CANNABIS' THERAPEUTIC POTENTIAL IN PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease is a neurodegenerative condition with distinct symptoms. Its current therapeutic approach, though effective, does not alter the progression of the disease and is associated with several side effects. Meanwhile, studies on Cannabis and its potential indicate varied evidence, gaining more ground in the therapeutic realm of Parkinson's disease regarding its efficacy in both motor and non-motor symptoms. The objective of this work was to analyze the effectiveness of Cannabis in patients with Parkinson's disease and its current therapeutic applicability. Studies highlight the anti-inflammatory and neuroprotective properties of phytocannabinoids, especially cannabidiol, which can modulate the Endocannabinoid System, positively influencing Parkinson's disease. It is noteworthy that formulations with cannabidiol and tetrahydrocannabinol demonstrate efficacy in both motor and non-motor symptoms, improving tremors, anxiety, pain, and emotional well-being, with mild adverse effects. It is important to emphasize the need for more controlled and rigorous research to deepen the understanding of phytocannabinoids and optimize the therapeutic use of Cannabis in Parkinson's disease.

Keywords: Cannabis, Parkinson’s Disease, Cannabinoids, Cannabidiol, Tetrahydrocannabinol

RESUMO

A Doença de Parkinson é uma condição neurodegenerativa que possui sintomas distintos. Sua abordagem terapêutica atualmente, apesar de eficaz, não altera a progressão da doença e está associada a diversos efeitos colaterais. Enquanto isso, estudos sobre a Cannabis e seu potencial apontam evidências variadas e ganham mais espaço na terapêutica da Doença de Parkinson quanto a sua eficácia em sintomas motores e não motores. O objetivo do trabalho foi analisar a eficácia da Cannabis em pacientes com Doença de Parkinson e sua atual aplicabilidade terapêutica. Estudos destacam as propriedades anti-inflamatórias e neuroprotetoras dos fitocanabinoides, especialmente o canabidiol, que podem modular o Sistema Endocanabinóide, influenciando positivamente na Doença de Parkinson. Destaca-se que formulações com canabidiol e tetraidrocanabinol demonstram eficácia em sintomas motores e não motores, melhorando tremores, ansiedade, dor e bem-estar emocional, com efeitos adversos leves. É importante ressaltar a necessidade de mais pesquisas controladas e rígidas para aprofundar a compreensão dos fitocanabinoides e otimizar o uso terapêutico da Cannabis na Doença de Parkinson.

Palavras-Chave: Cannabis, Doença de Parkinson, Canabinóides, Canabidiol, Tetraidrocanabinol

INTRODUCTION

In 1817, James Parkinson, in his work entitled “Na Essay on the Shaking Palsy”, provided the first description of the main motor clinical manifestations of this condition, which he termed “shaking palsy” or Parkinsonism.[23,24] This is a chronic, degenerative and progressive neurological condition that predominantly manifests with motor features exhibiting typical clinical symptoms such as resting tremor, bradykinesia, muscular rigidity and postural instability.[23,24]

Parkinson’s Disease (PD) is a widely recognized movement disorder known for its distinct motor characteristics. However, its impact extends beyond motor symptoms, as it also stands out for significant non-motor manifestations, including fatigue, sleep disorders, behavioral disturbances and autonomic and sensory symptoms.[24]

The primary pharmacological therapies used in treatment of PD consist of medications that either increase dopamine concentrations in the brain or stimulate dopamine receptors.[5] While these approaches effectively reduce motor symptoms, they don’t alter the progression of the disease and are associated with several side effects.[5]

Cannabis sativa L. is a plant originating from Central Asia, botanically divided into *Cannabis sativa* subsp. *sativa* and *Cannabis sativa* subsp. *indica cultivars*.[22] Documentary evidence points to the therapeutic use of Cannabis in China, Around 2700 BC, but it was only around 1960 that the main constituents of Cannabis were isolated and structured.[21]

Phytocannabinoids are the active compounds of the *Cannabis sativa L.* plant. Among them, Δ9-tetrahydrocannabinol (Δ9-THC) is the most prevalent compound,

known for its psychoactive effects.[4] Conversely, cannabidiol (CBD), the second most abundant compound, stands out for its non-psychoactive nature and pleiotropic properties.[4]

In the 1970s, studies began on the existence of other phytocannabinoids that, when mixed, could interfere with the effects of tetrahydrocannabinol (THC), including CBD.[18] Both CBD and THC have demonstrated potential therapeutic properties in combating inflammation, anxiety, neurodegeneration, and depressive processes, acting as antioxidants.[3]

The human body also produces cannabinoids, known as endocannabinoids.[22] The Endocannabinoid System (ECS), is involved in the body's homeostasis and can be divided into two main receptors: type 1 cannabinoids (CB1), more commonly found in the Central Nervous System (CNS), and type 2 cannabinoids (CB2), more common in the peripheral and immune systems.[16]

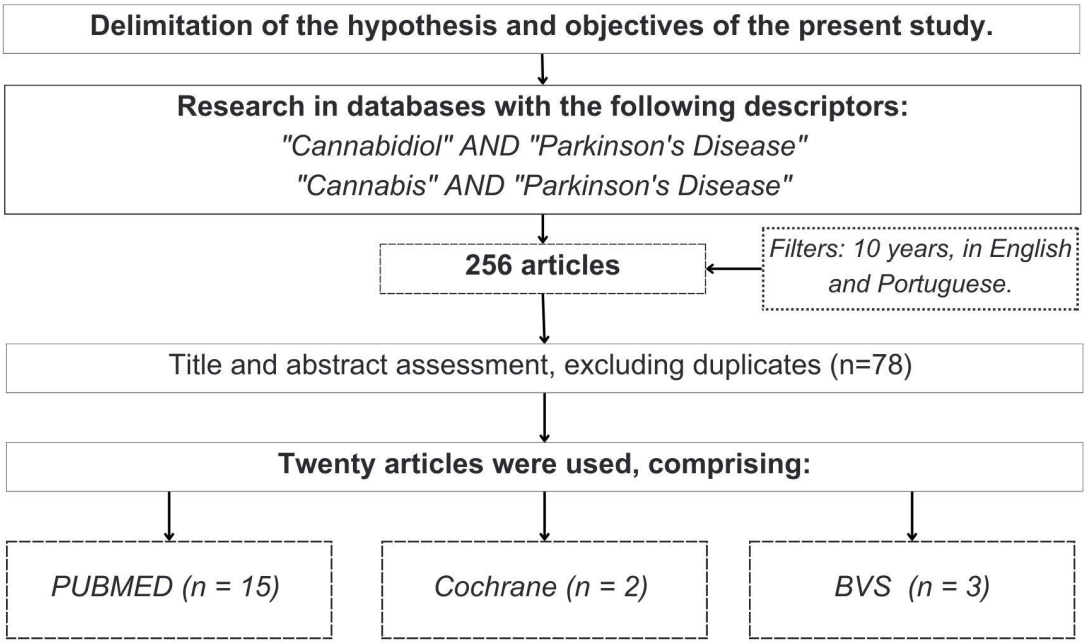
Currently, according to the book *"Medicinal Cannabis: Prescription Guide"* [23], conventional therapy for Parkinson's Disease has limited efficacy in addressing non-motor symptoms. Meanwhile, pharmacological studies on the role of the ECS in Parkinson's Disease are expanding[21], and the therapeutic potential of Cannabis in PD indicates varied evidence, gaining more recognition as an associated therapy to better control both motor and non-motor symptoms of the disease.

METHODS

The work is an Integrative Review that aims to synthesize knowledge and incorporate the applicability of studies in practice. The PICO strategy (Participant, Intervention, Comparison and Outcomes) was used to formulate the guiding question for this study. To guide the integrative review, the following question originated: Are there evidence (O) regarding the effectiveness of Cannabis (I) in patients with Parkinson's Disease (P) and what is its current applicability?

The methodological process was divided into stages (Figure 1). Initially, the objectives of the integrative review were defined based on the formulation of the study hypothesis, followed by the definition of search descriptors and research databases. PUBMED, BVS and Cochrane were chosen as the databases, and a search was conducted using the following descriptors: "Cannabidiol" AND "Parkinson's Disease" and "Cannabis" AND "Parkinson's Disease", corresponding to 293 articles. Then, 10 years, English and Portuguese filters were applied, refining the search to 256 articles. After evaluating titles and abstracts, and excluding duplicates, 78 articles remained for analysis, with articles used in their entirety.

Figure 1. Flowchart of studies selection



In the table of results, studies in humans with PD and systematic reviews were included (Table 1), listing the following data: the name of the main author, type of study, level of evidence, exposure time, type of cannabinoid, dose, route of administration and research outcomes. In total, 11 articles were selected to compose the table results.

RESULTS

Table 1. Studies and reviews on the potential of Cannabis.

Main Author	Type of Study	Level of Evidence	Exposure Time	Dose, Type of Cannabinoid and Route of Administration	Results
Bahji, A	Systematic Review	1A	-	-	The review highlights that cannabinoid-based products are effective alleviating symptoms of PD, but their effects depend on the concentration of THC and CBD. Higher concentrations of THC contribute to an improvement in psychological and behavioral symptoms, agitation and sleep disorders, but there is a presence of underlying cognitive deterioration. Meanwhile, higher concentrations of CBD have shown improvement in motor symptoms such as dyskinesia and chorea. Despite evidence of efficacy of cannabis in patients with neurodegenerative diseases like Parkinson's, there is still uncertainty regarding the differential benefits of plant-based cannabinoids and synthetic cannabinoids, as well as the profile of patients with stable or unstable levodopa use.
Domen, C	Randomized Controlled Trial, Double-Blind	2B	2 weeks Cognitive test administered 1-3 hours after medication	1,25 mg/kg/day to 1,25 mg/kg twice per day in at least 6/6 hours. Orally, in solutions of 100 mg/ml CBD and 3.3 mg/ml THC in sesame oil.	There is evidence of improvement in motor symptoms in PD, but patients using a placebo had better outcomes. It is noted that there is a difference in the effects and actions of Cannabidiol in the studied patients, as there is a discrepancy in effect related to dose, drug composition and route of administration used, which was not analyzed in the study.
Peres, F. F.	Systematic Review	1A	-	-	The article highlights a protective role of cannabidiol in movement disorders, but investigative studies are limited and there is a variation in dose and treatment duration. Preclinical studies in animals show promising results in motor symptoms, but clinical trials do not yield the same outcome. Therefore, it is suggested that CBD may have a preventive rather than therapeutic role in patients with Parkinson's disease.

Holden, K. S.	Cross-sectional observational study	2C	Majority > 6 months Minority < 1 year	High doses of THC were considered > 50 mg and high doses of CBD were considered > 200 mg	Patients, during the study, reported subjective improvement in symptoms related to Parkinson's Disease after using Cannabis. The research also concluded that medications with higher levels of THC are more beneficial for PD symptoms than medications with higher concentrations of CBD. However, it also found that higher concentrations of THC also lead to more adverse effects. The study suggests further controlled and rigorous research to analyze different types of Cannabis in Parkinson's patients.
Patricio, F.	Systematic Review	3A	-	-	The evidence suggests the clinical utility of CBD for the treatment of LIDs (levodopa-induced dyskinesias) and motor symptoms of PD (Parkinson's Disease), as well as the neuromodulatory, neuroprotective, and antidyskinetic effects of CBD in animal models and PD patients. Despite promising results for the pharmacology of CBD, uncertainties remain regarding dosages and mechanisms of action. However, the essential role of CBD as an antioxidant and anti-inflammatory is asserted, as these processes are important in the pathogenesis of PD.
Junior, N. C. F.	Systematic Review	1A	-	-	The evidence indicates that cannabinoids can influence the development and manifestations of PD (Parkinson's Disease) and LID (levodopa-induced dyskinesias). Various mechanisms, ranging from direct changes in critical neurotransmitters such as dopamine and glutamate to indirect anti-inflammatory effects, seem to be involved. CBD appears to be one of the most promising drugs in preclinical trials.
Costa, A. C.	Systematic Review	1A	-	-	There is evidence that cannabinoids have shown significant therapeutic impact, attenuating signs and symptoms such as inflammation, oxidative stress, pain, stress, movement disorders, tremors, stiffness, bradykinesia, L-DOPA-induced dyskinesia, mood disorders, and insomnia. Adverse effects, such as changes in cognition, ataxia, motor skills, dysphoria, and dependence, are typically dose-dependent on THC. Cannabinoids constitute a promising pharmacological approach for the treatment of neuropsychiatric disorders in the elderly.

Chagas, M. N. H.	Clinical Trial	1B	6 semanas	75 mg/day to 300 mg/day Orally, CBD powder purity of 99.9% dissolved in corn oil.	Evidence indicates significant improvements in functioning and well-being measures for PD patients without psychiatric comorbidities treated with 300 mg/day CBD. However, no statistically significant differences in motor symptoms were observed
Farias, S. M.	Randomized, double-blind, crossover clinical trial	1B	1 day	300 mg Oral route, CBD powder with 99.9% purity dissolved in corn oil	The study demonstrated a reduction in anxiety and a decrease in tremor amplitude. However, despite the positive outcome regarding tremor amplitude, there was no difference in the variables measured by the acceleration sensor in terms of tremor frequency.
Leehey, M. A.	Open-Label Dose-Escalation Study	3B	10-15 days	5 to 20-25 mg/kg/day Oral administration of highly purified CBD (Epidiolex 100mg/ml)	A relatively high dose of CBD, 1600 mg/day, with THC concentration < 0.15%, orally administered, is associated with mild adverse effects. The results suggest that CBD has a beneficial effect on MDS-UPDRS total and motor scores, nocturnal sleep, and emotional and behavioral control, and these improvements remained significant after a 2-week discontinuation of CBD.
Kanjanarangsichai, A	Prospective, double-blind, randomized, and controlled clinical trial	1B	8 weeks	15.59 mg/day of CBD and 0.61 mg/day of THC	The research highlights that the use of a CBD/THC formulation at lower doses did not show improvement in functional tests for Parkinson's Disease but indicated an enhancement in serum levels of albumin, globulin, and the albumin/globulin ratio. It also emphasizes the need for further research at higher doses of CBD/THC.

DISCUSSION

Parkinson's Disease

Parkinson's Disease is characterized by progressive neurodegeneration of dopaminergic neurons, predominantly in the compact part of the substantia nigra, the striatum and, to a lesser extent, the subthalamic nucleus of the basal ganglia.[6] It is known that the loss of neurons is associated with mitochondrial dysfunction, oxidative stress and reduced protein degradation, leading to the degeneration of the nigrostriatal pathway, initiating motor symptoms and the accumulation of Lewy bodies (aggregates of α-synuclein and ubiquitin in neurons).[23] This chronic disorder is characterized by classical motor symptoms but also presents with non-motor symptoms. The primary therapeutic approach focuses on alleviating motor symptoms; however, it does not alter the course of the disease, necessitating the use of adjunctive therapies for other symptoms. Nevertheless, even with such interventions, effectiveness is limited and comes with a high potential for inducing significant adverse reactions.[11]

The primary role of dopamine in the basal ganglia is the regulation of the motor circuit. When the dopaminergic system is activated, it promotes an increase in movement, whereas its inhibition leads to hypokinesia. Dopamine deficiency in the striatum is associated with alterations in the basal ganglia, such as a decrease in the number of dendritic spines in the medium spiny neurons of the striatum, as well as changes in neuronal connectivity in both striato-pallidal and striato-nigral pathways.[3]

Regarding the stimulation of oxidative stress and inflammation in Parkinson's Disease, there is observed mitochondrial dysregulation characterized by an increase in energy production and, consequently, the release of reactive oxygen species,

resulting in damage and cell death due to the reduction in energy production caused by increased oxidative stress. These findings are associated with decreased mitochondrial activity and are correlated with dementia and apoptosis.[5]

The inflammatory process in PD follows a bidirectional dynamic. Inflammation not only activates but also potentiates apoptotic pathways in dopaminergic cells. The death of these cells, in turn, generates inflammatory markers that stimulate cell death signaling, leading to a "vicious cycle".[5]

Currently, there is no treatment to prevent the progression of PD, but rather for the control of its main symptoms.[13] Levodopa is the most commonly prescribed drug for PD treatment, acting by converting into dopamine in the brain and is responsible for controlling motor effects such as stiffness, bradykinesia and tremors.[23] However, its long-term efficacy is compromised and is associated with motor adverse effects, such as dyskinesias.[14] The decrease in effectiveness occurs due to progressive neurodegeneration causing fluctuations in the treatment response, known as the “on-off effect”, where, during the “on” periods, the effect of L-Dopa is present, controlling motor symptoms, and, during the “off” periods, the drug’s effect ceases and motor symptoms reappear.[13]

In chronic medication use, the development of levodopa-induced dyskinesias is observed during periods when the drug has a motor symptom-relieving effect (the “on” period), potentially progressing to irreversible dyskinesia.[13] Additionally, there is the phenomenon of “wearing off”, defined as the reappearance of motor symptoms in less than four hours after the last dose. This phase progressively deteriorates until the “off” state becomes more pronounced.[24]

Non-motor treatment is personalized for each patient, with this effectiveness limited and the symptoms can have a significant impact on the quality of life of individuals with PD.[23] There is also a need for psychiatric support to address psychosocial symptoms that may develop, in addition to symptomatic medication.[24]

Cannabis and Endocannabinoid System

The Endocannabinoid System is primarily composed of two G protein-coupled receptors, known as cannabinoid receptors 1 and 2 (CB1 and CB2), along with endocannabinoid neurotransmitters N-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG), as well as enzymes involved in the synthesis and degradation of endocannabinoids.

The synthesis of endocannabinoids AEA and 2AG occurs on demand after stimuli such as cellular depolarization or receptor stimulation, playing a neuromodulatory role. Anandamide is synthesized through the catalyzing enzyme N-acyl-phosphatidylethanolamine phospholipase (NAPE-PLD), while 2-AG is synthesized through the α and β isoforms of diacylglycerol lipase. Regarding the degradation of AEA and 2-AG, the main responsible enzymes are fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL).[3]

The interaction of ECS neurotransmitters with cannabinoid receptors occurs in a retrograde manner.[3] Endocannabinoids are released from the postsynaptic neuron and receptors are located in the presynaptic region, with calcium-dependent and independent pathways regulating the release of AEA and 2-AG.[6]

In central nervous system, CB1 receptors are the most predominant G-protein coupled receptors, widely expressed throughout the striatum, in the basal ganglia present in excitatory projections from the subthalamic nucleus to the internal globus

pallidus and in the pars reticulata of the substantia nigra, also found in the dendrites and presynaptic axon terminals of GABAergic medium spiny neurons. Additionally, they are found at the level of excitatory corticostriatal glutamatergic terminals. On the other hand, CB2 receptors are found at lower levels than CB1, present in specific areas of the brain such as the hypothalamus, brainstem, hippocampus and pars reticulata of the substantia nigra.Their presence is discreet in healthy brains but becomes significantly expressed in neurological diseases such as Parkinson's Disease.[4]

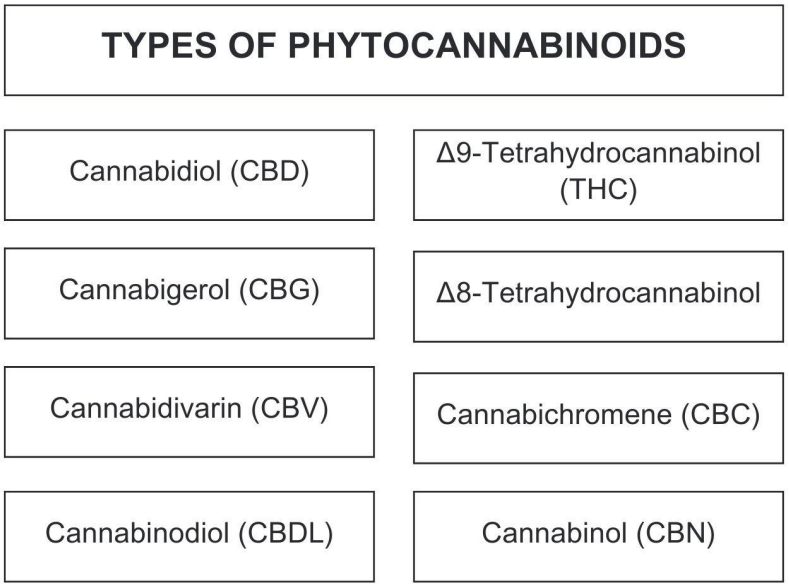
Furthermore, in neuroinflammatory conditions, there is an overexpression of CB2 receptors in both microglia and astrocytes, suggesting a potential target for promoting neuroprotection. Through the activity of CB2, or the combination of CB1 and CB2, the modulating effects of astrocytic activity in brain injury are mediated, promoting an anti-inflammatory action. This action is primarily mediated by CB2 activation, which plays a trophic role, provides anti-inflammatory mediators and reduces chemokine levels in astrocytes. This, in turn, demonstrates the ability to rescue damaged neurons.[3]

There is a notable functional interaction between cannabinoid and dopaminergic neurotransmission. This is evident when the CB1 receptor is co-expressed with dopamine D1 receptors in the striatum. Additionally, when stimulated, the CB1 receptor reduces glutamate release in the striatum. This effect is frequency-dependent and is associated with dopamine D2 receptors.[3]

Plants of the Cannabaceae family, specifically Cannabis sativa, produce phyto-complexes (or phytocannabinoids) responsible for their various therapeutic properties. There are several types of phytocannabinoids known, but the most

studied and well-known are THC and CBD (Figure 2). It is important to emphasize that phytocannabinoids are defined as compounds present in the extract of the Cannabis plant, different from endogenous cannabinoids produced by the body's own ECS.

Figure 2. Main types of phytocannabinoids



Phytocannabinoids demonstrate neuroprotective, anti-inflammatory and antioxidant capabilities. In studies by Giuliano et al., animals treated with CBD showed increased survival of dopaminergic neurons accompanied by motor performance recovery. However, in Bahji et al.,THC appears to have no effect on dopamine D2 receptors, explaining why pure forms of THC such as Nabilone and Dronabinol do not show improvement in motor deficits in studies.

Studies indicate that CBD reduces the production of prostaglandins and nitric oxide synthase, indicating a pathway for anti-inflammatory and antinociceptive effects. Additionally, CBD metabolites, such as 7-OH and 7-COOH-CBD, one of the most concentrated metabolites, have anti-inflammatory effects and inhibit the

formation of nitric oxide, reactive oxygen species and tumor necrosis factor-alpha. Another metabolite, 6-oxo-CBD, exhibits anticonvulsant activity.[3]

CBD increases levels of anandamide inhibiting fatty acid amide hydrolase (FAAH), consequently activating CB1, CB2 and TRPV-1 receptors. Furthermore, CBD has antioxidant and anti-inflammatory properties, partially mediated by its actions on TRPV-1, mitochondria and PPARγ.[19]

CBD exhibits the ability to inhibit the psychoactive effects of Δ9-THC. The exact mechanism is not fully understood, but likely involves CB1 receptor antagonism, as Δ9-THC-like psychotropic effects depend on CB1 receptor activation.[4]

The amygdala is directly related to the symptoms of conditioned fear and the fight or flight response. Its reduction is also associated with manifestations of anxiety in Parkinson's disease. CBD has demonstrated the ability to modulate the cingulate cortex and amygdala during the processing of stimuli related to stress and anxiety.[10]

A significant number of patients with Parkinson's disease (PD) present anxiety disorders, clinically linked to the severity of motor symptoms, motor fluctuations and the duration of the disease. Activation of the CB1 neuroreceptor has been associated with reducing unconditional fear and facilitating extinction of conditioned fear. These findings suggest a relationship between CB1 activation and emotional regulation, resulting in anxiolytic effects.[10]

Pharmacology of Cannabinoids

The first approved medicinal cannabis consisted of an oral spray with a 1:1 concentration of CBD and THC for patients with multiple sclerosis, but currently, they

are more commonly found in the form of oils and tinctures for faster absorption and higher plasma concentration of THC and CBD.[13]

The administration mechanism of cannabinoids is highly variable, with the main studied administration routes being oral, sublingual, and inhalation. Among these, vaporization has been considered the most promising due to its potential to improve bioavailability without demonstrating risks to the consumer.[3] In Klumpers and Thacker, THC is absorbed more rapidly through inhalation, either by smoking or vaporization, while the oral route has a slower absorption.

The pharmacokinetics of CBD depends on factors such as the route of administration, the type of product administered, the presence of food in the digestive tract, and drug interactions. The study revealed that ingesting food before the administration of an aerosol containing THC/CBD increased the maximum concentration and prolonged the time to reach that concentration.[3]

CBD metabolism primarily occurs through oxidation and hydroxylation at various points in the molecule, leading to a complex degradation process. Another pathway involves β-oxidation and biotransformation of the pentyl side chain, along with hydroxylations at positions C-6 and C-7. The main excretion process of CBD occurs in the feces, with several metabolites excreted by the kidneys.[3] As for THC, inhalation metabolism avoids the first-pass effect, resulting in fewer psychotropic effects caused by metabolites when ingested orally. When ingested orally, THC elimination is mainly through the feces.[22]

Human Studies

In a double-blind clinical trial involving 21 patients divided into three groups, including a placebo group, a group with CBD at a dosage of 75 mg/day, and another

with CBD at 300 mg/day, over a period of 6 weeks, Significant improvements were observed in functioning and well-being measures in Parkinson's disease (PD) patients without psychiatric comorbidities treated with 300 mg/day CBD. This improvement correlated with factors such as "emotional well-being" and "mobility." The enhancement in emotional well-being results from CBD's action on non-motor symptoms of PD.[8]

However, no statistically significant differences were found in the UPDRS scale, which assesses behavior, mood, activities of daily living, motor examination, and complications in the groups receiving CBD at dosages of 75 mg/day and 300 mg/day. The study has limitations due to the small sample size and the majority of patients being in the early stages of the disease.[8]

Additionally, the study investigated the relationship between CBD administration and BDNF levels, as well as the ratios of NAA and Cr metabolites associated with neuronal viability. No significant changes were observed, possibly attributed to the short 6-week duration, which might be insufficient to detect measurable changes in spectroscopy measures related to neuronal viability. It's important to note that neuronal viability was not extensively explored in Parkinson's disease in this study.[8]

In a controlled, randomized, double-blind clinical trial, Parkinson's disease (PD) patients underwent acute administration of 300 mg of CBD during two experimental sessions, each lasting approximately 3 hours. These administrations occurred when the effects of antiparkinsonian medications were active. The results revealed that CBD significantly reduced anxiety induced by the Simulated Public

Speaking Test (SPST) and decreased tremor amplitude, as measured by an accelerometer.[10]

These findings align with the anxiolytic effects of CBD. However, there was no statistically significant difference in variables related to tremor frequency, and acute CBD administration had no impact on self-reported negatives during public speaking, as measured by the SPST.[10]

Oral administration of Epidiolex at high CBD doses, approximately 1600 mg/day, with a THC concentration below 0.15%, showed an association with mild adverse events, including diarrhea, drowsiness, fatigue, and possibly hepatotoxicity in individuals with PD. Of these, only diarrhea was correlated with increased dosage and may be related to sesame oil present in the medication formulation. Additionally, there was a transient increase in liver enzymes, mainly alkaline phosphatase, observed in 5 patients. However, only one of them exhibited symptoms related to a cholestatic process that resolved after discontinuation of the medication.[12]

The results highlighted the beneficial effects of CBD associated with 15% THC concentration, including a decrease in the mean scores of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total and motor at maximum doses compared to baseline. Furthermore, significant improvement was observed in non-motor assessments, such as SCOPA-Sleep nighttime and the shortened Emotional and Behavioral Control. In summary, improvements were seen in MDS-UPDRS total and motor scores, nighttime sleep, and emotional and behavioral control. It is essential to note that these benefits persisted after a 2-week discontinuation of CBD associated with 15% THC administration.[12]

In a survey study (Holden et al., 2022), over 30% of respondents reported better outcomes with products containing higher THC concentrations, including a reduction in medication for pre-existing Parkinson's-related symptoms such as nausea, vomiting, tremor, pain , anxiety, sexual dysfunction, and insomnia. On the other hand, patients preferred products with higher CBD concentrations due to the balance of symptom improvement and adverse effects. Products with higher THC levels showed worsening of adverse symptoms such as dry mouth, dizziness, worsened cognition, and balance.[20]

In a double-blind, placebo-controlled randomized study, Domen et al. noted that the placebo group showed improvement in several neuropsychological tests, while the CBD/THC group did not show improvement in only one neurological test. The study also states that it is uncertain whether the study's findings reflect acute cognitive effects or more short-term use, as cognitive tests were applied after participants had completed the 2-week exposure time and reached a stable state of THC and CBD concentration.

Also in Kanjanarangsichai et al., through a prospective randomized double-blind and placebo-controlled trial, two groups were separated, with the CBD/THC group receiving low doses of 15.59 mg/day and 0.61 mg/day, respectively. The trial showed no significant difference between the two groups in tests such as Time Up and Go (TUG), 5 Times Sit to Stand (5TSTS), and Unified Parkinson’s Disease Rating Scale (UPDRS). On the other hand, the CBD/THC group showed improvement in serum tests such as albumin, globulin, and the albumin/globulin ratio compared to the placebo group.

In the same study, patients expressed concerns about the drug's side effects based on previous trials, leading to a reduction in the previously tested dose range of 75-300 mg/day. Therefore, the study could not present results on functional severity, anxiety, depression, or even disease severity.[15]

Improvement was evident with the exclusive use of CBD only at higher doses, starting from 200 mg/day, with a significant positive effect exclusively on non-motor symptoms, primarily related to anxiety reduction and emotional well-being, positively impacting quality of life. In research conducted by Farias et al. (2020), improvements were identified in tremor amplitude related to the Simulated Public Speaking Test (SPST), correlating the finding with the possibility of reduced tremor amplitude due to improved anxiety.

Studies using drugs with a combination of CBD and THC showed both motor and non-motor improvements at high doses of 20-25 mg/kg/day with a 15% THC concentration. Mild adverse effects such as diarrhea, drowsiness, fatigue, and possibly hepatotoxicity were also observed, with only diarrhea being related to increased dosage. On the other hand, studies using higher THC concentrations (high doses > 50 mg/day) showed better motor and non-motor outcomes, such as tremor, movement, pain, sleep, depression, anxiety, and nausea. However, a worsening of adverse effects such as dry mouth, constipation, and dizziness was also observed.[20]

CONCLUSION

Current therapeutic approaches for Parkinson's Disease face challenges in managing disease progression and the adverse effects associated with chronic levodopa use. The discovery of phytocannabinoids, such as CBD, highlights neuroprotective and anti-inflammatory properties, improving patients' quality of life. Clinical results emphasize complex individual responses but point to a significant contribution of the Endocannabinoid System in Parkinson's Disease management, enabling innovative therapeutic pathways using cannabinoids. The exclusive use of high-dose CBD has shown improvements in non-motor symptoms and quality of life, with mild adverse effects. Meanwhile, the use of formulations with high CBD concentrations and low THC concentrations has indicated effects on both motor and non-motor symptoms. However, further controlled research is still needed to investigate the effects of CBD and CBD/THC at higher doses, with more prolonged exposure times and specific formulations for a better therapeutic delineation.

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