and institutions to the field of *cannabis* research. Leading figures like Vincenzo Di Marzo and Daniele Piomelli have been pivotal in advancing knowledge, supported by institutions such as the University of California and the National Research Council in Italy. The United States leads research output, with collaborations with Canadian *cannabis* companies enhancing its position. Key publication sources, including "Drug and Alcohol Dependence" and the "Journal of *Cannabis* Research," facilitated knowledge dissemination. The study revealed an upward trend in *cannabis* research publications from 2010 onwards, indicating growing interest and investment in this field. Collaborative networks among countries and institutions are crucial, combining diverse expertise and perspectives to advance therapeutic applications of *cannabis*. The bibliometric analysis underscores the importance of establishing rigorous research standards, exploring new therapeutic applications, and evaluating the long-term and societal impacts of *cannabis* use. Continued collaboration among researchers, regulators, and clinicians is essential to translate scientific advances into tangible patient benefits. Future research should focus on multidisciplinary studies and international regulatory harmonization to enhance the effectiveness and comparability of *cannabis* research.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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