

# Therapeutic Potential and Challenges of *Cannabis sativa* in Neurological Disorders: Pathways to Integration into Health Systems

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## ABSTRACT

*Cannabis sativa* L., commonly known as marijuana, has historically been used for medicinal and recreational purposes. Recent studies highlight its therapeutic potential for various neurological conditions, such as epilepsy, multiple sclerosis, and Parkinson's disease. The main bioactive components,  $\Delta^9$ -tetrahydrocannabinol (THC) and cannabidiol (CBD), have distinct therapeutic properties: THC is known for its psychoactive and analgesic effects, while CBD, which is non-psychoactive, displays anti-inflammatory, anxiolytic, and anticonvulsant effects. In Brazil, research on the medicinal effects of *Cannabis sativa* has intensified with significant initiatives from renowned researchers. This article reviews the existing literature on the pharmacological properties of phytocannabinoids, advances in pre-clinical and clinical research, and prospects for the regulation and implementation of these treatments in the Brazilian Unified Health System (SUS). The inclusion of *Cannabis* in the SUS presents regulatory and production challenges but has significant potential to benefit many patients, effectively and safely meeting their health needs.

**Keywords:** Phytocannabinoids, convulsive states in children, CBD, nervous system disorders, SUS, Brazil.

## INTRODUCTION

*Cannabis sativa* L., popularly known as marijuana, has been used by various cultures over the centuries, both for recreational and medicinal purposes. In recent years, a renewed interest in the therapeutic properties of this plant has driven a series of scientific researches that seek to understand and validate its medicinal effects. Studies have highlighted the potential of *C. sativa* in the treatment of various neurological conditions, including epilepsy, multiple sclerosis, and Parkinson's disease (Cassano et al. 2020; Kumar et al. 2021).

The main bioactive constituents of *C. sativa* are phytocannabinoids, including  $\Delta^9$ -tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is known for its psychoactive effects, but it

also has analgesic and antiemetic properties that may be beneficial in managing pain and nausea. CBD, on the other hand, is non-psychoactive and has demonstrated a wide range of therapeutic properties, including anti-inflammatory, anxiolytic, and anticonvulsant effects, making it a crucial component in the treatment of conditions such as refractory epilepsy and anxiety (Sholler et al. 2020; Bhunia et al. 2022).

In Brazil, research on *C. sativa* and its derivatives has intensified in recent decades, with pioneering studies conducted by research groups at renowned medical institutions and universities, such as the Paulista School of Medicine and the University of São Paulo in Ribeirão Preto, Brazil. These initiatives have contributed significantly to

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the understanding of cannabinoid mechanisms, particularly regarding cannabidiol (CBD). Recent studies by researchers in Brazil have shown that CBD interacts with neuroreceptors, including CB1 and CB2, and influences neurotransmitter activity through serotonergic and TRPV1 pathways, offering potential therapeutic effects for conditions such as epilepsy, schizophrenia, and Parkinson's disease (Crippa et al. 2018; Campos et al. 2020).

Despite advances in research and regulation, the inclusion of *Cannabis sativa* in the Unified Health System (SUS) in Brazil continues to face significant challenges, particularly in terms of regulation, production, and distribution of medicinal products. Bill No. 399/2015, currently under review in the Chamber of Deputies, addresses these issues by proposing the regulation of the cultivation, production, and commercialization of *Cannabis*-based products for medicinal, veterinary, and industrial purposes. The bill allows controlled cultivation of *Cannabis* exclusively by authorized companies, supervised by the National Health Surveillance Agency (Anvisa) for medicinal use and the Ministry of Agriculture for industrial purposes. It also includes provisions for using the plant in the SUS *Farmácia Viva* program and regulates the import and export of seeds and derivatives to ensure safe, regulated access for patients in need (BRASIL, Projeto de Lei nº 399/2015; De Souza et al. 2022).

This article reviewed the literature on the therapeutic effects of *C. sativa* on neurological diseases, focusing on its potential integration into the Brazilian Unified Health System (SUS). The review addressed the pharmacological properties of the main phytocannabinoids, advances in preclinical and clinical research, and the prospects for the regulation and implementation of these treatments. The goal was to provide an up-to-date knowledge base that can guide public health policies and optimize treatments available to patients in Brazil.

## METHODOLOGY

### Scope of the review and description of the Study

This narrative review seeks to answer the guiding question: "What is the potential effect of *C. sativa* in the therapeutic/treatment of neurological diseases and its use in the Brazilian health system?" The objective is to explore and synthesize the existing knowledge about the therapeutic effects of *C. sativa* in the treatment of neurological diseases, and to present aspects related to its possible inclusion in the SUS.

### Search strategy and inclusion/exclusion criteria

Comprehensive searches were conducted in electronic databases, including PubMed/Medline,

Scopus, Web of Science, and SciELO, with no date restriction. The keywords used were "*Cannabis sativa*," "cannabinoids," "CBD," "THC," "neurological diseases," "Unified Health System," "Brazil," and "regulation." Only these descriptors were applied, and they were used in their complete form. The searches were conducted in three languages—Portuguese, Spanish, and English—using the Boolean operators "AND" and "OR" to combine the search terms. Additionally, references cited in the reviewed articles were examined to identify further relevant studies.

The included studies addressed:

Pharmacological properties of the main phytocannabinoids (THC, CBD, CBG, among others).

Evidence from clinical and preclinical research on the use of cannabinoids in neurological diseases such as epilepsy, multiple sclerosis and Parkinson's disease.

Analysis of the regulation and implementation of *Cannabis*-based treatments in Brazil and other countries.

Studies that were not available in the specified languages (Portuguese, Spanish or English) were excluded. Data presenting original data as well as literature reviews containing new synthetic or meta-analytical analysis were included.

The initial selection of articles was based on the analysis of titles and abstracts, followed by a thorough evaluation of potentially relevant texts to determine their final inclusion. The evaluation period was from January 2024 to October 2024. For each table, research articles conducted from 2006 to October 2024 were considered.

## Data analysis

A critical analysis of the selected literature was conducted, highlighting the main findings, identifying gaps in knowledge, and discussing the implications of the results for clinical practice and public health policy in Brazil. The results were organized into thematic sections to provide a comprehensive and coherent view of the therapeutic effects of *Cannabis sativa*, and the possibilities of its inclusion in the SUS.

## RESULTS

A total of 150 articles were initially selected, which, after a evaluation based on established, were narrowed down to 55 articles used to construct the tables of results. Of these 55 articles, 42 were further cited and integrated into the discussion, emphasizing their relevance in analyzing the therapeutic effects of *Cannabis sativa* in neurological diseases and exploring its potential inclusion in the Brazilian

Unified Health System (SUS).

The reviewed studies highlight the significant therapeutic potential of *C. sativa* and its components, especially THC and CBD, across various neurological conditions. The detailed findings are presented in the tables below, organized by specific themes. Each study is summarized, highlighting the authors, publication year, title, study design, objectives, information on effects or safety, and relevance to public health policies and practices. The research includes legislative analyses, technical reviews, and qualitative studies, providing a broad view of the scientific, legal, and social considerations involved in integrating *Cannabis*-based therapies into health services. These studies served as a foundation for the discussion that follows.

The table 1 presents some studies related to the implementation of *Cannabis sativa*-based treatments in public health systems, with a focus on the Brazilian Unified Health System (SUS). Each study is summarized, highlighting the authors, publication year, title, study design, objectives, information on effects or safety, and relevance to public health policies and practices. The research includes legislative analyses, technical reviews, and qualitative studies, providing a broad view of the scientific, legal, and social considerations involved in integrating *Cannabis*-based therapies into health services.

Table 2 compile nine researches investigating the effects of *C. sativa* in the treatment of chronic pain, exploring the application of cannabinoids such as cannabidiol (CBD) and others in pain management, including neuropathic pain.

**Table 1.** Analysis of *Cannabis* implementation in Brazilian Public Health Systems.

Author(s)	Year	Title	Study Design	Theme/Objectives	Effects/Safety (Numerical Data)	Relevance
Fundação Oswaldo Cruz (Fiocruz) et al.	2023	Technical Note: Current state of evidence on therapeutic uses of <i>Cannabis</i> and derivatives and the demand for regulatory advancements in Brazil	Technical Review	Present scientific evidence on therapeutic treatments based on <i>Cannabis</i> and its derivatives.	Not applicable	Provides technical support for the incorporation of <i>Cannabis</i> -based treatments into the SUS.
Lopes, R. et al.	2023	States approve the distribution of medical <i>Cannabis</i> by SUS amid federal uncertainty	Legislative Analysis	Discuss the approval of state laws for the distribution of <i>Cannabis</i> -based products through the SUS.	Not applicable	Highlights state initiatives that can serve as models for national implementation in the SUS.
Castro, C. G. S. O. de et al.	2024	Interview: Researchers discuss the medical use of <i>Cannabis</i> , regulation, and studies	Qualitative Interview	Analyze legal actions against the federal government for access to <i>Cannabis</i> products and discuss regulation and related studies.	Not applicable	Provides insights into the legal and regulatory challenges for incorporating <i>Cannabis</i> treatments into the SUS.
Ribeiro, S. et al.	2022	Health: Research and use of <i>Cannabis</i> have advanced in Brazil in recent years	Bibliographic Review	Review the progress of research and the legal use of medical <i>Cannabis</i> in Brazil over the past decade.	Not applicable	Contextualizes scientific and legal progress, supporting the feasibility of implementation in the SUS.
Oliveira, M. B. de et al.	2020	The self-cultivation of <i>Cannabis</i> and social technology	Descriptive Study with Qualitative Analysis	Analyze the self-cultivation of <i>Cannabis</i> for medicinal purposes in Brazil and its characterization as social technology.	Not applicable	Offers insights into home-grown <i>Cannabis</i> production and its potential integration into the SUS.

**Table 2. *Cannabis sativa* and chronic pain.**

Author(s)	Year	Title	Study Design	Theme/ Objectives	Effects/Safety (Numerical Data)	Statistical Significance	Relevance
Moreira GA et al.	2022	Cannabidiol for the treatment of refractory epilepsy in children: A critical review	Critical Review	Use of cannabidiol in refractory epilepsy in children	Reduction in seizure frequency by up to 50%	Statistically significant ( $p < 0.05$ )	Critical analysis of efficacy and safety of cannabidiol in epilepsy
Pantoja-Ruiz C et al.	2022	<i>Cannabis</i> and pain: A scoping review	Scoping Review	Comprehensive review on the effectiveness of <i>Cannabis</i> in treating pain	Varied effectiveness across studies	Mixed results; some studies showed significance	Summarizes current understanding and identifies research gaps
Peters EN et al.	2022	Pharmacokinetics of cannabichromene in a medical <i>Cannabis</i> product	Pilot Study	Pharmacokinetics of cannabichromene with cannabidiol and THC	Cannabinoid absorption peaks at 2-4 hours	Limited significance due to small sample size	Explores absorption rates, informing dosage guidelines
Petzke F et al.	2022	<i>Cannabis</i> -based medicines and medical <i>Cannabis</i> for chronic neuropathic pain	Clinical Analysis	Analysis of clinical evidence for <i>Cannabis</i> use in neuropathic pain	Pain relief reported in 60% of patients	Statistically significant ( $p < 0.01$ )	Provides evidence-based recommendations for neuropathic pain management
Quintero JM et al.	2022	A systematic review on cannabinoids for neuropathic pain administered by other routes	Systematic Review	Cannabinoid delivery methods for neuropathic pain	Effectiveness depends on administration route	Statistically significant for non-oral routes	Evaluates alternative delivery methods for optimal treatment outcomes
Villanueva MRB et al.	2022	Efficacy, safety, and regulation of cannabidiol on chronic pain: A systematic review	Systematic Review	Evaluating the efficacy and safety of cannabidiol in chronic pain	40-60% pain reduction; mild adverse effects	Statistically significant in most studies reviewed	Highlights regulatory challenges and therapeutic potential
Bennici A et al.	2021	Safety of medical <i>Cannabis</i> in neuropathic chronic pain management	Safety Analysis	Evaluates safety and efficacy of <i>Cannabis</i> in neuropathic pain	Adverse effects in 10-15% of patients	Statistically significant for pain relief ( $p < 0.05$ )	Assesses risk-benefit profile for chronic pain patients
Campos RMP et al.	2021	Cannabinoid therapeutics in chronic neuropathic pain: From animal research to humans	Translational Study	From animal research to human applications in neuropathic pain	Animal studies show 70% efficacy; human trials vary	Statistically significant in animal models ( $p < 0.01$ )	Bridges preclinical and clinical research for treatment insights
Argueta DA et al.	2020	A balanced approach for cannabidiol use in chronic pain	Review	Evaluates effects and safety of cannabidiol in chronic pain management	Pain reduction of 30-50%; minimal side effects	Statistically significant in some trials ( $p < 0.05$ )	Advocates for a balanced, patient-centered approach to pain management

In turn, Table 3 focuses on studies evaluating the use of cannabinoids for epilepsy control,

highlighting the potential of CBD in treatments for refractory forms of this condition.

**Table 3. *Cannabis sativa* and epilepsy.**

Author(s)	Year	Title	Study Design	Theme/Objectives	Effects/Safety (Numerical Data)	Statistical Significance	Relevance
Oshiro CA; Castro LHM	2022	Cannabidiol and epilepsy in Brazil: A current review	Current Review	Review of the use and regulation of cannabidiol for epilepsy in Brazil	Not applicable	Not applicable	Provides an overview of the regulatory landscape and therapeutic use in Brazil.
Golub V; Reddy DS	2021	Cannabidiol therapy for refractory epilepsy and seizure disorders	Therapeutic Review	Cannabidiol therapies in difficult-to-control conditions	Seizure reduction of 40-70% in treatment groups	Statistically significant ( $p < 0.05$ )	Highlights the efficacy of cannabidiol for hard-to-control seizures.
Arzimanoglou A et al.	2020	Epilepsy and cannabidiol: A guide to treatment	Treatment Guide	Discussion on guidelines and use of cannabidiol in treating epilepsy	Dose-dependent seizure reduction observed	Statistically significant in controlled trials ( $p < 0.01$ )	Provides practical treatment guidelines for clinicians.
Morano A et al.	2020	Cannabinoids in the treatment of epilepsy: Current status and future prospects	Analytical Review	Current state and future prospects of cannabinoids in epilepsy treatment	Efficacy varies by cannabinoid and dosage	Mixed statistical significance across studies	Analyzes current use and potential future developments in cannabinoid therapies.
Ryan M.	2020	Cannabidiol in epilepsy: The indications and beyond	Indication Review	Discussion on the indications for cannabidiol in epilepsy and beyond	Not applicable	Not applicable	Expands on current and potential future indications for cannabidiol use.
Silva GD et al.	2020	Cannabidiol in the treatment of epilepsy: A focused review of evidence and gaps	Evidence Review	Focused review on evidence and knowledge gaps on cannabidiol use	Identifies gaps in safety data for long-term use	Some studies show significance, others do not	Points out areas needing further research to optimize treatment protocols.
Doyle A; Harvey J	2019	Cannabis and epilepsy	Comprehensive Review	Review on the use of <i>Cannabis</i> in epilepsy treatment	Reduction in seizure frequency; some adverse effects	Statistically significant in select studies ( $p < 0.05$ )	Provides a broad overview of <i>Cannabis</i> use and its effects in epilepsy management.

Table 4 presents research focused on the potential of cannabinoids in a variety of neurological

disorders, providing valuable insights into case studies and clinical analyses.

**Table 4. *Cannabis sativa* and miscellaneous neurological disorders.**

Author(s)	Year	Title	Study Design	Theme/Objectives	Effects/Safety (Numerical Data)	Statistical Significance	Relevance
Bhunia S et al.	2022	Cannabidiol for neurodegenerative disorders: A comprehensive review	Comprehensive Review	Review on the use of cannabidiol in neurodegenerative disorders	Neuroprotective effects noted in preclinical studies	Statistically significant in animal models ( $p < 0.01$ )	Provides a broad overview of evidence and highlights therapeutic potential
Kumar P et al.	2021	Pharmacological properties, therapeutic potential, and legal status of <i>Cannabis sativa</i> L.: An overview	Overview Study	Overview of pharmacological properties and therapeutic potential	Varied effects; legal status differs by region	Not applicable	Summarizes the pharmacological basis and legal considerations
Cassano T et al.	2020	From <i>Cannabis sativa</i> to cannabidiol: Promising therapeutic candidate for neurodegenerative diseases	Therapeutic Discussion	Discussion on the therapeutic potential of cannabidiol in neurodegenerative diseases	Cannabidiol shows potential in reducing neuroinflammation	Statistically significant in preclinical data ( $p < 0.05$ )	Discusses mechanisms and highlights potential treatments for neurodegeneration
Cristino L; et al.	2020	Cannabinoids and the expanded endocannabinoid system in neurological disorders	Systematic Exploration	Exploration of the relationship between cannabinoids and the endocannabinoid system	Positive modulation of neuroinflammatory pathways	Statistically significant effects on neuroprotection ( $p < 0.01$ )	Provides insights into the endocannabinoid system's role in neuroprotection

Table 5 encompasses studies examining the effects of cannabinoids on neurodegenerative diseases

such as Alzheimer's and Parkinson's, investigating their neuroprotective properties and therapeutic potential.

**Table 5. *Cannabis sativa* and neurodegenerative diseases.**

Author(s)	Year	Title	Study Design	Theme/Objectives	Effects/Safety (Numerical Data)	Statistical Significance	Relevance
Calapai F et al.	2022	Pharmacological aspects and biological effects of cannabigerol and its synthetic derivatives	Pharmacological Study	Study of the pharmacological effects of cannabigerol, a lesser-known compound in <i>Cannabis</i>	Demonstrated anti-inflammatory and neuroprotective effects	Statistically significant in vitro ( $p < 0.01$ )	Explores the therapeutic properties of a lesser-known cannabinoid
Legare CA et al.	2022	Therapeutic potential of <i>Cannabis</i> , cannabidiol, and cannabinoid-based pharmaceuticals	Review	Broad discussion on the therapeutic potential of various cannabinoids	Varied therapeutic effects across different conditions	Mixed significance in reviewed studies	Provides an overview of therapeutic applications of multiple cannabinoids
Viana MB et al.	2022	<i>Cannabis sativa</i> and cannabidiol: A therapeutic strategy for the treatment of neurodegenerative diseases?	Assessment Study	Assessment of the therapeutic potential of <i>Cannabis sativa</i> and cannabidiol in neurodegenerative diseases	Positive results in preclinical neurodegenerative models	Statistically significant in preclinical studies ( $p < 0.05$ )	Evaluates potential applications for neurodegenerative conditions
Ferreira-Junior NC et al.	2020	Biological bases for a possible effect of cannabidiol in Parkinson's disease	Biological Exploration	Exploration of the biological basis of the therapeutic potential of cannabidiol in Parkinson's	Neuroprotective mechanisms identified	Statistically significant in animal models ( $p < 0.01$ )	Discusses biological mechanisms supporting cannabidiol use in Parkinson's
Patricio F et al.	2020	Cannabidiol as a therapeutic target: Evidence of its neuroprotective and neuromodulatory function in Parkinson's disease	Evidence Review	Evaluation of the neuroprotective properties of cannabidiol in Parkinson's	Reduced neuroinflammation and motor symptoms	Statistically significant improvements ( $p < 0.05$ )	Highlights cannabidiol's neuroprotective role in Parkinson's treatment

*continue*

**Table 5. continuation**

Author(s)	Year	Title	Study Design	Theme/Objectives	Effects/Safety (Numerical Data)	Statistical Significance	Relevance
Rieder CR	2020	Cannabidiol in Parkinson's disease	Clinical Discussion	Discussion on the use of cannabidiol as a potential treatment for Parkinson's	Improved motor function reported in some patients	Some studies show significance, others do not	Reviews clinical evidence supporting cannabidiol use for Parkinson's
Meyer T et al.	2019	Real world experience of patients with amyotrophic lateral sclerosis (ALS) in the treatment of spasticity using THC:CBD	Observational Study	Analysis of the efficacy of THC:CBD in treating spasticity in ALS	60-80% of patients reported spasticity relief	Statistically significant results ( $p < 0.05$ )	Provides real-world evidence of THC:CBD effectiveness in ALS spasticity
Bergamaschi MM et al.	2011	Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients	Clinical Trial	Investigation into the anxiolytic effect of cannabidiol in social phobia	Anxiety reduction of 30-40% compared to placebo	Statistically significant reduction ( $p < 0.01$ )	Demonstrates the anxiolytic potential of cannabidiol in social settings

In addition, Table 6 explores general reviews and case studies on the medical use of

*Cannabis*, understanding a variety of clinical contexts and discussing efficacy and safety.

**Table 6. General reviews and case studies.**

Author(s)	Year	Title	Study Design	Theme/Objectives	Effects/Safety (Numerical Data)	Statistical Significance	Relevance
Hidding U; Mainka T; Buhmann C	2024	Therapeutic use of medical <i>Cannabis</i> in neurological diseases: A clinical update	Clinical Update	Clinical update on the use of medicinal <i>Cannabis</i> in neurological diseases	Reported symptom relief in patients; varied responses by condition	Statistically significant in multiple conditions ( $p < 0.05$ )	Summarizes recent advancements and highlights areas needing more research
De Souza MR; Henriques AT; Limberger RP	2022	Medical <i>Cannabis</i> regulation: An overview of models around the world with emphasis on the Brazilian scenario	Regulatory Overview	Discussion about different regulatory models for medicinal <i>Cannabis</i> globally and in Brazil	Not applicable	Not applicable	Provides a comprehensive comparison of international regulatory frameworks and Brazil's status
Kopustinskiene DM et al.	2022	<i>Cannabis sativa</i> L. bioactive compounds and their protective role in oxidative stress and inflammation	Experimental Study	Study on bioactive compounds in <i>Cannabis</i> and their protective effects against oxidative stress and inflammation	Demonstrated reduction in oxidative markers by 30-50%	Statistically significant in vitro and in vivo ( $p < 0.01$ )	Supports the potential therapeutic role of <i>Cannabis</i> bioactives in managing inflammation
Ingram G; Pearson OR	2019	<i>Cannabis</i> and multiple sclerosis	Systematic Review	Review of the use of <i>Cannabis</i> in the treatment of multiple sclerosis symptoms	Spasticity reduction and improved mobility in patients	Statistically significant for symptom management ( $p < 0.05$ )	Reviews evidence supporting <i>Cannabis</i> use in managing multiple sclerosis symptoms
Carlini ELA	2006	The history of marijuana in Brazil	Historical Analysis	Historical analysis of the evolution of <i>Cannabis</i> use and legislation in Brazil	Not applicable	Not applicable	Provides context on the historical regulation and cultural impact of <i>Cannabis</i> in Brazil

Finally, Table 7 includes studies that discuss less conventional therapeutic applications of *Cannabis*, exploring innovative uses and

pharmacokinetics of cannabinoids in alternative treatments.

**Table 7. *Cannabis sativa* and other therapeutic applications.**

Author(s)	Year	Title	Study Design	Theme/ Objectives	Effects/Safety (Numerical Data)	Statistical Significance	Relevance
Ross IA	2023	<i>Cannabis</i> and Multiple Sclerosis	Narrative Review	Discussion on the use of <i>Cannabis</i> in the treatment of multiple sclerosis	Not applicable	Not applicable	Explores therapeutic strategies for MS-related symptoms
Sirbu CA et al.	2023	<i>Cannabis</i> and Cannabinoids in Multiple Sclerosis: From Experimental Models to Clinical Practice—A Review	Systematic Review	Review on the use of <i>Cannabis</i> and cannabinoids in MS treatment	Not applicable	Highlights trends and identifies knowledge gaps	Evaluates progress and future research directions
Solmi M et al.	2023	Balancing Risks and Benefits of <i>Cannabis</i> Use: Umbrella Review of Meta-analyses of Randomized Controlled Trials and Observational Studies	Umbrella Review	Critical analysis of <i>Cannabis</i> use, balancing risks and benefits	Summarized across multiple conditions	Provides statistical synthesis of clinical outcomes	Summarizes outcomes across diverse studies
Haddad F; Dokmak G; Karaman R	2022	The Efficacy of <i>Cannabis</i> on Multiple Sclerosis-Related Symptoms	Clinical Trial	Assessing the efficacy of <i>Cannabis</i> in treating MS symptoms	Reduction in spasticity (25%) and fatigue (15%)	Statistically significant improvements in symptom relief	Demonstrates therapeutic potential for MS symptom management
Kopustinskiene DM et al.	2022	<i>Cannabis sativa</i> L. Bioactive Compounds and Their Protective Role in Oxidative Stress and Inflammation	Experimental Study	Discusses protective effects of <i>Cannabis</i> bioactive compounds	Decrease in oxidative stress markers (30-50%)	Significant reduction in inflammation markers ( $p < 0.01$ )	Supports the therapeutic role of <i>Cannabis</i> in managing inflammation
Pagano C et al.	2022	Cannabinoids: Therapeutic Use in Clinical Practice	Clinical Practice Review	Clinical applications of cannabinoids for various medical conditions	Documented use for chronic pain and anxiety relief	Recommends standardized protocols for treatment	Emphasizes need for evidence-based cannabinoid use
Shehata I et al.	2022	Cannabinoids and Their Role in Chronic Pain Treatment: Current Concepts and a Comprehensive Review	Comprehensive Review	Reviews cannabinoid efficacy in chronic pain management	Efficacy shown in pain reduction studies	Statistically significant ( $p < 0.05$ ) outcomes in pain management	Supports use of cannabinoids in chronic pain relief
Śmiarowska M et al.	2022	<i>Cannabis</i> and Cannabinoids: Pharmacology and Therapeutic Potential	Pharmacological Review	Reviews cannabinoid pharmacology and therapeutic uses	Emphasis on mechanism of action and patient response	Significant outcomes in therapeutic applications ( $p < 0.05$ )	Highlights the pharmacological relevance of cannabinoids
Ozarowski M et al.	2021	Cannabidiol in Neurological and Neoplastic Diseases: Latest Developments on the Molecular Mechanism of Action	Mechanistic Review	Describes molecular mechanisms of CBD in neurological/neoplastic contexts	Mechanistic insights on CBD interaction with neural pathways	Relevance in cancer and neurodegenerative treatment research	Explores molecular basis for therapeutic use of CBD
Radwan MM et al.	2021	Cannabinoids, Phenolics, Terpenes and Alkaloids of Cannabis	Phytochemical Study	Study on <i>Cannabis</i> component chemistry	Analysis of synergistic effects among phytochemicals	Highlights bioactive potential for medicinal applications	Details chemical complexity of <i>Cannabis</i>
Fragoso YD; Carra A; Marcias MA	2020	<i>Cannabis</i> and Multiple Sclerosis	Systematic Review	Reviews <i>Cannabis</i> use for symptom management in MS	Spasticity and pain reduction (30-40%)	Clinical significance in MS symptom relief	Supports symptom relief benefits in MS patients
Sholler DJ et al.	2020	Therapeutic Efficacy of Cannabidiol (CBD): A Review of the Evidence from Clinical Trials and Human Laboratory Studies	Evidence Review	Reviews evidence for CBD's efficacy across various conditions	Reduction in seizure frequency by 40%	Strong statistical support for antiepileptic effects ( $p < 0.001$ )	Highlights CBD's role in seizure management

*continue*

**Table 7. continuation**

Author(s)	Year	Title	Study Design	Theme/ Objectives	Effects/Safety (Numerical Data)	Statistical Significance	Relevance
Schabas AJ et al.	2019	<i>Cannabis</i> -Based Product Use in a Multiple Sclerosis Cohort	Observational Study	Efficacy of <i>Cannabis</i> products for MS patients	Improved mobility and reduced spasticity in 60% of participants	Statistically significant symptom improvements ( $p < 0.05$ )	Demonstrates real-world effectiveness in MS treatment
Wu J	2019	<i>Cannabis</i> , Cannabinoid Receptors, and Endocannabinoid System: Yesterday, Today, and Tomorrow	Review Article	Evolution of endocannabinoid system understanding	Explores historical and modern developments	Foundation for future receptor-targeted therapies	Presents a comprehensive history of cannabinoid science
Schier AR et al.	2012	Cannabidiol, a <i>Cannabis sativa</i> Constituent, as an Anxiolytic Drug	Clinical Study	Anxiolytic potential of cannabidiol	Anxiety reduction by 25% in controlled environments	Statistically significant reduction in anxiety ( $p < 0.01$ )	Provides clinical evidence for anxiolytic effects
Carter GT et al.	2010	<i>Cannabis</i> and Amyotrophic Lateral Sclerosis: Hypothetical and Practical Applications, and a Call for Clinical Trials	Review Article	Potential <i>Cannabis</i> use in ALS management	Discusses spasticity and pain relief	Calls for more clinical trial data	Encourages further ALS-specific research
Zuardi AW et al.	2006	Cannabidiol, a <i>Cannabis sativa</i> Constituent, as an Antipsychotic Drug	Clinical Review	Assesses antipsychotic properties of CBD	Observed reduction in psychotic symptoms by 30%	Statistically significant effects ( $p < 0.05$ )	Supports potential antipsychotic use of CBD

## DISCUSSION

### *Cannabis sativa* and bioactive constituents

Globally, *C. sativa* has been used medicinally and recreationally for thousands of years. There are more than 550 chemical compounds in *Cannabis*, with more than 100 phytocannabinoids identified, including  $\Delta^9$ -tetrahydrocannabinol (THC) and cannabidiol (CBD). The biological effects of phytocannabinoids are primarily mediated by cannabinoid receptors 1 (CB1R) and 2 (CB2R). Endocannabinoids, cannabinoid receptors, and other molecules responsible for their biosynthesis and metabolism make up the endocannabinoid system (Wu 2019; Kumar et al. 2021; Kopustinskiene et al. 2022; Śmiarowska et al. 2022).

Phytocannabinoids are chemical compounds unique to *C. sativa* and include THC known for its psychoactive, and analgesic effects that can help in relieving pain, nausea, and stimulating appetite. CBD, on the other hand, is non-psychoactive, and has demonstrated a wide range of therapeutic properties, including anti-inflammatory, analgesic, anxiolytic and anticonvulsant properties. It is often used in the treatment of refractory epilepsy, anxiety, chronic pain, and sleep disorders, among other neurological disorders such as Parkinson's disease (Sholler et al. 2020; Pagano et al. 2022).

CBG (cannabigerol), CBN (cannabinol), CBC (cannabichromene) among others have also been studied for their potential therapeutic benefits, including antibacterial, anti-inflammatory, and

neuroprotective properties (Calapai et al. 2022; Peters et al. 2022).

Other chemical constituents include terpenes, which are aromatic compounds found in many other plants, including *C. sativa*. Not only do they contribute to the aroma and flavor of the plant, but they can also interact with cannabinoids to produce different therapeutic effects. Some common terpenes found in *Cannabis* include myrcene (with relaxing and sedative properties), limonene (with antidepressant and anti-stress properties), and pinene (with anti-inflammatory and bronchodilator properties). On the other hand, flavonoids are antioxidant compounds that have been linked to a variety of health benefits, including anti-inflammatory, neuroprotective, and anticancer properties (Radwan et al. 2021).

In addition, a large number of recent studies on the neuroprotective and anti-inflammatory effects of CBD and its molecular targets have also been reviewed (Viana et al. 2022). Due to its wide range of pharmacological activities such as antioxidant, anti-inflammatory, and neuroprotective properties, CBD is accepted for the treatment of a number of neurodegenerative diseases (Cassano et al. 2020; Ozarowski et al. 2021; Bhunia et al. 2022).

One of the most prominent areas of research is the use of CBD in the treatment of refractory epilepsy, especially in children. Clinical studies have shown that CBD can significantly reduce the number of seizures in patients with epilepsy, including Dravet

syndrome and Lennox-Gastaut syndrome (Doyle et al. 2019; Silva et al. 2020; Morano et al. 2020; Ryan 2020; Golub et al. 2021; Moreira et al. 2022; Oshiro et al. 2022; Solmi et al. 2023, Hidding et al. 2024).

Patients with multiple sclerosis (MS) often report benefits of *C. sativa* use in relieving symptoms such as spasticity, pain, insomnia, and fatigue. Research indicates that both THC and CBD may have anti-inflammatory and neuroprotective properties that may be beneficial for MS patients (Schabas et al. 2019; Ingram et al. 2019; Fragoso et al. 2020; Haddad et al. 2022; Ross 2023; Sirbu et al. 2023).

Preclinical and clinical studies suggest that *Cannabis* can help control neurodegenerative diseases such as Parkinson's disease, among others, whose main symptoms are tremors, muscle stiffness, and bradykinesia. Some patients report improved quality of life and sleep capacity with *C. sativa* use (Cristino et al. 2020; Cassano et al. 2020; Bhunia et al. 2022; Viana et al. 2022).

*Cannabis sativa* has been investigated as a treatment option for neuropathic pain, which is pain caused by damage or dysfunction of the nervous system. Both THC and CBD have shown potential in relieving neuropathic pain in preclinical and clinical studies (Argueta et al. 2020; Pantoja-Ruiz 2022; Campos et al. 2021; Bennici et al. 2021; Quintero et al. 2022; Petzke et al. 2022; Shehata et al. 2022; Villanueva et al. 2022).

Although there is less specific research on the use of *Cannabis* in amyotrophic lateral sclerosis (ALS), some studies suggest that it may help in the management of symptoms such as spasticity, excessive salivation, and pain, thereby improving patients' quality of life (Carter et al. 2010; Meyer et al. 2019).

While *Cannabis*-based medicines have demonstrated sufficient safety, efficacy, and consistency for regulatory approval in spasticity in multiple sclerosis (MS) and Dravet and Lennox-Gastaut syndromes, many therapeutic challenges remain. However, there are reasons to believe that cannabinoids may be effective for a number of different diseases and syndromes, there is limited objective data supporting the use of raw materials such as CBD oil, *Cannabis* extracts and/or *Cannabis* itself (Legare et al. 2022)

### Research on *Cannabis sativa* in Brazil

In Brazil, research with *C. sativa* intensified in 1960, at then Paulista School of Medicine (now part of Federal University of São Paulo - UNIFESP) with the so-called sons, such as Prof. E.A. Carlini, and later grandchildren and great-grandchildren of Professor of Pharmacology José Ribeiro de Valle, from the then Paulista School of Medicine (now UNIFESP) (Carlini 2010).

On the other hand, the "grandchildren of the

Valley", mainly A.W. Zuardi, continue to this day the research with cannabinoids, notably cannabidiol. In fact, the group from the Faculty of Medicine of the University of São Paulo in Ribeirão Preto, released by Prof. Antonio Zuardi and with some of his former interns ("the great-grandchildren of Valle"), in their respective universities of origin, presents itself today as the most important cannabinoid research group in Brazil (Carlini 2006).

In this context, it is important to highlight the contribution of Professor Raphael Mechoulam, who died in 2023, an Israeli organic chemist born in Bulgaria and professor at the Department of Natural Materials at the School of Pharmacy of the Faculty of Medicine of the Hebrew University of Jerusalem. Thus, Dr. Mechoulam's academic and scientific legacy is immense and includes collaboration with Brazilian researchers at all levels. As a scientist who has always been committed to translating his knowledge to society, he has helped turn Brazil into an epicenter of research on *C. sativa* in general and CBD in particular (Crippa et al. 2023). Thus, several researches have been conducted in Brazil to investigate the therapeutic effects of *C. sativa* and its compounds. Universities, research institutions, and pharmaceutical companies are exploring a variety of potential applications, from the development of new drugs to clinical studies to evaluate the efficacy and safety of *C. sativa* use in different medical conditions (Zuardi et al. 2006; Bergamashi et al. 2011; Schier et al. 2012; Rieder 2020; Ferreira-Júnior et al. 2020; Patricio et al. 2020). Brazil is positioning itself as an important center of research in this area, which can result in significant benefits for patients who benefit from the medicinal use of the plant.

An agreement signed in 2016 between the University of São Paulo (USP) and a Brazilian pharmaceutical company made it possible to conduct a multicenter, placebo-controlled clinical trial in children with refractory epilepsy. The results of this study are being evaluated by the National Health Surveillance Agency (ANVISA); however, a partial analysis contributed to ANVISA's market approval of the first phytopharmaceutical containing pure CBD in April 2020 (Zuardi and Crippa 2023).

On the other hand, the Brazilian Agricultural Research Corporation (Embrapa) has all the conditions to start research aimed at hemp production in Brazil, even though it does not have a germplasm bank with varieties of *Cannabis*. Embrapa has the capacity to work and assist with the development of *Cannabis* varieties that do not have psychoactive substances. The different aspects that would involve research on *Cannabis* at Embrapa can occur involving the company's expertise in its different Units, adding teams that work with genetic improvement, among others. This was one of the

statements made by researcher Daniela Bitencourt, from Embrapa Genetic Resources and Biotechnology (Brasília-DF), when she listed a series of economic, social and agronomic advantages that Brazil can obtain from the cultivation of the plant, including the agricultural sector, currently, one of the concerns with the planting and production of *Cannabis* in the country is the THC component, EMBRAPA is able from a scientific point of view to produce a genetic variety with known and previously established concentrations in relation to the components of *Cannabis* (Bitencourt 2024).

The Institutional Program on Drug Policies, Human Rights, and Mental Health of Fiocruz (Ordinance No. 192, of March 8, 2023) aims to provide subsidies, based on scientific literature, to institutions responsible for the legislation, regulation, research, production, standardization, distribution, and use of *Cannabis* and derivatives for therapeutic purposes (Fundação Oswaldo Cruz 2023).

The present research with the highest level of evidence – clinical trials, systematic reviews and meta-analyses – is conclusive or substantial for some health conditions regarding the safety and efficacy of cannabinoids in reducing symptoms and improving health. The following conditions stand out: 1. Chronic pain – Different formulations containing cannabinoids have a significant reduction in pain in people diagnosed with certain types of chronic pain (Boyaji et al. 2020; Kostenberg et al. 2022; Mohammed et al. 2022; Villanueva et al. 2022;). Dozens of randomized controlled trials undergoing meta-analyses showed that the reduction in pain was greater in the cannabinoid group compared to the control group; 2. Refractory epilepsy (Mannucci et al. 2017; Devinski et al. 2021; von Wrede et al. 2021; Oshiro and Castro 2022) – a meta-analysis study with six randomized clinical trials demonstrated a significant decrease in seizure frequencies in the cannabinoid-treated group compared to the control group. In general, the participants were resistant to the reference drugs and found cannabinoids to be an effective treatment to attenuate seizures; 3. Spasticity (Zettl et al. 2016; Meyer et al. 2019; Patti et al. 2020; Hansen et al. 2023) – more than a dozen randomized controlled trials have shown a significant effect of cannabinoid treatment in reducing spasticity due to multiple sclerosis; 4. Nausea, vomiting, and loss of appetite (Parker et al. 2011; Rock et al. 2021) – cannabinoids have been effective in reducing nausea and vomiting linked to chemotherapy. A meta-analysis showed the effectiveness of cannabinoids in increasing appetite compared to control groups and 5. Neuropsychiatric disorders (Campos et al. 2016; Campos et al. 2017; Elsaid et al. 2019; Ozarowski et al. 2021; Joca and Guimarães 2024) – such as Parkinson's disease and sleep disorders – have

shown significant improvement in symptoms. Thus, three human studies have tested CBD in patients with PD: an open-label study, a case series, and a randomized controlled trial. These studies reported therapeutic effects of CBD on non-motor symptoms. Additional research is needed to elucidate the potential effectiveness of CBD in PD and the underlying mechanisms involved. (Ferreira-Junior et al. 2020). More recently evidence shows the use of cannabinoids as anti-apoptotic drug and as an anti-cancer agent (Seltzer et al. 2020; Shalata et al. 2020; Hinz and Rammer 2022; Wang et al. 2023; Faiz et al. 2024; Younes et al. 2024).

In addition to those mentioned above, the potential safety and efficacy of the therapeutic use of cannabinoids has been researched for dozens of other conditions as their use in symptoms associated with Autism Spectrum Disorder (ASD) (Fusar et al. 2020; Mostafavi and Gaitanis 2020; Aran et al. 2021; Silva et al. 2022; Hacoheh et al. 2022).

### **Brazilian legislation and the use of *Cannabis sativa***

Bill 399/2015, which is pending in the Chamber of Deputies, provides for the regulation of the cultivation, production, research, industrialization and commercialization of *Cannabis*-based products for medicinal and therapeutic purposes. The main goal is to ensure safe and regulated access to *Cannabis*-based treatments for patients who need them. PL 399/2015 establishes strict criteria for the cultivation of the plant and the production of medicines, with the aim of ensuring the quality and efficacy of the products available on the market (Brasil, Projeto de Lei nº 399/2015).

In Brazil, there has been an evolution of the regulatory framework since 2015, although there are still pending points to be addressed, including the cultivation of the species and access to it for scientific research purposes. Building a regulatory model that provides access to good quality *Cannabis*-based medicines that can meet patient needs is still a challenge in the coming years, requiring the involvement of diverse stakeholders, including regulators, members of the academic community, prescribing professionals, and patients (De Souza et al. 2022).

To date, Anvisa has approved 23 *Cannabis* products based on RDC No. 327/2019, (Resolution of the Collegiate Board - RDC No. 327, December 9, 2019) nine of which are based on *Cannabis sativa* extracts and 14 on cannabidiol. Cannabidiol Ease Labs 100 mg/ml; Prati-Donaduzzi Cannabidiol 20; 50, and 200 mg/ml; NuNature Cannabidiol 17.18 and 34.36 mg/ml; Farmanguinhos Cannabidiol 200 mg/ml; Verdemed Cannabidiol 50 mg/ml; Promediol *Cannabis sativa* extract 200 mg/ml; *Cannabis sativa*

extract Zion Medpharma 200 mg/ml; Cannabidiol Verdemed 23.75 mg/ml; Cann10 Pharma *Cannabis sativa* extract 200 mg/ml; Greencare *Cannabis sativa* extract 79.14 mg/ml; *Cannabis sativa* extract Ease Labs 79.14 mg/ml; Belcher Cannabidiol 150 mg/ml; Aura Pharma Cannabidiol 50 mg/ml; Greencare Cannabidiol 23.75 mg/ml; Active Pharmaceutica Cannabidiol 20 mg/ml; Greencare *Cannabis sativa* Extract 160.32 mg/ml; Mantecorp Farmasa *Cannabis sativa* Extract 160.32 mg/ml; *Cannabis sativa* extract Mantecorp Farmasa 79.14 mg/ml; Cannabidiol Promediol 200 mg/ml; Cannabidiol Collect 20 mg/ml; Cannabidiol Mantecorp Farmasa 23.75 mg/ml; e *Cannabis sativa* extract CannaBr 10 mg/ml.

### **Inclusion of *Cannabis sativa* products in the Unified Health System (SUS)**

CBD is a recognized novel treatment for epilepsy. Future well-designed studies and public health strategies are needed to offer widespread access to CBD, and to improve the quality of life of people living with epilepsy in Brazil (Oshiro *et al.* 2022). Thus, it is considered crucial that Brazil positions itself at the forefront of this process, investing decisively in national scientific production of *Cannabis* products. It is essential to ensure, through the Unified Health System (SUS), a comprehensive and efficient regulation that enables the production, prescription and free and universal access by the Unified Health System - the SUS - to a wide range of pharmaceutical forms of *Cannabis* and derivatives, always supported by solid evidence of safety and therapeutic efficacy. Institutional Program on Drug Policy, Human Rights, and Mental Health (Fiocruz 2023).

The inclusion of *Cannabis* especially CBD in the SUS would need to ensure that all patients who benefit from it have access, regardless of their socioeconomic condition or place of residence. This could involve creating care programs for low-income patients and equitably distributing treatment centers across the country. In summary, the inclusion of *Cannabis* in the SUS in Brazil presents several possibilities for therapeutic use, but also significant challenges that would need to be addressed at the medical, legal, social and political levels (Do Amaral and Posso 202; Relatório de Análise de impacto regulatório sobre produtos de *Cannabis* para fins medicinais, ANVISA, Brasília 2024).

In the context of Possibilities and Challenges for Inclusion in the SUS, recent pre-clinical studies (Henderson *et al.* 2023) indicate that oral administration of CBD at doses up to 150 mg/kg in rats over periods of 14 to 90 days did not result in significant adverse effects. The results show that CBD is well tolerated and associated with few

serious adverse effects (AEs) at therapeutic doses in both children and adults, as evidenced by studies focusing on the treatment of epilepsy and psychotic disorders. Common side effects included fatigue, diarrhea, and changes in appetite/weight. However, further research is needed to fully understand CBD's action on liver enzymes, drug transporters, and drug interactions (Iffland and Grotenhermen 2017; Lattanzi *et al.* 2018; Scholler *et al.* 2020).

In epilepsy, CBD has demonstrated remarkable efficacy. Clinical studies indicate that doses of 20 mg/kg/day reduced seizure frequency by more than 50% compared to placebo (RR, relative risk, 1.74, CI, confidence interval, 95% 1.24 to 2.43), with a number needed to treat (NNT, the number of patients who need to be treated for one to benefit) of 8 (95% CI 6 to 17). CBD also improved quality of life (RR 1.73, 95% CI 1.33 to 2.26), though it increased the risk of adverse effects (RR 1.24, 95% CI 1.13 to 1.36) and serious adverse effects (RR 2.55, 95% CI 1.48 to 4.38). Additionally, observational studies reinforce these findings, with 48.5% of patients reporting significant seizure reductions and 55.8% reporting improved quality of life (Stockings *et al.* 2018).

Furthermore, the use of CBD has shown efficacy in syndromes such as Dravet and Lennox-Gastaut, with studies indicating consistent therapeutic benefits, despite the need for caution regarding drug interactions (Huestis *et al.* 2019; Chesney *et al.* 2020; Silva *et al.* 2020). However, the long-term efficacy and safety of CBD, as well as its use in medical conditions beyond epileptic syndromes, still require further investigation (Madeo *et al.* 2023).

The inclusion of CBD in the SUS faces regulatory and production challenges, but its implementation could bring significant economic and social benefits. Developing clearer regulations and encouraging domestic cannabis production could facilitate patient access to effective treatments. The analysis of available data reinforces the need to balance therapeutic benefits with logistical challenges, providing a solid basis for advocacy and future discussions on the inclusion of these treatments in the public health system.

### **CONCLUSION**

The results reviewed in this article indicate that *C. sativa* and its components, especially THC and CBD, have relevant therapeutic potential for several neurological conditions. The inclusion of these treatments in the Unified Health System (SUS) in Brazil can bring significant benefits to patients with refractory epilepsy, multiple sclerosis, Parkinson's disease, and other neurological diseases. However, implementation faces regulatory and production

challenges that need to be overcome to ensure safe and effective access to these treatments.

The regulation proposed by Bill 399/2015 is an important step to ensure that Brazilian patients can benefit from these scientific advances. It is crucial that Brazil continues to invest in research and development of *Cannabis*-based products to fully take advantage of its therapeutic benefits.

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## AUTHORS' CONTRIBUTIONS

Conceptualization, Methodology, Writing – Original Draft: PEAA; Supervision, Writing – Review & Editing: MMFF; Data Curation, Writing – Review & Editing: LKAML; Supervision, Funding Acquisition, Writing – Review & Editing: GSBV; Writing - Review & Editing: JMCX. All authors have read and approved the final manuscript.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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