



Exploring the Therapeutic Potential of Cannabidiol in Children with Cerebral Palsy: An Integrative Review

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Abstract

Introduction

The first clinical trials involving cannabidiol in humans were documented in the 1970s. However, it was in the 1990s that the discovery of an endogenous cannabinoid signaling system sparked interest in the therapeutic potential of cannabis for treating nervous system disorders, including epilepsy.

Objective

To identify scientific evidence regarding the use of cannabidiol in children with cerebral palsy.

Methods

This study presents an integrative review using the PubMed, Scopus, ScienceDirect, and Embase databases in April 2024. The search descriptors included “Cannabidiol,” “Cerebral Palsy,” and “Child.” Nine articles that met the inclusion and exclusion criteria were included.

Results

The findings highlight the therapeutic potential of cannabinoids in cerebral palsy, focusing on knowledge, safety, and challenges in prescribing these substances. Additionally, research, regulation, and education emerged as key elements for understanding and properly implementing this treatment.

Conclusion

Medicinal cannabinoids show promise in treating children with cerebral palsy, particularly in managing spasticity, pain, and seizures. Further research is needed to define their exact role, but early results suggest that cannabinoids could be a safe and effective therapeutic option, especially for severe cases.

Keywords

Cannabidiol; Cerebral Palsy; Child.

Introduction

The efficacy of cannabis in treating epilepsy was first reported in 1800 B.C. Early clinical trials with cannabidiol (CBD) in humans were documented in the 1970s, but it was during the 1990s, following the discovery of an endogenous cannabinoid signaling system, that interest grew in the therapeutic potential of cannabis for treating nervous system disorders, including epilepsy.¹

Mechoulam and Shvo (1963) first described two compounds, the psychoactive delta-9-tetrahydrocannabinol (THC) and the non-psychoactive CBD. Studies have shown that both THC and CBD exhibit anticonvulsant properties in models involving *in vitro* experiments and animals. However, most research indicates that CBD is more effective in reducing epileptic activity compared to THC, which has a higher potential to cause cognitive impairment and chronic psychiatric disorders. Other beneficial properties of CBD include neuroprotective, anti-inflammatory, and antioxidant effects.²

Despite the illegal status of cannabis in many countries, recent evidence suggests its potential efficacy in treating epilepsy, mainly in refractory patients.^{1,2}

Cerebral palsy (CP) is a non-progressive disorder of posture and movement resulting from a non-progressive malformation or lesion in the brain, leading to a range of comorbidities in children, including epilepsy, intellectual disability, behavioral, musculoskeletal, and nutritional issues, sleep problems, and pain.³

Epilepsy is considered one of the most common comorbidities, with a global prevalence of approximately 50 million people.⁴ Although numerous antiepileptic drugs have been approved over the last two decades, there remains a need for more options, as one-third of epileptic patients suffer from drug-resistant epilepsy.⁵

In the past decade, several countries and institutions have shown great interest in investigating the role of CBD and its efficacy in treating pediatric epilepsy⁶, particularly when associated with CP. As a result, the U.S. Food and Drug Administration (FDA) approved its use in 2018 for treating seizures in children who meet the established criteria.⁷

CBD was the first FDA-approved drug containing a purified substance derived from cannabis and the first authorized to treat patients with Dravet syndrome. However, the medical prescription of CBD remains controversial. While some members of the medical community support its use and present it as a treatment option, others remain hesitant to prescribe and recommend the drug.⁶

The history of the therapeutic use of cannabis, particularly CBD, in treating epilepsy reveals a trajectory of significant discoveries and advancements over the centuries. Nonetheless, the ongoing controversy surrounding its use underscores the need for continued research, discussion, and guidance to ensure the safe utilization of this drug. Therefore, given the importance of this topic, this study aims to identify scientific evidence on the use of cannabidiol in children with cerebral palsy.

Methods

This study is an integrative review aimed at synthesizing existing knowledge, identifying research gaps, and proposing new studies. The process was systematic and rigorous, without applying time restrictions to include as many relevant articles as possible on the

subject.

We followed six key stages: 1) identification of the topic and the guiding research question, 2) establishment of inclusion and exclusion criteria, 3) definition of the information to be extracted from the selected studies and their characterization, 4) evaluation of the included studies, 5) interpretation of the results, and 6) presentation of the review and synthesis of knowledge.⁸

Initially, we formulated the guiding question using the PICO strategy: P (Population): children; I (Interest): use of CBD; and Co (Context): cerebral palsy. Consequently, we adopted the research question: What is the scientific evidence on the use of CBD in children with cerebral palsy?

Next, we established the inclusion criteria, which comprised original articles published in Portuguese and English, without any time limits, and related to the guiding research question. As for exclusion criteria, we excluded grey literature (theses, dissertations, monographs, books, book chapters, congress abstracts, proceedings, programs, and government reports), opinion articles, letters to the editor, brief communications, editorials, and integrative reviews.

The data collection took place in April 2024 using electronic databases: PubMed Central (PMC), Scopus (Elsevier), Embase, and ScienceDirect. We applied Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH) in Portuguese and their English equivalents: "Cannabidiol/Cannabidiol," "Paralisia Cerebral/Cerebral Palsy," and "Criança/Child."

The search strategies were adapted to each database based on the PICO strategy and its keywords and entry terms. We applied the OR boolean operator to distinguish terms and AND to associate them, resulting in the following search expression: (((("cannabidiol"[MeSH Terms] OR "cannabidiol"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields])) AND ("cerebral palsy"[MeSH Terms] OR "cerebral"[All Fields] AND "palsy"[All Fields]) OR "cerebral palsy"[All Fields])) AND ("epilepsy"[MeSH Terms] OR "epilepsy"[All Fields])).

Once we retrieved the publications, we organized the studies using Microsoft Excel® to identify and exclude duplicates, counting repeated studies only once. We reviewed the titles and abstracts to include studies closely related to the research topic, followed by a full-text reading to confirm their eligibility. We included studies that fully addressed the research question, resulting in a final sample of nine scientific articles.

The information from the articles was organized into a table containing data on the title, year of publication and country, objectives, outcomes, and level of evidence (Table 1). We assessed the level of evidence following the hierarchical classification of Melnyk and Fineout Overholt¹⁰, which classifies evidence into seven levels. I: evidence from systematic reviews, meta-analyses, or clinical guidelines based on systematic reviews of randomized controlled trials (RCTs); II: evidence from at least one RCT; III: evidence from well-designed controlled trials without randomization; IV: evidence from well-designed cohort and case-control studies; V: evidence from systematic reviews of descriptive and qualitative studies; VI: evidence from a single descriptive or qualitative study; and VII: evidence from expert opinions or expert committee reports. We grouped the studies into three categories according to their characteristics.

Ethical approval was waived, as this was a review of publicly available data without human involvement.

Results

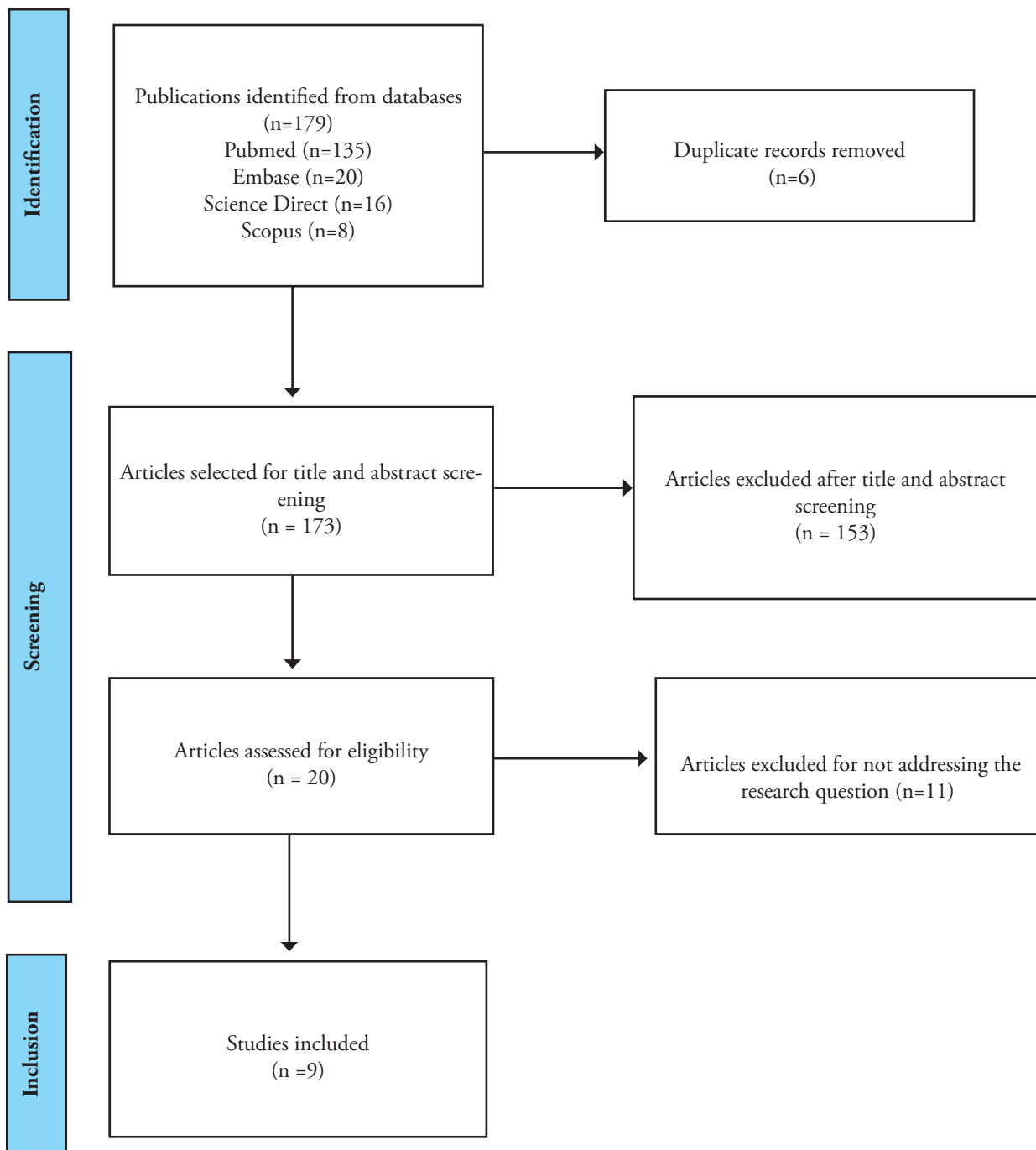
We used a flowchart adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹¹ to present the search and selection stages of the articles. Figure 1 outlines the process of identifying, screening, determining eligibility, and including the studies according to the databases consulted. Initially, we identified 35 publications, of which 20 met the eligibility criteria. However, only nine were included in the final sample.

Regarding the publication timeframe, the articles were published between 2019 and 2024. Most of the selected studies were published in 2023 (three), followed by two in 2022, and one each in 2019, 2020, 2021, and 2024. All the articles were written in English. As for geographic origin, the studies were conducted in Canada (n=3), Switzerland (n=2), Germany (n=2), South Korea, and Argentina, each with one study.

Figure 1. Flowchart illustrating the study selection process included in the integrative review. Brazil, 2024.

In terms of evidence level, the sample included one study with level I evidence, two studies with level II evidence, one study with level IV evidence, and five studies with level VI evidence. Based on the analyzed articles, the sample from this review is summarized in the synoptic table (Table 1).

Table 1. Characterization of the articles by authors, year, country of publication, objectives, outcomes, and level of evidence. Brazil, 2024.



Source: Page et al.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

Study	Year and country	Objective/Type of study	Outcome	Level of evidence
A1) Purified cannabidiol as add-on therapy in children with treatment-resistant infantile epileptic spasms syndrome ¹²	2024 Argentina	Evaluate the highly purified CBD oil as an add-on therapy for patients with epileptic spasm syndrome. Case-control study	In addition to improvements in spasms, the study observed benefits in communication, behavior, and sleep. Researchers suggest that CBD may serve as an effective and safe therapeutic option, particularly for patients with Down syndrome and cerebral palsy.	IV
A2) Prescription Practices of Medical Cannabinoids in Children with Cerebral Palsy - A Survey of the Swiss Cerebral Palsy Registry ¹³	2023 Switzerland	Evaluate cannabinoid prescription practices in children with cerebral palsy. Cross-sectional study	Physicians primarily prescribe CBD for epilepsy, spasticity, and pain, showing moderate efficacy with side effects such as drowsiness and fatigue. Further research, including randomized clinical trials, must explore additional potential indications.	VI
A3) Characteristics of Epilepsy in Children with Cerebral Palsy: A Single Tertiary Center Study ¹⁴	2023 South Korea	Describe the characteristics of epilepsy in patients with cerebral palsy (CP). Retrospective descriptive study	The main indications for treatment included epilepsy, spasticity, pain, behavioral issues, sleep disturbances, and dystonia. The study emphasizes the need for more clinical trials to establish appropriate indications.	VI
A4) Use and caregiver reported efficacy of medical cannabis in children and adolescents in Switzerland ¹⁵	2021 Switzerland	Examine the clinical and epidemiological characteristics of medical cannabis treatment. Retrospective descriptive study	Products containing THC were shown to reduce pain and seizures, while CBD products lowered the frequency of seizures. More treatment guidelines and clinical trials are required to assess the long-term efficacy of medicinal cannabis in young patients.	VI
A5) Medical cannabinoids: a pharmacology-based systematic review and meta-analysis for all relevant medical indications ¹⁶	2022 Germany	Evaluate the efficacy, retention, and adverse events across various medical conditions. Systematic review and meta-analysis	Cannabinoids have demonstrated positive benefits for various medical conditions, such as epilepsy, chronic pain, and Parkinson's disease. High quality evidence supports their use in treating chronic pain and spasticity in multiple sclerosis patients.	I
A6) Characterizing the Use of Nabiximols (Δ^9 -Tetrahydrocannabinol-Cannabidiol) Buccal Spray in Pediatric Patients ¹⁷	2023 Canada	Describe the use of nabiximols in hospitalized children. Clinical trial	The study concluded that Nabiximols was prescribed to children across all age groups, mainly for pain and nausea/vomiting, underscoring the need for further research, especially prospective randomized clinical trials.	II
A7) Dosage Related Efficacy and Tolerability of Cannabidiol in Children With Treatment-Resistant Epileptic Encephalopathy: Preliminary Results of the CARE-E Study ¹⁸	2019 Canada	Evaluate the efficacy and tolerability of Cannabidiol (CBD) dosing in children with treatment-resistant epileptic encephalopathy. Clinical trial	Regarding effectiveness, all seven participants experienced improvements in seizure frequency, scores on the Modified Quality of Life in Childhood Epilepsy Questionnaire (QOLCE), and electroencephalogram (EEG) scores, with three participants becoming seizure-free.	II
A8) Clinician views on and ethics priorities for authorizing medical cannabis in the care of children and youth in Canada: a qualitative study ¹⁹	2022 Canada	Outline clinicians' perspectives, ethical priorities, and values regarding the authorization of medical cannabis. Qualitative study	Participants, representing various clinical specialties and experiences, highlighted the importance of regulatory reforms and additional research to enhance care for pediatric patients who might benefit from cannabis-based products.	VI
A9) A Survey on Cannabinoid Treatment of Pediatric Epilepsy Among Neuropediatricians in Scandinavia and Germany ²⁰	2020 Germany/Scandinavia	Understand attitudes toward the use of cannabinoids in pediatric epilepsy treatment among pediatric neurologists in Scandinavia and Germany. Qualitative study	The study underscores the need for careful monitoring of interactions with other antiepileptic medications when prescribing CBD therapy. With the likely availability of an approved CBD product and recent clinical trial results, it is expected that the approach to CBD-based therapy for pediatric refractory epilepsy will evolve in the future.	VI

We created a table that groups the articles based on the similarity of their content within each section (Table 2).

Table 2 - Categorization of selected articles based on content similarity

Categories	Articles
The therapeutic potential of cannabinoids in cerebral palsy	A2, A4, A5
Knowledge on the use and prescription of medicinal cannabinoids	A6, A8, A9
Research and regulation on the therapeutic use of cannabinoids in the treatment of epilepsy	A1, A3, A7

Based on the analysis, we categorized the studies into three main themes: the therapeutic potential of CBD, knowledge regarding the use and prescription of CBD, and research and regulation in the therapeutic use of CBD. We discussed the findings in relation to the scientific literature, which we will address in the following section.

Discussion

In this section, we will address topics related to the therapeutic potential of cannabinoids in cerebral palsy, epilepsy, and medicinal use. We will discuss aspects such as knowledge, safety, and challenges in prescribing cannabinoids, as well as research, regulation, and education as key points for understanding and adequately implementing this treatment.

The therapeutic potential of cannabinoids in cerebral palsy Literature has described a wide range of therapeutic approaches and medications for managing symptoms in patients with cerebral palsy (CP). Medications are often prescribed to manage epilepsy and movement disorders associated with this condition.²¹ In addition to conventional drugs, cannabinoids have been increasingly used in various clinical settings, particularly in pediatrics.¹³ Epilepsy is among the top three indications for the use of cannabinoids in children with CP, given the promising results observed in treating specific forms of childhood epilepsy.²² Spasticity is the second most common condition treated with cannabinoids, followed by pain, which is frequently reported as a symptom as well.¹³ Beyond seizure control, which is the primary criterion for CBD use, evidence from parental reports highlights improvements in sleep and behavior, which are also significant in enhancing the quality of life for these children.^{22, 23, 24}

This perspective is supported by a study conducted with caregivers in California (USA), which concluded that CBD could be a beneficial adjunct for children with CP, particularly for those with more severe symptoms. Caregivers reported significant improvements in emotional health, spasticity, and pain, reinforcing the perception of CBD's efficacy.^{15, 16, 25}

Additionally, children with complex movement disorders, which encompass various neurological conditions, may also benefit from cannabinoid treatment. These disorders are often associated with severe orthopedic complications, chronic pain, feeding difficulties,

constipation, and sleep disturbances, further justifying additional investigations into the efficacy of medicinal cannabinoids.²⁶ CBD appears to act synergistically, enhancing THC's beneficial effects by reducing its psychoactivity, allowing patients to tolerate higher doses and complement the antispasmodic effects of THC.²⁷ The mechanisms of action of cannabinoids in CP include antispasmodic, anti-inflammatory, and anticonvulsant properties. Although mild to moderate adverse effects have been reported, no long-term side effects were identified, suggesting a favorable safety profile.²⁸

However, more research must be conducted, including larger and more diverse samples, along with longer follow-up periods, to accurately elucidate the role of cannabinoids in CP.^{28, 29}

Despite these needs, the data available so far suggest that cannabinoids may represent an effective and safe therapeutic alternative for children with CP, especially those facing more severe forms of the disease. Continuing studies is essential to solidify these findings and expand treatment options for this population.

Knowledge of the use and prescription of medicinal cannabinoids

The increasing acceptance and use of medicinal cannabinoids as therapeutic alternatives for various medical conditions have sparked significant debate regarding the safety, efficacy, and regulation of these substances.¹⁹⁻²⁰ The U.S. Food and Drug Administration (FDA) has approved a highly purified oral CBD solution specifically for treating seizures associated with certain epileptic syndromes in patients aged two years and older.³⁰

A long-term study involving 607 patients with refractory epilepsy administered doses ranging from 2 to 10 mg/kg/day, gradually increasing to a limit of 25 to 50 mg/kg/day.³¹ Results showed that 52% of the patients experienced at least a 50% reduction in seizure frequency after 12 weeks, and this rate remained stable over 96 weeks. The most frequently reported adverse effects were diarrhea and drowsiness, but most patients (76%) reported improvements in their quality of life, suggesting that the benefits of the treatment may outweigh the inconveniences.³²⁻³³

However, a study conducted in Australia with psychiatrists and psychiatry residents revealed that more than half of the participants still had difficulty distinguishing between the therapeutic indications of CBD and THC, highlighting knowledge gaps that could affect clinical practice.³⁴

CBD is particularly recommended for childhood epileptic syndromes such as Dravet and Lennox-Gastaut, as well as for psychiatric conditions in adults, with doses ranging from 200 to 800 mg/day, divided into two or three administrations. The main side effects include hypersensitivity, elevated liver transaminases, drowsiness, and, in rare cases, suicidal thoughts and an increased risk of seizures with abrupt discontinuation.³³

On the other hand, THC is indicated for treating chemotherapy-induced nausea and vomiting, chronic pain, anorexia and weight loss associated with human immunodeficiency virus (HIV), neuropathic pain, and muscle spasticity in multiple sclerosis, with doses typically ranging from 10 to 30 mg/day, divided into two or three doses. THC's side effects are more varied and can include drowsiness, dry mouth, and, in rare cases, hallucinations and dependence.³³ This variability in side effect profiles highlights the importance of selecting the appropriate substance and dosage for

each patient.

A European study identified that among physicians treating epilepsy in children and adolescents, only 48% prescribed pure CBD, indicating that many professionals still use preparations containing THC. When CBD was prescribed, dosages ranged from less than 10 mg/kg to as much as 50 mg/kg per day, with 20 mg/kg showing efficacy in clinical trials, although some patients may require higher doses. The safety of higher doses is supported by the lack of conclusive data establishing a maximum safe limit.³⁰

Another study that analyzed the use of CBD-enriched cannabis oil in patients with West Syndrome showed promising results, with a significant reduction in seizure frequency in several patients aged 16 to 22 months. The initial dose was 2 mg/kg/day, increased to an average of 12 mg/kg/day. Some patients also showed improvements in electroencephalogram (EEG) results. The observed side effects were mild and temporary, with no increase in liver enzymes, indicating a favorable safety profile.³⁴

Additionally, researchers in Israel investigated the use of CBD-enriched cannabis oil extract in patients with drug resistant epilepsy, with more than half of the participants experiencing a greater than 50% reduction in seizures, supporting the efficacy of the treatment. However, 46% of the patients reported adverse reactions, which was a primary reason for discontinuation.¹

Moreover, a cannabinoid oral spray containing THC and CBD has been used in adults for conditions related to cancer pain and spasticity. However, using this spray in children presents challenges, especially regarding documentation and measurement of efficacy, emphasizing the need for clearer protocols and more robust investigations.¹⁷

In summary, as medicinal cannabinoid treatment options expand, the reviewed studies provide valuable contributions regarding their indications and efficacy. Differentiating between CBD and THC, understanding their associated side effects, and ensuring adequate training for healthcare professionals are crucial factors to consider in cannabinoid therapy.

Research and regulation of cannabinoid use in epilepsy treatment

The increasing popularity of CBD as a therapeutic alternative makes it essential for its use to be backed by solid scientific evidence. Enhanced research can expand our understanding of the effects, benefits, and potential risks associated with cannabidiol, promoting its acceptance and safe use in clinical practice.

Cannabinoids such as THC and CBD interact with CB1 and CB2 receptors in the endocannabinoid system. While THC acts as a partial agonist at these receptors and produces psychotropic effects, CBD demonstrates low affinity, suggesting that its antiepileptic activity is not directly linked to the endocannabinoid system. This highlights the importance of continuing to investigate CBD's therapeutic properties.³⁵

Studies suggest the "entourage effect," which refers to the synergistic action of multiple components of the cannabis plant, may lead to greater efficacy than isolated use of CBD or THC, enhancing tolerance and the therapeutic potential of cannabinoids.³⁵ Moreover, research shows that THC has anticonvulsant effects in 61% of cases examined but also pro-convulsant potential in a small percentage of studies conducted across six animal species.³⁵ In contrast, CBD and cannabidivarin exhibited anticonvulsant properties in 80.5%

of evaluations without displaying pro-convulsant effects.³⁶

These findings have fueled the use of pure CBD and CBD enriched cannabis extracts in treating epilepsy in humans, though reports on efficacy and side effects vary, requiring careful analysis to fully understand these outcomes.³⁶

Studies have demonstrated significant benefits in seizure control, showing reductions in seizure frequency, along with improvements in sleep, alertness, and mood when treated with CBD-rich cannabis extracts. However, a key limitation of these studies lies in the diversity of epilepsy types analyzed and variations in chemical compositions, dosages, administration methods, and manufacturing processes.^{12,14,18,24} This creates inconsistency in the quality and reliability of available products, especially homemade ones, which often lack strict quality controls. Reports of products containing little to no CBD or quantities far below those claimed underscore the need for adherence to regulatory standards.³⁷

Examples of products meeting strict standards exist, such as the cannabis extract marketed in Israel, which offers CBD to-THC ratios of 2:1, 5:1, and 20:1, with the latter being the most common. This extract has shown efficacy in controlling seizures in refractory patients.² Most patients treated with this extract experienced significant reductions in seizure frequency, along with improvements in behavior, alertness, motor skills, and sleep.

Although the available evidence is promising, the efficacy and safety of CBD-enriched cannabis extracts still need confirmation through controlled clinical trials. Nevertheless, substantial data support the use of pure CBD in managing refractory epilepsy, especially in conditions like Dravet syndrome and Lennox-Gastaut syndrome.³⁸ Despite existing gaps, cannabinoids are emerging as a viable and promising alternative for treating refractory epilepsies.

Therefore, cannabinoids prove therapeutically effective for various medical conditions, provided their pharmacological specificities are considered. Conducting research and implementing regulations are essential to ensure the quality and safety of cannabis-based products in the treatment of refractory epilepsy. The use of standardized products and the execution of controlled clinical trials are crucial to validate the efficacy of cannabis extracts containing CBD.

Conclusion

We found that the use of medicinal cannabinoids for treating children with cerebral palsy (CP) shows promising results, particularly in controlling spasticity, pain, and seizures. Despite significant improvements in patients' quality of life and the relatively low incidence of adverse events, further research is necessary to define the precise role of cannabinoids in managing CP. However, current findings suggest that cannabinoids may offer an effective and safe therapeutic option, especially for children with more severe forms of the condition.

As the prescription of medicinal cannabinoids continues to raise both interest and uncertainty, the reviewed studies provide essential insights into their usage and efficacy. Understanding the differences between CBD and THC, their respective indications, and side effects are critical factors to consider when opting for this treatment approach.

Cannabinoids have therapeutic efficacy for various medical conditions, provided their specific pharmacological properties are carefully considered. Continued research and regulatory frameworks

are crucial to ensuring the quality and safety of cannabis-based products in the treatment of refractory epilepsy. Standardized products and controlled clinical trials are vital to validating the efficacy of cannabis extracts containing CBD. Furthermore, educating healthcare professionals about cannabis is key to reducing stigma and fostering informed decision-making.

One limitation of this study is its language selection, focusing only on English and Portuguese, which may have excluded relevant research published in other languages and underrepresented Latin American contexts. The absence of databases such as LILACS and SciELO restricts the generalizability of these findings. Nevertheless, this study stands out by offering valuable insights into academic production in the chosen languages, thus contributing to advancing knowledge in the field.

The practical implications of this research on the use of cannabinoids, particularly CBD, in managing symptoms in patients with CP and other medical conditions are significant. The study highlights an expansion of therapeutic options, presenting CBD as an effective and safe alternative for treating symptoms like epilepsy, spasticity, and pain, thereby enriching healthcare professionals' strategies. Additionally, the possibility of personalized treatment is reinforced as improvements are seen in seizure control and patients' overall quality of life.

Education and training for healthcare professionals are essential, given the need to bridge knowledge gaps regarding CBD's therapeutic indications. Moreover, comprehensive studies are crucial to generating robust evidence that justifies incorporating cannabinoids into clinical practice, especially considering the potential side effects that require close monitoring.

Finally, implementing an interdisciplinary treatment approach and properly regulating available products are crucial for ensuring the safety of cannabinoids in clinical settings. In this regard, promoting open dialogue between healthcare professionals, patients, and caregivers is vital for making well-informed, evidence-based decisions.

Authorship and contributions

Harmuch, Camila: Conception and design of the study; Data collection; Data analysis and interpretation; Statistical analysis; Manuscript writing;

Devechi, Anny CR: Conception and design of the study; Data collection; Data analysis and interpretation; Statistical analysis; Manuscript writing;

Barbosa, Cecily: Conception and design of the study; Data collection; Data analysis and interpretation; Statistical analysis; Manuscript writing;

Lima, Ana LS: Conception and design of the study; Data collection; Data analysis and interpretation; Statistical analysis; Manuscript writing;

Pini, Jéssica S: Critical revision of the manuscript; Approve the final manuscript and assumption of responsibility.

Jaques, André E: Critical revision of the manuscript; Approve the final manuscript and assumption of responsibility.

Paiano, Marcelle: Critical revision of the manuscript; Approve the final manuscript and assumption of responsibility.

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