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IS CANNABINOID AN ALTERNATIVE TO THE CURRENT PHARMACOLOGICAL TREATMENT FOR THE REDUCTION OF PARKINSON'S DISEASE SYMPTOMS?

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Abstract: Parkinson's disease (PD) is a highly prevalent disease worldwide, generally with a higher incidence in the population over 60 years of age. PD is classified as a neurodegenerative disease, as it begins with the wear and tear of cells in a region in the brain called the substantia nigra, which is responsible for producing dopamine that drives neurotransmitters. Current treatment is based on levodopa replacement therapy and is given by L-DOPA-induced dyskinesia (LID). However, the pharmacological therapy of LID over the years presents uncontrollable motor movements, in addition to symptoms such as depression, anxiety, sleep disturbance, cognitive dysfunction and pain, severely impairing the quality of life of patients. In order to minimize these effects, there was a need to enable other forms of treatment for PD, cannabinoid-based drugs (CBD) for this condition have been an alternative. The purpose of this article is to analyze whether CBD would be an effective alternative to treating Parkinson's disease. The method of analytical review of medical literature used the search for the words "cannabinoids", "parkinson's disease" and "treatment" on the platforms of the National Lybrary of Medicine and the Capes Periodical. The result was Inconclusive due to the scarce number of samples in the studies and the insufficient time for their observation, allowing the occurrence of a bias and compromising the studies evaluated. Therefore, although the research is promising, it is early to define the salutary effect of cannabinoids in the treatment of Parkinson's disease.
Keywords: Cannabinoids, Parkinson's disease, Treatment.

INTRODUCTION

Today Parkinson's is the second most common disease among the elderly population, affecting mainly people over

60 years of age. Its main neuropathological indications are obtained by the neuronal loss of the substantia nigra of the brain, identified by motor symptoms, which refers to a deficiency of dopamine in the striatum, in addition to intracellular inclusions that contain omega-synuclein (Ω-synuclein) aggregates. (1)

Although there is involvement of several cell types throughout the central and peripheral nervous system, from the initial stage of the disease, the clinical diagnosis depends mainly on the presence of bradykinesia, as well as other cardinal motor characteristics. The underlying molecular pathogenesis comprises multiple pathways and mechanisms, such as: Ω-synuclein protease; mitochondrial function, oxidative stress, calcium homeostasis, axonal transport and ending neuroinflammation. (two)

One of the main symptoms is irregular tremor, very characteristic in PD, with rigidity, postural instability and resting tremor being common. However, it is known that PD may be related, in addition to motor symptoms, to anxiety, depression, sleep disturbance, cognitive dysfunction, pain, and a general decline in the patient's quality of life. (two)

Currently, first-line medication occurs through dopamine precursors, such as LID, whose function is to correct this dopamine deficiency in the body. However, the current treatment available does not have the ability to be neuroprotective or even to alleviate the most common symptoms of the disease. (3)

In addition, the administration of dopaminergics presents an efficient response only in the initial phase of PD, that is, the chronic use of the medication results in fluctuations of effects with periods of dyskinesia induced by LID and, consequently, the motor complications affect patients again after two years. of continuous use. (4)

Thus, in the last decade there has been a greater interest in alternatives to the current treatment for dopaminergics such as endocannabinoids (ECS), which act on type 1 cannabinoid receptors (CBD) and aim to modulate the activity of dopamine and other transmitters in the body. basal ganglia, thus making this new substance a potential drug. (1)

Extracted from an ancient and psychotropic plant with the scientific name cannabis sativa, CBD has a complex pharmacology, which shows to contain several mechanisms in addition to psychotropics. Its by-products are increasingly being investigated by the scientific community, both in humans and animals, as a way of proving its beneficial effects in neuropsychiatric disorders. (two)

It is known that the great therapeutic value of CBD is concentrated in the component of tetrahydrocannabidiol (Δ9-THC). Recent studies suggest that, by increasing the levels of endogenous endocannabinoid anandamide (EAA) within the cerebrospinal fluid of symptomatic and untreated patients, these compounds would offer antiparkinsonian actives with neuroprotective properties. (3)

CBD is classified as a phytocannabinoid, meaning it is derived from the plant named cannabis sativa and extracted in the form of an oil. (5)

Thus, the role of cannabinoids is fundamental in suppressing toxicity, glial activation and oxidative damage that affect the degeneration of dopaminergic neurons, suggesting that CBD can contribute to the treatment of PD symptoms, in addition to promoting the reduction of LID. (3)

Based on this, it is understandable how PD is capable of causing a great impact on the patient's quality of life, since the motor and non-motor effects fail to correspond satisfactorily in a few years to dopaminergic therapy, and some are even aggravated by it. Dopaminergic refractoriness implies

the urgent need for medicine to find an alternative that targets other pharmacological systems that comprise a multimodal approach to therapy, with activity in the dopaminergic and non-dopaminergic system. (6)

Therefore, it is important to highlight that, although there are many studies concluded and an interest in the scientific exploration of the subject, medical indications need to be evidenced in the effectiveness of CBD treatment for PD symptoms, since, although these studies are promising, many authors point out gaps in clinical trials performed on humans with low samples and tests performed for a short time. (3)

METHODOLOGY

This is a review of articles published in the databases of: *National Library of Medicine* (PubMed) and in the Coordination for the Improvement of Higher Education Personnel (Periódicos Capes).

The keywords used in the English descriptor were "Cannabidiol", "Parkinson's disease" and "Treatment", using the Boolean "AND" in the advanced search. Full texts, available in Portuguese and English, published between 2014 and 2022, of articles such as clinical trials, meta-analysis, observational studies and systematic review were chosen as inclusion criteria.

For the exclusion criteria, articles without relevance to the topic of cannabidiol in the treatment of PD, as well as duplicate articles in the two searched databases, were eliminated.

As a result of the total search, 1,154 articles were found between the two platforms, searched until January 9, 2022. Among these, 77 in the PubMed database and a total of 1,077 in the Capes database. Using full texts as inclusion criteria in PubMed and adding the period from 2014 to 2022, 77 articles remained. Finally, selecting the type of study applied as clinical trial, meta-analysis, observational studies and systematic review, a total of 7 articles remained. Of these, 3 were not related to the topic, leaving 4 articles for PubMed. At Capes, adding the period from 2014 to 2021, 827 articles remained. Of which, using the Boolean "expand more results" and including filters for the type of article such as clinical trial and cannabidiol, 29 articles remained. Of these 29 articles, 2 were in duplicate with the results found in PubMed and 10 articles were not related to the research topic, thus leaving 18. That said, and adding the two databases, 20 articles were analyzed in total.

Finally, this study was based on the following research question: would cannabinoids be an alternative to the current pharmacological treatment to improve the symptoms of Parkinson's disease?

RESULT

Analyzing Table 1, it can be seen that the results of the sum of the analyzed articles were 10 for positives, 9 for Inconclusives and only 1 for negative.

Among the 10 articles with positive results, Santos Pereira proves in a clinical study carried out in mice with striatal neuroinflammation and dyskinesia developed by the use of L-DOPA, that they contained a glial response associated with the increase of two pro-inflammatory cytokines, also determined by the tumor necrosis factor-alpha (TNF-α) and interleukin-1beta. Once CBD use was started for 6 continuous weeks, these mice were able to decrease LID intensity and TNF-α levels without causing further inflammation afterwards. (7)

Another clinical study and positive result, submitted 24 PD patients in a human clinical trial designed by Faria, which statistically showed a significant decrease in anxiety levels in CBD users, but without observation of success for bradykinesia tests. (8)

However, 9 articles found inconclusives the use of CBD to improve symptoms and as a treatment for Parkinson's, pointing out the lack of evidence of a correlation between the use of cannabidiol and the relief of PD symptoms. According to Carlos Rieder, the research group from the Faculty of Medicine of Ribeirão Preto, University of São Paulo and its measurement in animals and humans in pre-clinical studies involving the use of CBD contained a small sample and the period of short duration, contrary to the recommendations of the Movement Disorder Society's Evidence-Based Medicine Committee for PD treatments. Although the author highlighted the results as "interesting", he noted that no conclusions can yet be drawn, reiterating the importance of conducting more specific studies to assess the safety profile and long-term adverse effects of cannabidiol against its potential. therapy in PD. (6)

Another highlight in a study considered Inconclusive referred that observational studies showed the subjective relief of PD symptoms, but that the evidence is insufficient to support its application in clinical practice as a treatment of Parkinson's motor symptoms, lacking better quality data. (3)

In addition, only one study was negative for CBD as a treatment for Parkinson's, which Hande took a contrary position, stating that there is currently no regulation of CBD products, and therefore the Federation Drugs Administration (FDA) is still unable to regulate the quality and assurance of its potential benefits as well as its side effects. In this study, with a contrary position, the premise about the scarcity of evidence for the popular uses of cannabidioids was reinforced, although with great expectations for new studies and more precise results. (9)

DISCUSSION

It is possible to establish analytically the main conclusions that lead to CBD as an alternative treatment capable of improving the quality of life of patients with PD, since it is proven that the long-term induction of dyskinesia by L-DOPA in hermiparkinsonian mice contains a large glial inflammatory response, restricted to the dorsal part of the striatum and depleted (saturated) in dopamine. The occurrence of astrocytes was particularly prominent within the striatal area, relating the severity of LID to increased levels of TNF-Δ and IL-1β. It was therefore corroborated that CBD treatment, in addition to efficiently decreasing the development of LID in dyskinetic mice, also selectively reduced striatal TNF-alpha levels, without developing other indicators of striatal inflammation, including IL-1β. (7)

In a clinical trial carried out by Crivelaro do Nascimento, CBD was suggested as responsible for reducing the nociception of animals with selective loss of the nigrostriatal dopaminergic pathway, also indicating an ability to promote an analgesia effect to the same subjects submitted to the study. (4)

In fact, the tests on injured mice showed that CBD acted with effects capable of reducing the depletion of PD and attenuating the neuronal oxidative stress caused by it. As mentioned by Cassano, by increasing the expression of this superoxide stimulated by the use of CBD, the cell defended against oxidative stress and attenuated the neurodegeneration of nigrostriatal dopaminergic fibers that occur in PD. This study was based on the thesis on the observation that CBD as a used treatment can reduce neuronal death in the striatum that occurs after the administration of 3-nitropropionic acid (3NP), a mitochondrial complex II inhibitor. Furthermore, CBD was able to completely abolish the atrophy of

neurons named GABAergic, known for their stabilizing functions within the neuronal nervous system. (13)

Likewise, in human studies, a double-blind, placebo-controlled randomized clinical trial indicated that CBD tested positively among 24 individuals with PD who underwent 2 experimental sessions with a dosage of 300mg of CBD, alleviating anxiety and anxiety. amplitude of tremors. These data were confirmed by means of the Visual Analog Mood Scale (VAH), the Self-Assessment Scale during Public Speaking (ADFP), in addition to the statistical analysis using the repeated measures variance scale (VMR).

A new consideration evidenced by this study was the analysis of CBD in the interaction between anxiety and motor signals, since the increase in anxiety can lead to worsening of dyskinesia in patients with PD. Thus, the study indicated that CBD alleviated ADFP-induced anxiety and reduced tremor amplitude during the experimental test.

Also according to Faria, the amygdala is a mechanism directly related to fear, which is conditioned to fight-or-flight behavior. In a neuroimaging study in PD patients showed that CBD reduced the effectiveness of the connection between the cingulate cortex and the amygdala during the processing of stimuli composed of fearful facial expressions. Thus, these observations suggest that chronic administration of CBD may be an alternative treatment for parkinsonian patients with symptoms of anxiety. (10)

However, although the Positives results were presented in greater amounts in isolation, they proved to be small compared to the results of Negatives or Inconclusives studies, partially invalidating the claim that CBD is an effective treatment in the attenuation of Parkinson's symptoms. In line with the observation made by Koppel (10), there is a need for larger samples and for a longer period of time, in double-blind, placebo-controlled and randomized clinical trials in patients with PD, in order to corroborate the efficacy and mechanisms involved in the treatment. CBD in movement disorder. Even so, to indicate in the studies the putative effects, such as for the prevention of serious side effects induced by L-DOPA and the prevention of the progression of PD. Finally, relate the safety profile of CBD to possible interactions with other antiparkinsonian drugs and their presumptive side effects. (1)

Only the study prepared by Faria was against the proposals for the Positive effects of CBD on PD and among them, the clinical study using placebo versus CBD, Faria found dissatisfaction in improving the quality of sleep of Parkinson's patients. Finally, the indication of the research carried out did not find evidence of improvement in PD symptoms and was terminated due to lack of evidence. (11)

CONCLUSION

When evaluating the present studies, it is still not possible to make a statement about the safety of use and the therapeutic effects of CBD in PD. It will be necessary to expand these studies into clinical trials in humans with the presence of a greater number of samples and observed for a longer period. Only this way will they be able to better prove the regression of motor and non-motor symptoms in PD patients and, equally, determine their dosages, duration of use and their neuroprotective effects.

Furthermore, it is urgent to regulate CBD at the FDA for a specific quality control that provides the pharmacological safety essential to patients using this substance.

Finally, this article still remains Inconclusive CBD as a treatment for the

symptoms of parkinsonian patients, since the lack of evidence warrants the continuity of studies as a form of safe consumption for doctors and patients under its true potential effect and its adverse implications in the medium and long term.

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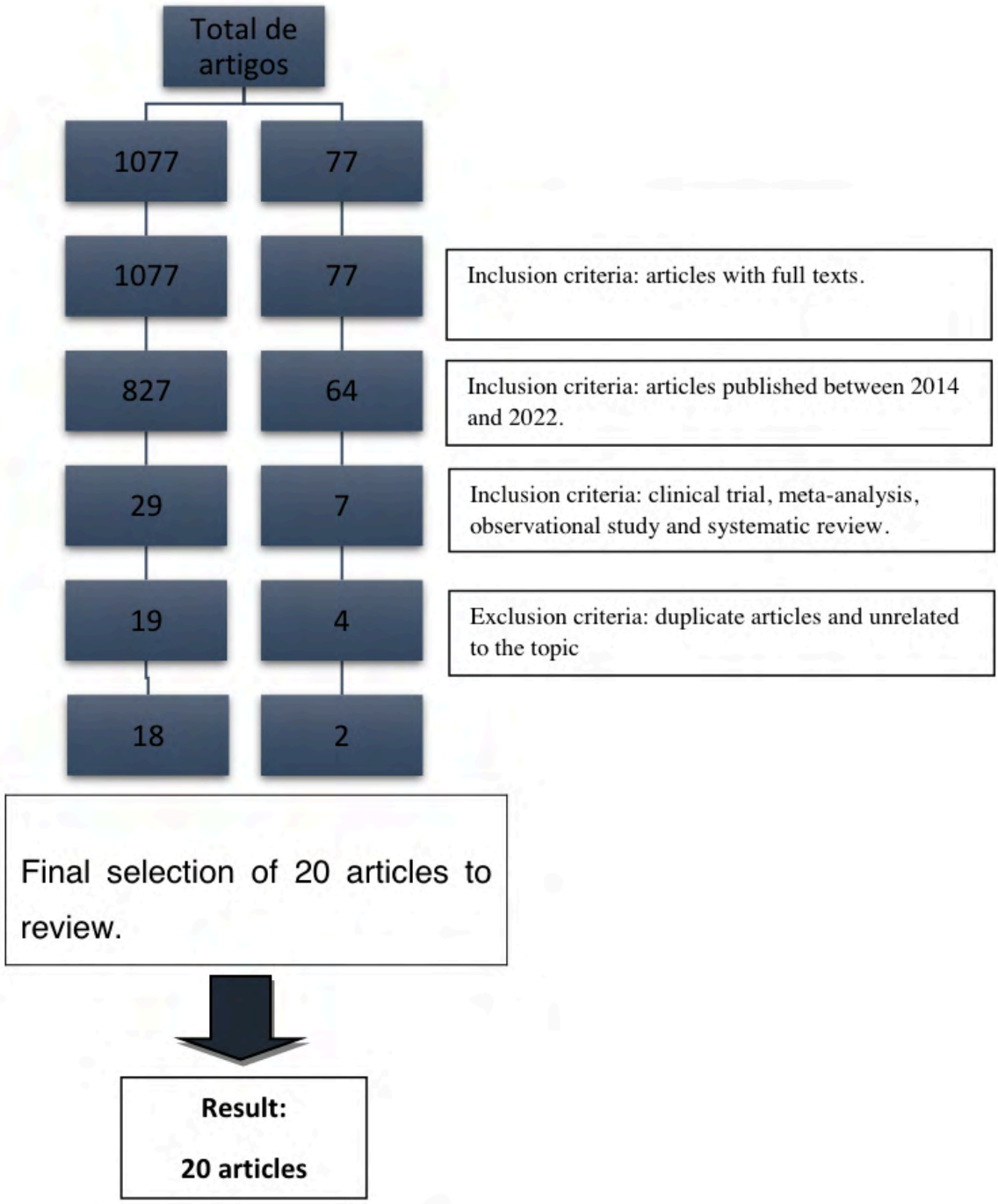

Figure 1. Article search results.

Source: Author, 2022.

Autor	Ano	Metodologia de estudo	Resultado
(12)	**2021**	Systematic review	**Inconclusive**
(1)	**2020**	In vivo and in vitro clinical trial	**Positive**
(3)	**2021**	Observational study	**Inconclusive**
(13)	**2020**	Systematic review and meta-analysis of clinical studies	**Inconclusive**
(14)	**2020**	Systematic review and meta-analysis of clinical studies	**Positive**
(8)	**2016**	Systematic review	**Positive**
(15)	**2020**	Clinical trial	**Positive**
(7)	**2020**	In vivo and in vitro clinical trial; Cellular and molecular analyses; Statistical analysis	**Positive**
(6)	**2020**	In vivo and in vitro clinical trial; Randomized clinical trial; open pilot	**Inconclusive**
(4)	**2020**	Randomized clinical trial; Double-blind; placebo controlled	**Positive**
(16)	**2020**	In vitro clinical trial	**Positive**
(17)	**2020**	Systematic review	**Inconclusive**
(11)	**2020**	Randomized clinical trial; Double-blind; placebo controlled	**Positive**
(18)	**2021**	Randomized, double-blind, placebo-controlled clinical trial	**Inconclusive**
(2)	**2019**	Randomized clinical trial	**Positive**
(19)	**2018**	Evidence-based study	**Inconclusive**
(13)	**2015**	Systematic review and meta-analysis of clinical studies.	**Inconclusive**
(20)	**2014**	Double-blind exploratory trial	**Inconclusive**
(10)	**2014**	Systematic review	**Inconclusive**
(9)	**2019**	Systematic review and meta-analysis of clinical trials	**Negative**

Table 1. Exposure of articles according to author, year of publication, study methodology and results.

Source: Author, 2022.