Beyond conventional therapy: cannabinoids as an alternative in parkinson's disease

Além da terapia convencional: canabinóides como alternativa ao mal de parkinson

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ABSTRACT  
Parkinson's disease (PD) is a neurodegenerative pathology on the rise worldwide. There is a demand for new therapeutic options that contribute to more quality of life and autonomy for people with PD. Recent studies suggest the therapeutic potential of medicinal cannabinoids for neurological pathologies. This manuscript aimed to review the use of medicinal cannabinoids in PD to provide an updated overview and verify new demands. A scoping review was conducted with the search of references in Databases, grey literature, and manual search. Articles in Portuguese, Spanish, or English with no date restriction were included. Ninety-five articles published between 1990 and 2022 were eligible for the final sample, originating mainly in the USA and Brazil. As for the administration, the oral route was the most common and several symptoms showed improvement after the use of cannabinoids, highlighting: rest tremor, muscle rigidity, bradykinesia, dyskinesia, pain, insomnia, and anxiety. The most common undesirable effects were: dizziness, drowsiness, hallucinations, and xerostomia. It was observed studies with sample bias, recall bias, information bias and non-response bias, and low quality of evidence. To produce the evidence desired by all actors interested in the use of medicinal cannabinoids and their products, double-blind, multicentre randomized clinical trials are necessary with experimental, control and placebo, and follow-up groups, to evaluate the neurological potential of the cannabinoids in PD and elaborate systematic review protocols without language restriction, with a larger number of Databases and grey literature.

Keywords: cannabinoids, medicinal cannabinoids, CBD, THC, Parkinson.

RESUMO  
A doença de Parkinson (DP) é uma patologia neurodegenerativa em ascensão em todo o mundo. Há uma demanda por novas opções terapêuticas que contribuam para uma maior qualidade de vida e autonomia para as pessoas com DP. Estudos recentes sugerem o potencial terapêutico dos canabinóides medicinais para patologias neurológicas. Este manuscrito teve como objetivo rever o uso de canabinóides medicinais em DP para fornecer uma visão geral atualizada e verificar novas demandas. Uma revisão de escopo foi conduzida com a pesquisa de referências em bancos de dados, literatura cinza e pesquisa manual. Artigos em português, espanhol ou inglês sem restrição de data foram incluídos. Noventa e cinco artigos publicados entre 1990 e 2022 foram elegíveis para a amostra final, originários principalmente dos EUA e do Brasil. Quanto à administração, a via oral foi a mais comum e vários sintomas apresentaram melhora após o uso de canabinóides, destacando-se: tremor de repouso, rigidez muscular, bradicinesia, discinesia, dor, insônia e ansiedade. Os efeitos indesejáveis mais comuns foram: tonturas, sonolência, alucinações e xerostomia. Foram observados estudos com viés amostral, viés
de recordação, viés de informação e viés de não-resposta e baixa qualidade de evidência. Para produzir a evidência desejada por todos os atores interessados no uso de canabinóides medicinais e seus produtos, são necessários ensaios clínicos randomizados duplamente cegos e multicéntricos, com grupos experimentais, de controle e placebo, e de acompanhamento, para avaliar o potencial neurológico dos canabinóides em DP e elaborar protocolos de revisão sistemática sem restrição de linguagem, com um maior número de bases de dados e literatura cinza.

**Keywords**: canabinóides, canabinóides medicinais, CBD, THC, Parkinson.

### 1 INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative pathology on the rise worldwide. Recent research confirms the global increase in the prevalence and incidence of PD (Ou et al., 2021). Three aspects stand out in PD: the rapid growth in the number of cases; the absence of modified drugs; and the scarce information on its financial, socioeconomic, and occupational impacts. These elements are significant, given the decline in productivity and monthly income of individuals with Parkinson's and their family caregivers, along with the associated direct and indirect medical expenses (Yang et al., 2020; Dahodwala et al., 2021; Bovolenta et al., 2017).

Cannabinoids are separated into three groups, Phytocannabinoids, Endocannabinoids, and Synthetic cannabinoids (Lim; Se; Lee, 2017). The endocannabinoid system is a crucial regulatory system involved in physiological homeostasis. Originally identified from studies on the mechanism of action of the psychotropic ingredient of some varieties of cannabis, Δ 9 -tetrahydrocannabinol (THC), it is defined as the ensemble of two 7-transmembrane-domain and G protein-coupled receptors (GPCRs) for THC-cannabinoid receptor type-1 (CB 1 R) and cannabinoid receptor type-2 (CB 2 R), their two most studied endogenous ligands, the "endocannabinoids" N-arachidonylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG), and the enzymes responsible for endocannabinoid metabolism (Everett et al., 2021; Khan; Lee, 2014; Di Marzo; Piscitelli, 2015).

Cannabidiol (CBD) has shown promising potential in preclinical studies as a treatment for various neurological disorders, such as epilepsy, multiple sclerosis, and Parkinson's disease. Its neuroprotective properties enable it to protect the brain from damage...
caused by inflammation, oxidative stress, and excitotoxicity. Additionally, CBDV, a structural analog of CBD, holds promise in treating PD by inhibiting the aggregation of α-synuclein (α-syn). The phenolic hydroxyl groups in CBDV play a crucial role in reducing α-syn aggregation and safeguarding dopaminergic (DAergic) neurons from damage and degeneration. While CBDV does not directly interact with α-syn or inhibit its fibril formation, it effectively prevents oxidative stress and α-syn accumulation in worms through mediation by DAF-16 (Dawidowicz; Olszowy-Tomczyk; Typek, 2021; Chagas et al., 2014a; Peball et al., 2020; Andre; Hausman; Guerriero, 2016; Gonzalez-Cuevas et al., 2023; Wang et al., 2023).

The increased prevalence of PD in the coming decades due to population aging and increased survival (Safarpour et al., 2015; Yang et al., 2020) challenges the scientific community to investigate new therapeutic options that go beyond symptomatic treatment, options that are effective in palliative treatment, interruption or reversal of concomitant pathological processes and with fewer side-effects (Russo, 2018) and contribute to a better quality of life, to prolong the patient’s autonomy and in return reduce the cost to the State (Bovolenta; Felício, 2016). In this context, recent studies have explored the therapeutic potential of medicinal cannabinoids, mainly CBD and CBD-rich extracts in neurological pathologies (Thanabalasingam et al., 2021; Whiting et al., 2015).

2 MATERIAL AND METHODS

In this scoping review, a systematic approach was employed to map and synthesize the body of evidence concerning the use of cannabinoids in the treatment of PD. The primary objective was to identify sources and knowledge gaps. Adhering to the guidelines set by PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) the aim was to assess the breadth, variety, and characteristics of the available evidence, summarize findings from a knowledge base that is methodologically diverse, and pinpoint unexplored areas in the literature to guide future research endeavors.

The literature search strategy encompassed database exploration, as well as the examination of pertinent citations from websites and grey literature, including platforms
like Google Scholar. On June 8, 2021, a comprehensive search was executed, with subsequent articles being incorporated after a manual search in electronic databases such as Medline/PubMed and Lilacs/BVS.

The search strategy employed descriptors and their synonyms, specifically: (Parkinson) AND (cannabis). Utilizing the MeSH (Medical Subject Headings) tool from the PubMed library, related terms were automatically integrated into the search, resulting in the following strategy: ("Parkinson’s disease"[MeSH Terms] OR "Parkinson disease"[All Fields] OR "Parkinson’s"[All Fields] OR "Parkinson"[All Fields]) AND ("cannabis"[MeSH Terms] OR "cannabis"[All Fields]).

2.1 ELIGIBILITY CRITERIA AND STUDY SELECTION

A comprehensive set of eligibility criteria was established to identify pertinent literature exploring the potential of cannabis-based medicine in alleviating motor and/or non-motor symptoms in patients with PD. The criteria for inclusion encompassed full articles accessible in electronic media, written in English, Portuguese, or Spanish, and providing relevant information on the subject matter. The studies deemed eligible for this analysis included systematic reviews, randomized and non-randomized clinical trials, observational studies, case reports, animal experimentation, and in vitro research. Additionally, pertinent review studies that did not exclusively focus on PD populations were also considered. Conversely, articles that were repetitive, not written in the specified languages, or did not provide relevant information concerning the potential of cannabis-based medicine in treating motor and/or non-motor symptoms in PD patients were excluded from the review.

2.2 CLASSIFICATION AND ANALYSIS OF INCLUDED STUDIES

The studies encompassed in this analysis were categorized based on the type of research conducted. For each category, the contexts, studied populations, study designs, used measures, and key findings were synthesized. Clinical studies that investigated the use of cannabinoids and those that assessed the prevalence of cannabinoid use among patients diagnosed with Parkinson's disease were highlighted. When a systematic review
was identified, the number of studies included in the review was tallied, as well as the total number of databases used, and the language criteria applied.

The results were presented in a narrative manner, in tables, and visual representations, to facilitate the understanding and interpretation of the data. This process enabled a comprehensive and detailed analysis of the existing literature on the use of cannabinoids in Parkinson's disease, assisting in identifying the research needs in the area, in compliance with the recommendations of the PRISMA-ScR (Tricco et al., 2018).

2.3 ARTICLE SELECTION AND INCLUSION PROCESS

A total of 288 articles in English, Portuguese, and Spanish were included without any date restriction. Articles that were repetitive or written in languages other than those specified in the inclusion criteria were excluded (Figure 1).

After the exclusion of duplicates, 171 articles remained, of which 63 were excluded by the reviewers according to the inclusion and exclusion criteria, leaving a total of 108 articles for the second decision round, when the articles were read in their entirety. In this second stage of choice, 37 articles were excluded, leaving 71 articles for data collection. Articles published after 08 June 2021 and others not identified through the database search strategy (n = 24) were added after the manual search.
3 RESULTS

A total of 95 articles were eligible for the final sample. The literature shows a prevalence of publications from the USA (n=20; 21%) and Brazil (n=17; 18.9%). The articles included were published between the years 1990 and 2022 with a higher frequency in the years 2020 (n=17; 17.9%) and 2021 (n=12; 12.6%) (Figure 2). Of the total number of articles, 56 (58.9%) were review articles, of which six were Systematic Reviews (SR), and eleven (11.6%) were clinical trials (Figure 3).
Figure 2. Trend of the number of publications on Cannabis and Parkinson's Disease, from 1990 to 2022 (n=95).

Source: Elaborado pelos autores com base nos dados coletados.

Figure 3. Classification of the selected articles by the level of evidence according to the Oxford pyramid.

Source: Developed by the authors based on the collected data.

Figures 2 and 3 reveal an upward movement in the number of publications with emphasis on the period from 2017 to 2022, in which six Systematic Reviews (SRs) were published.

SRs on the use of cannabinoids in the treatment of PD (Bougea et al., 2020; Prakash; Carter, 2021; Thanabalasingam et al., 2021; Bahji et al., 2022; Urbi et al., 2022; Lim; See; Lee, 2017) were published after 2017 (Table 1), and one of them made a
synthesis of pre-clinical data (Prakash; Carter, 2021). In intervention studies, the oral (Carroll et al., 2004; Faria et al., 2020; Leehey et al., 2020; de Almeida et al., 2021; Mesnage et al., 2004; Peball et al., 2020; Zuardi et al., 2009) and a Cannabinoid isolate (Faria et al., 2020; Chagas et al., 2014b; Leehey et al., 2020; de Almeida et al., 2021; Leehey et al., 2021) were the most commonly used (Table 2).

Table 1. Distribution of Systematic Reviews on cannabinoid use in Parkinson's disease.

<table>
<thead>
<tr>
<th>AUTHOR (YEAR) COUNTRY</th>
<th>CRITERIA</th>
<th>DATABASES</th>
<th>STUDIES INCLUDED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Language</td>
<td>No.</td>
<td>Total</td>
</tr>
<tr>
<td>Lim, See and Lee (2017)*</td>
<td>English</td>
<td>03</td>
<td>03</td>
</tr>
<tr>
<td>Bougea et al. (2020) Greece</td>
<td>English</td>
<td>01</td>
<td>14</td>
</tr>
<tr>
<td>Urbi et al. (2021)** Australia</td>
<td>Unrestricted</td>
<td>&gt;05</td>
<td>26</td>
</tr>
<tr>
<td>Prakash and Carter (2021) England</td>
<td>English</td>
<td>&gt;05</td>
<td>18</td>
</tr>
<tr>
<td>Thanabalasingam et al. (2021)* Canada</td>
<td>English</td>
<td>04</td>
<td>15</td>
</tr>
<tr>
<td>Bahji et al. (2022) Canada</td>
<td>English</td>
<td>03</td>
<td>11</td>
</tr>
</tbody>
</table>

*Evaluated several neurodegenerative disorders and psychiatric conditions. **With meta-analysis; RCT = Randomized Clinical Trial.

Source: Developed by the authors based on the collected data.

Several clinical studies have shown positive effects of cannabinoids in patients with PD and reported improvement in resting tremors, insomnia (Leehey et al., 2020; de Almeida et al., 2021) and pain (Shohet et al., 2017) There have also been studies that have observed no beneficial or adverse effects of these compounds in PD patients (Mesnage et al., 2004; Zuardi et al., 2009). Two studies used Cannabis "in natura" (Shohet et al., 2017; Frankel et al., 1990) with contrasting results.
Table 2. Intervention studies, Clinical Trials and case series, were selected to compose the review.

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>COUNTRY</th>
<th>N</th>
<th>PRODUCT USED</th>
<th>CHEMOTYPE</th>
<th>ROUTE OF ADMINISTRATION</th>
<th>DOSE</th>
<th>RESULT</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frankel et al. (1990)</td>
<td>England</td>
<td>5</td>
<td>Cannabis &quot;in natura&quot;</td>
<td>1 – (THC/CBD ≥10)</td>
<td>Inhalation</td>
<td>2-9mg? 2-9% THC</td>
<td>No alteration</td>
<td>Euphoria Dizziness</td>
</tr>
<tr>
<td>Zuardi et al. (2009)</td>
<td>Brazil</td>
<td>6</td>
<td>CBD isolate</td>
<td></td>
<td>Oral</td>
<td>150-400 mg/day 4 weeks</td>
<td>Decreased scores on the Unified PD Assessment Scale</td>
<td>None</td>
</tr>
<tr>
<td>Carroll et al. (2004)</td>
<td>England</td>
<td>19</td>
<td>Full Spectrum Extract</td>
<td>2 - (THC/CBD between 0.2 and 10)</td>
<td>Oral</td>
<td>2.5mg 0.146mg 4 weeks</td>
<td>No alteration</td>
<td>Dizziness, nightmares, Xerostomia, Constipation</td>
</tr>
<tr>
<td>Mesnage et al. (2004)</td>
<td>France</td>
<td>24</td>
<td>Synthetic cannabinoid (SR 141716)</td>
<td></td>
<td>Oral</td>
<td>20mg/day 16 days</td>
<td>No improvement</td>
<td>None</td>
</tr>
<tr>
<td>Chagas et al. (2014)</td>
<td>Brazil</td>
<td>21</td>
<td>CBD isolate</td>
<td></td>
<td>Oral</td>
<td>75 or 300mg/day 6 weeks</td>
<td>Quality of life</td>
<td>Not reported</td>
</tr>
<tr>
<td>Chagas et al., (2014)</td>
<td>Brazil</td>
<td>04</td>
<td>CBD isolate</td>
<td></td>
<td>-</td>
<td>REM sleep behavioural disorders</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Shohet et al. (2017)</td>
<td>Israel</td>
<td>20</td>
<td>Cannabis &quot;in natura&quot;</td>
<td></td>
<td>Inhalation</td>
<td>1g 40 weeks</td>
<td>Improvement in motor scores and pain symptoms</td>
<td>Not reported</td>
</tr>
<tr>
<td>Faria et al. (2020)</td>
<td>Brazil</td>
<td>24</td>
<td>CBD isolate</td>
<td></td>
<td>Oral</td>
<td>300mg/day 1 day</td>
<td>Resting tremors, anxiety</td>
<td>None</td>
</tr>
<tr>
<td>Leehey et al. (2020)</td>
<td>USA</td>
<td>13</td>
<td>CBD isolate Epidiolex®</td>
<td></td>
<td>Oral</td>
<td>100mg/ml 5 to 20-25 mg/kg/day 10-15 days</td>
<td>Improvement of resting tremors, insomnia</td>
<td>Drowsiness, Diarrhea, Increased liver enzymes Fatigue Dizziness</td>
</tr>
<tr>
<td>Pebbll et al. (2020)</td>
<td>Austria</td>
<td>47</td>
<td>Synthetic cannabinoid Nabilone</td>
<td></td>
<td>Oral</td>
<td>0.25 - 1.75mg 2 phases 4 weeks?</td>
<td>Insomnia, pain, anxiety</td>
<td>Dizziness Sleepiness Xerostomia Fatigue</td>
</tr>
<tr>
<td>Almeida et al. (2021)</td>
<td>Brazil</td>
<td>33</td>
<td>CBD isolate*</td>
<td></td>
<td>Oral</td>
<td>300mg/day 12 weeks</td>
<td>Insomnia</td>
<td>None</td>
</tr>
</tbody>
</table>

N=Sample size; CBD: Cannabidiol; THC: Tetrahydrocannabinol.
Source: Developed by the authors based on the collected data.
In the observational studies, most of the participants were male (Venderová et al., 2004; Lotan et al., 2014; Balash et al., 2017; Yust-Katz et al., 2017; Feeney et al., 2021; Micheli et al., 2020; Erga; Maple-Grødem; Alves, 2022; Holden et al., 2022; Finseth et al., 2015), reported oral and inhaled cannabinoid use (Tables 3), and were assessed using scales (Lotan et al., 2014; Yust-Katz et al., 2017) and questionnaires (Lotan et al., 2014; Balash et al., 2017; Finseth et al., 2015; Micheli et al., 2020; Yenilmez et al., 2021; Yust-Katz et al., 2017) presentially (Lotan et al., 2014) or by information and communication technologies, recorded as telephone interviews (Balash et al., 2017), e-mail (Feeney et al., 2021; Erga; Maple-Grødem; Alves, 2022; Holden et al., 2022) or online (Erga; Maple-Grødem; Alves, 2022). We also identified an online study with neurologists who followed patients with PD (Bega et al., 2017) to investigate prescription practices and experts' perceptions of the risks and benefits of cannabinoids. Most of these studies addressed the motor and non-motor symptoms of PD (Lotan et al., 2014; Balash et al., 2017; Micheli et al., 2020; Yenilmez et al., 2021; Feeney et al., 2021; Finseth et al., 2015; Paulson et al., 2021).

In the observational studies analyzed, the prevalence of cannabinoid use among persons with Parkinson's disease (PWP) varied significantly across different countries and populations. The studies included a diverse range of age groups and sample sizes, with the percentage of cannabinoid use among PWP ranging from 4.4% to 73.0% (Finseth et al., 2015; Holden et al., 2022). Notably, the highest prevalence was observed in a study conducted in the USA in 2022, which reported a 73.0% usage rate among 1,881 participants (Holden et al., 2022).

The observational studies included show self-reported improvement, mainly in the non-motor symptoms of PD, according to Table 3. Reports suggest beneficial effects of cannabinoids mainly on the following non-motor symptoms: pain and neuropsychiatric disorders.
<table>
<thead>
<tr>
<th><strong>AUTHOR, YEAR COUNTRY</strong></th>
<th><strong>PRODUCT USED CHEMOTYPE, POSITIVE RESULTS ADVERSE EFFECTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Venderová et al. (2004) Czech Republic</td>
<td>Cannabis “in natura” 1 – (THC/CBD ≥10) Resting tremor, bradykinesia, dyskinesia, muscle rigidity -</td>
</tr>
<tr>
<td>Lotan et al. (2014) Israel</td>
<td>Cannabis “in natura” 1 – (THC/CBD ≥10) Rest tremor, bradykinesia, muscle rigidity, Pain and insomnia Dizziness</td>
</tr>
<tr>
<td>Erga (2022) Norway</td>
<td>CBD Oil Hashish Street cannabis Sativex Improvement in motor function (69.5%), sleep (52.5%), pain (37.3%), neuropsychiatric symptoms Rarely reported</td>
</tr>
<tr>
<td>Paulson et al. (2021) USA</td>
<td>Different products Pain, sleep, anxiety Rigidity and tremor No negative impact on symptoms assessed</td>
</tr>
<tr>
<td>Yust-Katz et al. (2017) Israel</td>
<td>Pain (n=24; 77.0%) No reports</td>
</tr>
<tr>
<td>Yenilmez et al. (2021) Germany</td>
<td>Oral CBD THC Resting tremor, muscle rigidity, postural instability, pain, depression, anxiety, insomnia, cognitive deficit, urinary retention/incontinence Hallucinations, anxiety, euphoria, dizziness</td>
</tr>
<tr>
<td>Feeney et al. (2021) USA</td>
<td>High THC Low THC Pure CBD High CBD Low CBD Blend Resting tremor, bradykinesia, dyskinesia, muscle rigidity, postural instability, Anxiety, Pain, Depression, Insomnia, Urinary retention/incontinence Anxiety, hypotension, drowsiness, dizziness,</td>
</tr>
<tr>
<td>Micheli et al. (2020) Argentina</td>
<td>Oil 1 to 1095 days Resting tremor, muscle rigidity, depression, anxiety, insomnia Hallucinations, dizziness Drowsiness, motor worsening</td>
</tr>
<tr>
<td>Finseth et al. (2015) USA</td>
<td>Insomnia, mood and quality of life No reports</td>
</tr>
<tr>
<td>Balash et al. (2017) Israel</td>
<td>Cannabis “in natura” Flowers, leaves, oil 0.2 to 2.25 g/d Rest tremors, muscle rigidity, Pain, insomnia, cognitive deficit Hallucinations, cough, anxiety, euphoria, paranoia, dizziness</td>
</tr>
<tr>
<td>Holden et al. (2022) USA</td>
<td>Oral CBD THC THC/CBD Sleep, anxiety, agitation and pain Dry mouth, dizziness, cognitive deficit, increased appetite or weight, daytime sleepiness, imbalance, fatigue, palpitations, apathy and hallucinations</td>
</tr>
</tbody>
</table>

**CBD:** Cannabidiol; **THC:** Tetrahydrocannabinol

**Source:** Developed by the authors based on the collected data.
The most common adverse effects were: dizziness, drowsiness, hallucination, xerostomia, euphoria, anxiety, and fatigue. Another situation that deserves to be highlighted is the absence of adverse effects mentioned in six articles, of which four were intervention studies (Zuardi et al., 2009; Mesnage et al., 2004; Faria et al., 2020; de Almeida et al., 2021). Of these last three were with CBD, and another (Mesnage et al., 2004) with the cannabinoid antagonist rimonabant (SR 141716) which has already been withdrawn from the market due to the induction of suicidal ideation in obese patients.

Most observational data, although without appropriate controls, showed favorable results. However, SRs highlighted the risk of bias of RCTs and concluded that the evidence is insufficient to recommend the use of cannabinoids in the clinical therapy of motor symptoms of PD, mainly due to the quality of the data. Finally, the intervention with these compounds showed, in general, good tolerance, but its security - especially long-term - remains uncertain (Thanabalasingam et al., 2021; Bougea et al., 2020).

Only three in vivo studies so far have evaluated the activity of the endocannabinoid system in PW (Carroll et al., 2004; Faria et al., 2020; Leehey et al., 2020) (Table 4). A decrease in CB1 receptors in PWP was observed in all three studies.

Table 4. Synthesis of neuroimaging studies of the endocannabinoid system in people with Parkinson’s disease.

<table>
<thead>
<tr>
<th>AUTHOR (YEAR) COUNTRY</th>
<th>SAMPLE</th>
<th>RADIOMARKER</th>
<th>RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PWP</td>
<td>CONT</td>
</tr>
<tr>
<td>Van Laere et al. (2012)</td>
<td>Belgium</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Ceccarini et al. (2019)</td>
<td>Belgium</td>
<td>38</td>
<td>10</td>
</tr>
</tbody>
</table>
4 DISCUSSION

In this scoping review, the exploration of cannabinoids in the treatment of PD was meticulously mapped, reflecting the evolving interest in this research domain. Through a rigorous analysis, the selected studies were categorized by their methodological design, unveiling trends, outcomes, and gaps in the current literature. Oral administration of cannabinoids, prevalent in clinical trials and observational studies, showcased therapeutic potential across various symptoms associated with PD. These findings, coupled with the identification of under-researched areas, provide a robust foundation for subsequent discussion and guidance for future inquiries.

4.1 SYSTEMATIC REVIEWS (SRs) ON THE USE OF CANNABINOIDS IN PD TREATMENT

Language restriction is noted in these SRs and therefore, most of them gathered only studies published in the English language (Prakash; Carter, 2021; Thanabalasingam et al., 2021; Bahji et al., 2022; Bougea et al., 2020), and the search occurred, sometimes, in only a few databases (Bougea et al., 2020; Bahji et al., 2022). Therefore, the number of studies included in the SRs was small and ranged from 03 (Lim; See; Lee, 2017) to 26 (Urbi et al., 2022) (Table 1). In that context, they concluded, generally speaking, that despite studies showing relief in symptoms, the scientific evidence is insufficient to justify the inclusion of medicinal cannabinoids in clinical practice for the treatment of PD (Thanabalasingam et al., 2021; Bougea et al., 2020).

Thus, while preliminary findings suggest potential benefits of cannabinoids for PD symptom management, the limited scope and language restrictions of existing SRs

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<table>
<thead>
<tr>
<th>Name</th>
<th>Country</th>
<th>Sample Size</th>
<th>Radiomarker</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajalin et al. (2022)</td>
<td>Finland</td>
<td>16</td>
<td>[18F] FMPEP-d2</td>
<td>PWP: showed significantly lower amounts of the CB1 receptor, mainly in the off-stage; but an increase in availability was observed after medication.</td>
</tr>
</tbody>
</table>

[18F]MK-9470 and [18F] FMPEP-d2: radiomarkers, high-affinity, selective, inverse agonist, of cannabinoid receptor 1, developed for use in neuroimaging examinations; PWP: Person with Parkinson's Disease.

Source: Developed by the authors based on the collected data.
underscore the need for more comprehensive, multi-language, and multi-database studies to conclusively determine the role of cannabinoids in PD treatment.

4.2 INTERVENTION STUDIES: CLINICAL TRIALS AND CASE SERIES

The research carried out in Brazil with a dose of 300mg/day of CBD isolate, administered orally, observed no adverse effects among participants (Faria et al., 2020; de Almeida et al., 2021). However, some studies in other countries have reported adverse effects (Pebb et al., 2020; CB et al., 2004; Frankel et al., 1990), but one of them (Leehey et al., 2020) highlighted the positive effects on motor symptoms, night-time sleep, emotions, and behavior of the participants.

It is worth noting that of the controlled clinical trials, only one used Cannabis extract in the ratio (1.25 mg CBD:2.5 mg THC) (Carroll et al., 2004), the others used synthetic cannabinoids (SR 141716) and Nabilone (Pebb et al., 2020) or CBD isolate (Chagas et al., 2014a; Faria et al., 2020), not evaluating the pharmacological potential of the interaction between cannabinoids (Pebb et al., 2020; Mesnage et al., 2004).

When analyzing the data, one can see the need to evaluate the pharmacological potential of the interaction between different cannabinoids, in which the synergy of bioactive compounds from Cannabis, among them various types of phytocannabinoids and terpenes, can increase the activity of the endocannabinoids anandamide and 2-AG (Feeney et al., 2021; Kieburtz et al., 2021). In addition to this, it is necessary to investigate the neurological potential of THC, the interaction and ratio of THC/CBD and other cannabinoids, and their safer doses/kg/day for each PWP. Despite its adverse effects, its affinity for CB1, the most abundant receptor in the central nervous system, requires an analysis of this potential.

It is observed that many limitations occurred in the clinical trials (Table 2), which compromise the quality and level of evidence of these publications. Non-systematized clinical observations, diversity of products (vehicles, form of administration, compounds, among others), a variety of therapeutic schemes with doses, exposure/observation time, and use of non-comparable assessment instruments, which makes it difficult to generalize the results and to compare these studies and their effect estimates. It is worth mentioning
the absence of any Randomized Clinical Trial, Mega Trial, considering the second level in the hierarchy of evidence to register compounds.

Another difficulty, when researching cannabis in nature is knowing its origin, botanical classification, and chemical identification, which alters the concentration of its bioactive components. In addition, clinical trials have not analyzed the levels of active compounds in body fluids such as blood, cerebrospinal fluid, and urine.

4.3 OBSERVATIONAL STUDIES

The variation in the legal status of medicinal cannabinoids across different study locations is a significant factor that could have influenced the reported prevalence rates. A higher prevalence of cannabinoid use was observed among males diagnosed with Parkinson's disease, potentially attributable to the already documented gender difference in the incidence and prevalence of PD (Feigin et al., 2019), as well as the higher recreational use of Cannabis by men compared to women in the general population (Kohn; Kittel; Piette, 2004; Fattore; Fratta, 2010).

The observed disparities in the frequency of cannabinoid use across different samples and countries may be reflective of the participants' socio-cultural backgrounds, the health and social support systems available to them, and the legal status of these substances. Factors such as the lack of scientific evidence, reliable sources of information, and intergenerational barriers can also affect the decision to use cannabinoids for medicinal purposes.

Studies among PWP (n=339) from a movement disorder centre in Prague (Czech Republic) identified 25.0% of the consumption of cannabinoids of this group, 45.9% described some benefit in motor symptoms (Venderová et al., 2004). In another study, PD patients (n=22) were evaluated before and 30 minutes after smoking Cannabis in nature. The results showed significant improvement in motor and non-motor symptoms (Lotan et al., 2014).

The research conducted at the Parkinson's Foundation (Feeney et al., 2021) obtained a final sample of 1,064 respondents from 49 US states. The majority of participants (n=803; 75.5%) had not used cannabinoids during the last six months, mainly due to a
lack of evidence of efficacy (59.9%) and fear of side effects (34.9%). Among users of cannabinoids over the last six months (24.5%), there was a preference for nocturnal use and oral route. Many users in the group under analysis did not know how to inform about the daily dose administered (47.0%), the type/variety of *Cannabis*, and the concentration of CBD and THC (22.2%) and did not receive instructions/recommendations for use (56.1%). In this context, participants reported improvements in the following motor symptoms: stiffness and tremor, and in the following non-motor symptoms: anxiety, pain, and sleep disorders. The most common sources of information for PWP about the therapeutic potential of the plant were the internet/news, friends, or other people with PD. In that study, the higher the THC concentration, the better the self-reported efficacy for motor and non-motor symptoms in PWP.

In the study by Holden et al. (2022) more than half of the participants reported improvements in sleep, anxiety, agitation, and pain with cannabinoid use. In addition, after use, some decreased their consumption of prescribed medications for pain (26.8%), anxiety (18.6%), sleep (16.9%), depression (11.9%), and even parkinsonism (13.9%). They found that participants given doses >200 mg CBD (n = 37; 3.7%) reported improvements in balance, dyskinesia, cognition, and constipation at significantly higher frequencies than those taking <200 mg (n = 972; 96.3%) (Holden et al., 2022).

Cannabinoid consumption among patients with PD according to observational studies, positively impacted their lives with improvement in motor (Venderová et al., 2004; Balash et al., 2017; Feeney et al., 2021; Micheli et al., 2020; Yenilmez et al., 2021; Lotan et al., 2014; Paulson et al., 2021) and non-motor symptom (Holden et al., 2022; Balash et al., 2017; Feeney et al., 2021; Micheli et al., 2020; Yenilmez et al., 2021; Finseth et al., 2015; Paulson et al., 2021). The most cited adverse effect among patients was dizziness (Holden et al., 2022; Lotan et al., 2014; Feeney et al., 2021; Micheli et al., 2020; Yenilmez et al., 2021). However, the lack of information on plant taxonomy, preparation, concentration, dose, association with other drugs or therapies, and the presence of other comorbidities compromise the reliability of the reported therapeutic and adverse effects. This implies limited confidence in the effect of cannabinoids in these PD patient samples and low quality of evidence. The studies, in general, present sample bias, recall
bias, information bias, and non-response bias. It also highlights the non-face-to-face collection techniques without clarifying the cognitive capacity of the participants.

The recent studies from 2023 underscore the potential efficacy and safety of medical cannabis in the management of Parkinson's disease symptoms. One investigation observed improvements in a variety of symptoms following the initiation of medical cannabis treatment, including cramping, pain, and spasticity. Another phase 1b study found that diverse formulations of THC/CBD were well-tolerated by patients. Furthermore, a retrospective case-control study found no evidence of exacerbation of neuropsychiatric symptoms or disease progression in patients who utilized medical cannabis. These studies underscore the necessity for further research to evaluate the interaction between different cannabinoids and the safety and efficacy of medical cannabis in the treatment of Parkinson's disease (Di Luca et al., 2023; Goldberg et al., 2023; Turner; Hinson, 2023).

4.4 PRECLINICAL STUDIES ON CANNABINOIDS IN PARKINSON'S DISEASE

Studies in cells and animals have demonstrated the potential effect of cannabinoids on molecular processes characteristic of PD. In 2013, a study evaluated the effect of the mixture of Δ⁹-THC-CBD in a complex model of neurodegenerative diseases in mice with Park-2 gene mutation and Tau protein overexpression. The results showed that in mice treated with the mixture, in addition to the general improvement in behaviour (less stress-related abnormal behaviour, less self-and hetero-aggression, and less stereotypy), there was a significant reduction of intraneuronal monoamine-related free radicals produced during dopamine metabolism in the limbic system, decreased glucose in the cortex and hippocampus, increased reduced/oxidized glutathione ratio in the limbic system and reduced deposition of insoluble Tau-β-Amyloid aggregates (Casarejos et al., 2013).

In 2015, a study looked at the neuroprotective action of CBD on PC12 cells (a cell model used in neuronal differentiation studies). They detected a neuro-restorative effect, increased cell viability and differentiation, axonal and synaptic protein expression, and a protective effect against cell death and neuronal loss, even in the face of the toxic effects
induced by matrix metalloproteinase, a molecule active in PD (Muller; Morales; Reggio, 2019; Santos et al., 2015).

Here, the importance of preclinical research in evaluating and proving the in vitro and in vivo efficacy of Cannabis-derived products must be emphasized. Pre-clinical pharmacology and toxicology are essential for the clinical stage of research.

5 CONCLUSION

It is about two hundred years after the first description of PD by James Parkinson and Jean-Martin Charcot, many advances have been made in the understanding of its pathophysiologic mechanisms, yet, currently, no treatment stops or slows down the speed of disease progression.

There is a scarcity of studies with adequate and high-quality samples to meet the demand for the use of cannabinoids in movement disorders. The botanical-pharmaceutical quality of cannabis may offer advantages not served by the current single-target model (Russo, 2018).

Double-blind, Multicentre Randomized Clinical Trials with experimental, control, and placebo groups and follow-up are required (Figura; Koziorowski; Sławek, 2022). Furthermore, these studies should evaluate the neurological potential of THC, CBD, THC+CBD, and other cannabinoids in PD with the respective safer doses/kg/day for each case. It further highlighted the importance of evaluating the gender difference in the action of medicinal cannabinoids. Studies with high-quality evidence can confirm the beneficial, adverse, toxic effects, contraindications, and appropriate doses for each stage of PD and the subtypes of motor and non-motor symptoms.

Therefore, experimental evidence from preclinical and clinical research with adequate sample size is needed to assess the homeostasis of the endocannabinoid system, the efficacy and safety of different cannabinoids, and their mixtures. These results will be allies of professionals and patients in the clinical consultation and the respective cost-benefit evaluation.
REFERENCES


