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THERAPEUTIC USE OF MEDICINAL CANNABIS IN PEOPLE WITH DEGENERATIVE NEUROLOGICAL DISEASE

Uso terapeutico da cannabis medicinal em pessoas com doença neurológica degenerativa

Uso terapéutico de cannabis medicinal en personas con enfermedad neurológica degenerativa

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ABSTRACT

Objective: to present the state of the art of publications expressed in the world Scientific literature on the subject, as well as to identify the therapeutic benefits of medicinal cannabis in the treatment of neurodegenerative diseases, specifically, Parkinson's diseases, multiple sclerosis and Alzheimer's. **Method:** this is an integrative literature review, whose data search was performed in virtual librares. Web of Science, Scopus, Medline, Lilacs, Cochrane Library and Scielo from August to October 2021. **Results:** 158 articles were found. Twenty-three articles were selected to be read in full and 8 met the criteria of this review. **Conclusion:** evidence shows that although increasingly prescribed or authorized, medical cannabis or Cannabinoids for chronic pain remain controversial for many physicians.

DESCRIPTORS: Cannabis; Cannabis sativa; Medical marijuana; Nervous system diseases; Chronic pain; Chronic disease.

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RESUMO

Objetivo: apresentar o estado da arte das publicações expressas na literatura cientifica mundial sobre a temática, bem como identificar os benefícios terapêuticos da Cannabis medicinal no tratamento dos sintomas das doenças neurodegenerativas especificamente doenças de Parkinson, esclerose múltipla e Alzheimer. **Método:** trata-se de uma revisão integrativa da literatura, cuja busca de dados foi realizada nas bibliotecas virtuais. Web of Science, Scopus, Medline, Lilacs, Cochrane Library e Scielo no período de agosto a outubro de 2021. **Resultados**: foram encontrados 158 artigos. Vinte e tres artigos foram selecionados para serem lidos na íntegra e 8 atenderam aos critérios desta revisão. **Conclusão**: as evidências mostram que embora cada vez mais prescritos ou autorizados, a cannabis medicinal ou os Canabinóides para a doenças neurodegenerativas continuam a ser controversos para muitos médicos.

DESCRITORES: Cannabis; Cannabis sativa; Cannabis medicinal; Doenças do sistema nervoso; Dor crônica; Doença crônica.

RESUMEN

Objetivo: presentar el estado del arte de las publicaciones expresadas en la literatura científica mundial sobre el tema, así como identificar los beneficios terapéuticos del cannabis medicinal en el tratamiento de enfermedades neurodegenerativas, en concreto, las enfermedades de Parkinson, la esclerosis múltiple y el Alzheimer. **Método:** se trata de una revisión integradora de la literatura, cuya búsqueda de datos se realizó en bibliotecas virtuales. Web of Science, Scopus, Medline, Lilacs, Cochrane Library y Scielo de agosto a octubre de 2021. **Resultados:** se encontraron 158 artículos. Se seleccionaron veintitrés artículos para ser leídos en su totalidad y ocho cumplieron los criterios de esta revisión. **Conclusión:** la evidencia muestra que, aunque cada vez más se prescribe o autoriza, el cannabis medicinal o los cannabinoides para el dolor crónico siguen siendo controvertidos para muchos médicos.

DESCRIPTORES: Cannabis; Cannabis sativa; Cannabis medicinal; Enfermedades autoinmunes del sistema nervioso**;** Dolor crónico**;** Enfermedad crónica.

INTRODUCTION

Various physical, psychological benefits have been attributed to cannabis since it was first reported in 2,600 BC.[1] Cannabis burst onto the western medical horizon after its introduction by William O'Shaughnessy in 1838,[1] who described remarkable successes in treating epilepsy and rheumatic pain. Cannabis, or "Indian hemp," was quickly adopted by European physicians noting benefits in migraine and neuropathic pain, including trigeminal neuralgia.[2] These developments did not go unnoticed by neurology giants on both sides of the Atlantic, who similarly adopted its use in these indications.[3] The phytocannabinoids, cannabidiol (CBD) and delta-9-tetrahydrocannabinol (Δ9-THC), are the most studied extracts of cannabis sativas, include hemp and marijuana.4 Recently, it has been successfully used as an adjuvant treatment for malignant brain tumors, Parkinson's disease (PM), Alzheimer's disease (AD), multiple sclerosis (MS), neuropathic pain and childhood seizure disorders, Lennox-Gastaut and Dravet syndromes.[2–3] A new drug o, nabiximols (name adopted in the US; Sativex ®),[4] has currently gained regulatory approval in 30 countries for muscle spasticity associated with multiple sclerosis (MS) and in Canada for central neuropathic pain, and for opioid-resistant cancer pain.[5] Recent research has found cannabis use rates of 20% to 60% among patients with (MS).[6] A previous attempt to demonstrate neuroprotection in traumatic brain injury following intravenous administration of single doses of the non-intoxicating cannabinoid analog, dexanabinol, failed,[3,6] but hope remains for other preparations in stroke and other brain injury.[2,4,6] Summarizes the current status of cannabis-based drugs in neurological conditions not discussed in detail here, including sleep disorders,[5] glaucoma, lower urinary tract symptoms, social anxiety, Tourette's Syndrome, and schizophrenia.[7] This article will focus on several neurological syndromes that overlap in their pathophysiology or have not yet received concerted attention in clinical trials of cannabis-based drugs.[8] Multiple sclerosis (MS) is the leading immune-mediated, demyelinating, neurodegenerative disease of the central nervous system.[9] Cannabis compounds, namely Δ9-tetrahydrocannabinol (Δ9-THC), can limit the inappropriate neurotransmissions that cause MS-related problems.[4,7–8] medicinal cannabis is now licensed for the treatment of its symptoms.[9] However, studies point out that the endocannabinoid system may offer the potential to control other aspects of the disease.[10] Although there is limited evidence that cannabinoids in cannabis are having significant immunosuppressive activities[9–10] that will influence recurrent autoimmunity, there is evidence that they may limit the neurodegeneration that leads to progressive disability.[11] Parkinson's disease (MP) is a degenerative condition that affects dopaminergic neurotransmission in the basal ganglia, resulting in hypokinesia.[12] The disease can be precipitated by environmental factors,[11–12] such as pesticides and neuroleptic drugs or mutations in genes encoding various proteins (e.g., α-synuclein, parkin, PINK1).[13] The disease is associated with intracellular accumulation of misfolded proteins and Lewy bodies that lead to neurodegeneration[9,12–13] Oxidative stress, excitotoxicity, and neuroinflammation are additional features of the disease, which share similarities

with other neurodegenerative conditions.14 Current therapeutic strategies aim to increase dopaminergic transmission in the basal ganglia by administering dopamine precursors, such as L-DOPA,[11–12] however, in a proportion of patients, treatment efficacy declines over time.[9,12] They also appear to slow clinical progression in humans. Regardless of the diverse etiology, there are common features of neurodegenerative diseases,[8–9,11] such as neuroinflammation and oxidative stress, which contribute to neuronal cell loss.[7,9,11] Although (CBD)-based drugs can target these processes to confer neuroprotection, the ability to directly evoke pathways associated with cell survival is another interesting facet of (CBD) action.6-7 Neuronal survival depends on local concentration gradients and growth factors, neuronal viability can be increased consequently by increasing the availability of neurotrophic factors.[12]

In this context, bioactive compounds from Cannabis sativa have demonstrated antioxidant, anti-inflammatory, and neuroprotective effects in preclinical models of central nervous system diseases.[13] However, the majority of studies supporting the ability of cannabinoids to slow disease progression and prolong survival in (MS)[8,9–11] have been conducted in animal models, whereas the few clinical trials investigating cannabinoid-based drugs have focused only on relieving (MS)-related symptoms,8 not on controlling disease progression.10 While cannabinoids may have potential clinical benefits, their use is not without potential adverse effects and more research is needed to define their role in medical practice.[5,9–10] Studies indicate that (CBD) may have therapeutic potential in the treatment of neurological disorders (e.g., Huntington's disease, Parkinson's disease, and multiple sclerosis)7 and inflammatory bowel disease, as well as having antibacterial activity.[13] There is growing interest from the medical industry in the commercial use of medicinal cannabis products.[14] The objective of this study is to present the state of the art of the publications expressed in the world scientific literature on the topic, as well as to identify the therapeutic benefits of medicinal cannabis in the treatment of the symptoms of neurodegenerative diseases specifically Parkinson's disease, multiple sclerosis and Alzheimer's disease.[11]

METHODS

This is an integrative literature review study. The research question was defined using the PICO strategy. It is intended to answer the guiding question: Is medicinal cannabis (I) effective (O) in treating symptoms (C) in patients with degenerative neurological disease (P)? The keywords "medicinal cannabis" AND "Parkinson's" AND "Multiple Sclerosis" AND "Nervous System Diseases" were defined from the Health Science Descriptors (DeCS) vocabulary. These were combined using the Boolean operator AND in the electronic libraries: Web of Science, Scopus, Cochrane Library, Medline, LILACS, and SciELO. Inclusion criteria: publications of studies from 2017 to 2021, with abstracts and full texts available in the databases cited. Opinion articles, editorials, letters to the editor, duplicate articles, and publications that did not address the topic were excluded. A total of 158 studies were identified, of which 8 were selected for this review, presented through the PRISMA flowchart,[15] Figure 1. A form was prepared consisting of variables related to the identification of the article: Author/year/country and; characterization of the studies; research subjects, synthesis of results and level of evidence. Critical analysis of the selected works, comparing theoretical knowledge, identification of conclusions and implications resulting from this review, which enabled the understanding of the state of the art of knowledge production on the impact of cannabis in the treatment of pain in cancer patients. The level of evidence identified in the analyzed articles was classified according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[16] In this system, the quality of evidence is described in four levels: high, moderate, low, and very low, Chart 1.

Evidence from randomized clinical trials can be downgraded by lack of confidentiality of allocation, lack of blinding, incomplete follow-up, selective reporting of outcomes, and other limitations, such as early termination of the study for benefit and insufficient information to assess whether there is significant risk of bias.16 For each of these domains, the risk of bias is assessed, being classified as high risk, uncertain, and low risk of bias.

Chart 1 – Levels of Evidence, 2021.

Level	Definition	Implications
High	There is strong confidence that the true effect is close to the estimated one	It is unlikely that further work will modify confidence in the effect estimate
Moderate	There is moderate confidence in the estimated effect	Future work may modify confidence in the effect estimate, with the possibility of even modifying the estimate
Low	There is limited confidence in the effect	Future work is likely to have a major impact on our confidence in the effect estimate
Very Low	There is limited confidence in the effect. There is an important degree of uncertainty in the findings	Any effect estimate is uncertain

Source: The authors, 2021.

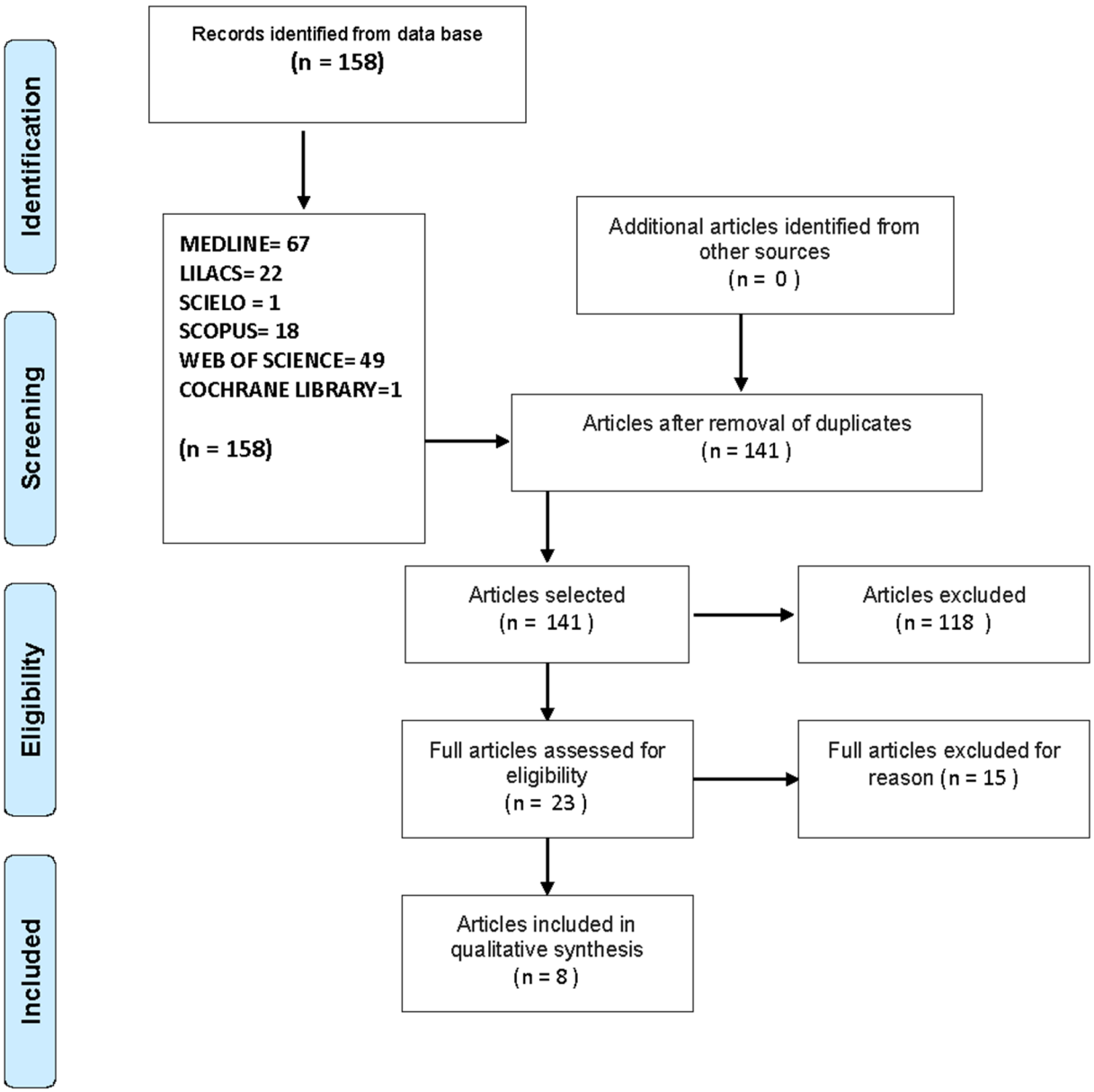

Figure 1 – Selection of articles by descriptors in the databases Rio de Janeiro, RJ, Brazil, 2021.
Source: The authors, 2021.

RESULTS

A total of 158 studies were identified in these databases, as illustrated in Figure 1, which followed the PRISMA15 recommendations to describe the literature search process. Of these, 17 duplicate articles were excluded, leaving 141 unique articles. Then, the titles and abstracts were read, observing the inclusion and exclusion criteria. As a result of this process, 118 articles were excluded, and another 23 articles met the eligibility criteria. We then started the full, in-depth reading of these studies by two reviewers, independently. Any disagreements between reviewers that arose during this stage were worked out and resolved by consensus, resulting in a final sample of 8 articles. The articles included in this synthesis, Table 1, were developed in eight different countries: United States (n=two), Australia (n=one), Canada (n=one), England (n=two) Canada (n=two) covering, in their completeness, as subjects, patients with neurodegenerative diseases - specifically Parkinson's, multiple sclerosis and Alzheimer's diseases, the object of this study does not delve into their stages. As for the method, most researchers used the quali-quanti approach to describe and analyze, in depth, the different dimensions of the therapeutic process with medical cannabis.

Table 1 – Categorization of the scientific production included in the review.

Title	Author/Country Year	Goal	Method	Result	Level of Evidence
The multiplicity of action of cannabinoids: implications for treating neurodegeneration	Gowran; Noonan; Campbell, 2020 USA	This article will discuss the experimental and clinical evidence supporting a potential role for CB-based therapies in the treatment of certain neurological diseases that have a neurodegenerative component.	Systematic review	The development of such therapeutic strategies will depend on a more detailed understanding of the role of the CB system in disease pathology, in order to exploit this knowledge and circumvent the disease process.	Very low
Cannabis therapeutics and the future of neurology	Russo, 2018 / Czech Rep.	Examining the intriguing promise that recent findings on cannabis-based medicines offer to neurological therapy	Systematic review	Current basic science and clinical investigations support the safety and efficacy of such interventions in the treatment of these currently intractable conditions, which in some cases share pathological processes, and the plausibility of interventions	Low
Review of the neurological benefits of phytocannabinoids	Maroon; Bost, 2018 / USA	We will emphasize the neuroprotective, anti-inflammatory, and immunomodulatory benefits of phytocannabinoids and their applications in various clinical syndromes.	Randomized Clinical Trial	In addition, psychiatric and mood disorders such as schizophrenia, anxiety, depression, addiction, post-concussion syndrome, and post-traumatic stress disorder are being studied with phytocannabinoids.	Moderate
Medicinal cannabis	Murnion, 2020 / Australia	To address the unique pharmacology of CBG, our current knowledge of its possible therapeutic utility, and its potential toxicological risks.	Cross-sectional study	In general, medical cannabis is not recommended for chronic non-oncologic pain. In fact, its psychoactive effects may cause insufficient impairment in multimodal, non-pharmacological pain control	Low
Neuroprotection in experimental autoimmune encephalomyelitis and progressive multiple sclerosis by cannabis-based cannabinoids	Pryce et al., 2018 / England	Here, we show that synthetic cannabidiol can delay the accumulation of inflammatory penumbra deficiency during experimental relapse of autoimmune encephalomyelitis (EAE) in ABH mice	Experimental Study	They also appear to slow clinical progression during MS in humans. Although a 3-year phase III clinical trial failed to detect a beneficial effect of oral Δ9-THC in progressive MS	Moderate
Cannabinoid control of neuroinflammation related to multiple sclerosis	Backer, 2019 / England	Whether cannabinoids can modify the neuroinflammatory element that drives recurrent neurological attacks and the accumulation of progressive disability	Systematic review	cannabinoids may inhibit activation, cytokine release, and migration of astroglia and microglial, which could limit nerve destruction during immune attack	Very low
Benefits and harms of medical cannabis: a scoping review of systematic reviews	Pratt et al., 2019 / Canada	Verify the effectiveness of cannabis in controlling the symptoms of neurodegenerative diseases	Review Study	Most reviews (43/72 60%) indicated an inability to draw conclusions, either due to uncertainty, inconsistent findings, lack of (high-quality) evidence, or by focusing their conclusion statement on the need for further research.	Low

Source: The authors, 2021.

DISCUSSION

Cannabis compounds, namely Δ9-tetrahydrocannabinol (THC), may limit the inappropriate neurotransmissions that cause multiple sclerosis-related problems highlights, Russo (2018).[17] In his research his results point out that the endocannabinoid system may offer the potential to control other aspects of the disease.[17] While there is limited evidence that cannabinoids from cannabis are having significant immunosuppressive activities that will influence recurrent autoimmunity the neurodegeneration that leads to progressive disability.[17] The study by Gowran; Noonan; Campbell (2020)[18] states that the endocannabinoid system may serve as a useful target for the treatment of motor dysfunction,[18] since the endocannabinoid system is expressed in the basal ganglia, where it regulates neurotransmitter release and motor activity.[18] This result is in line with research by Maroon and Bost (2018)[19] where they report that in patients with Parkinson's disease, endocannabinoid levels in the cerebrospinal fluid are increased.[19] The anti-inflammatory, antioxidant, and pro-neurogenic properties of (CBD) are features that may be relevant for the treatment of a number of neurodegenerative diseases.[19]

Backer's (2019)20 subsequent research demonstrated that the seizure threshold is mediated by the endocannabinoid system and that (THC) produced a 100% reduction in seizures, while phenobarbital and diphenylhydantoin did not.[20] Furthermore, animal studies demonstrated acute increases in endocannabinoid production and a long-term positive regulation of (CBD)[20] production as apparent compensatory effects counteracting the excitotoxicity of glutamate,[21] and that the anticonvulsant effect was present at subsedating levels.[22]

More recently, in 2019 Pratt et al.23 Published a study that evaluated (CBD) for intractable epilepsy in 16 patients with epileptic seizures.[24] Each patient received 200-300 mg daily of (CBD)25 or placebo along with antiepileptic medications for up to 4 months.26 They found that in the treatment group 7 of 8 responded with fewer seizures,[27] this result corroborates with studies by Pryce (2018)[28] where they point out that cannabis use decreases some symptoms associated with these disorders.[29] Cannabis use decreases pain and spasticity in people with (MS), decreases tremor, stiffness, and pain in people with Parkinson's disease, and improves quality of life in patients with (MS) by improving appetite and decreasing pain and muscle spasticity.[30] In late-stage Alzheimer's patients,[31] cannabis products may improve food intake, sleep quality, and decrease agitation in order to localize the source of discordance.[32] There are mixed data in animal models of epilepsy.[33] (THC) has been shown to be pro- and anticonvulsant.[34] Cannabidiol appears more promising, with some limited experience in humans.[35] Preliminary data from a study with cannabidiol (Epidiolex)[36] found benefit in treatment-resistant pediatric epilepsy.[37] This generated much debate in the community[38] and caused parents to illegally access cannabinoids for the treatment of children with catastrophic epileptic syndromes.[39]

CONCLUSION

It is imperative that the debate over the use of medical cannabis not be confused with the legalization of recreational marijuana. There is some evidence of therapeutic benefit for cannabis products in defined patient populations. While waiting for a regulatory framework, more defined products and more definitive data to be available, with appropriate legislation to prevent criminalization, for narrowly defined populations and diseases. Individual and community safety monitoring should be a component of any model. With the increasing use of medical cannabis, an understanding of the landscape of available evidence syntheses is needed to support evidence-based decision making. Future trials may also help elucidate the effect of cannabis in different contexts, thus future prospective studies should be guided by a standardized set in order to ensure consistency across studies and ensure relevance to patient-centered care.

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