

Review Article

The Therapeutic Potential of Cannabidiol in Parkinson's Disease: A Review of Mechanisms of Action and Clinical Effects

ABSTRACT

Aims: This study aims to investigate the potential therapeutic effects and mechanisms of cannabidiol (CBD) in the treatment of Parkinson's disease (PD). Specifically, it focuses on understanding the role of CBD in managing motor and non-motor symptoms and its neuroprotective properties.

Study design: This research is a literature review.

Place and Duration of Study: The study was conducted at the University of Gurupi, Paraíso do Tocantins, TO, in 2023.

Methodology: A comprehensive literature review was conducted using databases such as Medline (PubMed), Biblioteca Virtual de Saúde (BVS), and Scientific Electronic Library Online (SciELO). Articles published in Portuguese and English were included. The search terms used were "Parkinson's Disease," "CBD," and "Treatment." The selection criteria focused on studies exploring the mechanisms of action, anti-inflammatory, and analgesic properties of CBD in the context of PD. Articles unrelated to the use of CBD for PD treatment or not exclusively focusing on CBD administration were excluded.

Results: The review included findings from seven scientific articles. Key outcomes indicate that CBD exhibits neuroprotective effects, reduces global symptom scores, and does not produce adverse motor effects. Notably, CBD was found to protect against cell death induced by neurotoxins like MPP+ and provide potential anti-inflammatory benefits by modulating cytokine release.

Conclusion: CBD shows promise as a therapeutic agent in PD due to its neuroprotective, anti-inflammatory, and analgesic properties. However, the clinical use of CBD remains limited and controversial, requiring further research to validate its efficacy and safety in treating PD. This summary provides an overview of the findings and methodologies covered in the full text, highlighting the potential and challenges of using CBD in Parkinson's disease treatment.

Keywords: *Cannabidiol (CBD), Parkinson's Disease, Neuroprotection, Anti-inflammatory effects, Motor symptoms.*

1. INTRODUCTION

“James Parkinson, in "An Essay on the Shaking Palsy," describes the disorder as involuntary movement, with decreased muscle strength in parts that are not in action and even when at rest, with a tendency towards a flexed posture and festinating gait”[1].

“This marks the first recorded description of Parkinson's disease in the literature. PD is primarily idiopathic; however, currently, the identification of genetic mutations has contributed to its diagnosis. There are two genes associated with the autosomal dominant form of PD: SNCA/ α -synuclein (PARK1) and leucine-rich repeat kinase 2 (LRRK2, PARK8), and four genes with loss-of-function mutations in the autosomal recessive form of PD: (PRKN, DJ-1, PINK1, and ATP13A2). Parkin mutations are the second most common genetic cause of L-dopa-responsive parkinsonism, frequently associated with patients exhibiting the first symptoms before the age of 40, known as juvenile parkinsonism” [2].

“The pathophysiology of Parkinson's disease is characterized by the degeneration of dopaminergic neurons, particularly in the area known as the substantia nigra of the basal ganglia, leading to a subsequent reduction of dopamine in the striatum”[3]. “PD is classified within the group of synucleinopathies, where the protein alpha-synuclein accumulates in neural tissue, forming Lewy bodies, a pathological hallmark of this group of diseases. The accumulation of Lewy bodies precedes neuroimaging signs of neuronal death, with Lewy bodies being eliminated when the neurons carrying them die. There is neuronal cell loss accompanied by three distinct intraneuronal alterations: the Lewy body, the pale body, and the Lewy neurite”[4]. “Damage to the neurons of the nigrostriatal tract may be related to factors such as oxidative stress, reduced protein degradation, glutamate excitotoxicity, neuroinflammation, and mitochondrial dysfunction. The neurodegeneration observed in Parkinson's disease (PD) is likely caused by programmed cell death (apoptosis) or necrosis, both resulting from oxidative stress”[5].

“The onset of the disease is gradual, and early symptoms may go unnoticed or be misinterpreted for a long time. Its identification is based on a syndromic pattern marked by a set of motor symptoms, with the characteristic triad including resting tremor, bradykinesia, and joint rigidity. Resting tremor presents as involuntary, rhythmic, and oscillatory movement, while bradykinesia is described as a progressive decrease in speed and amplitude of movements, including minor symptoms such as hypomimia and hypophonia. In rigidity, there is an increase in muscle tone, leading to resistance in passive movement”[6]. “Additionally, other mechanisms are affected; non-motor symptoms in PD involve a wide range of functions, including regulation of the sleep-wake cycle, cognitive function, mood regulation, autonomic nervous system function, as well as sensory function and pain perception. Consequently, adverse signs such as hallucinations, dementia, gastrointestinal dysfunction, and anxiety are identified”[7].

“Parkinsonian syndrome is linked to several risk and protective factors, including advanced age, family history, dietary factors, medications, exposure to toxic environmental substances, comorbidities such as obesity and type 2 diabetes, habits, and metabolic syndrome. Conversely, extensive group studies and combined analyses indicate that smoking tobacco is associated with a lower likelihood of PD occurrence, as nicotine appears to exert a beneficial effect on brain health, offering a neuroprotective effect. The global incidence rate of PD in women aged 40 and above was 37.55 per 100,000 person-years and 61.21 in men aged 40 and above. There is a noted increase in incidence for both men and women with age”[8].

“Science has not yet discovered treatments for PD that promise to reverse the neuronal degeneration. Available therapeutic interventions can improve disease symptoms, with notably higher efficacy in those involving the motor system, primarily through the administration of dopamine precursors, such as levodopa (L-DOPA), aiming to restore reduced dopamine levels in the striatum, characterizing a palliative pharmacotherapy”[9]. “However, it soon became evident that there are significant limitations to L-dopa therapy. After 5 to 10 years of treatment, there is an association with the development of a range of complications. Tardive dyskinesia, a notable extrapyramidal side effect, is the main complication in motor response. Neuropsychiatric complications develop in up to 40% of patients, and dementia in up to 30%. The mechanism responsible for the development of these disorders is not fully understood, but it has been speculated that they may result from excitotoxic damage to targets of the subthalamic nucleus (STN), whose neurons use glutamate as a neurotransmitter and are hyperactive in the parkinsonian state”[10].

“Currently, there is discussion regarding the use of Cannabidiol (CBD) as a potential alternative strategy for the treatment of Parkinson's disease. Several in vitro experiments have demonstrated promising neuroprotective effects of CBD in PD models. Cannabidiol was first isolated from the cannabis plant in the late 1930s and early 1940s, and its structure was elucidated in 1963”[11]. “The non-psychoactive CBD exhibits a plethora of effects, many of which may be of therapeutic importance. Its actions have been observed in both laboratory animals and humans, including sedative/hypnotic, anticonvulsant, neuroprotective, cardiovascular, and anti-inflammatory effects”[12].

In 1988, a binding site for THC was identified, and in 1990 the first cannabinoid receptor was cloned, followed shortly by the identification of a second receptor, defining the nomenclature of CB1 for the first receptor and CB2 for the second. CB1 is the most abundant GPCR receptor (G-protein-coupled receptor) in the brain, while CB2 is present in immune system cells, characterizing these as the primary sites of action for CBD [13]. Cannabinoid receptors, endocannabinoids (endogenous agonists of cannabinoid receptors), and the enzymes that catalyze their synthesis and degradation constitute the Endocannabinoid System, which has enabled the investigation of the use of CBD for the treatment of various diseases [14].

Preclinical in vitro and in vivo studies using PD models demonstrate that CBD has anti-parkinsonian properties, reducing overall PD symptom scores without producing motor or other adverse effects. However, in medicine, there is still controversy regarding its use, as the number of studies on the subject is insufficient [15]. Marijuana, derived from *Cannabis sativa*, being an illicit and illegal drug used for recreational and addictive purposes, generates more disagreement regarding its therapeutic use. Thus, the aim of this study is to elucidate promising results involving the administration of CBD for the treatment of Parkinson's disease.

2. METHODOLOGY

This literature review was conducted to investigate the use of cannabidiol (CBD) in the treatment of Parkinson's disease (PD). Data collection was carried out using the following electronic databases: PubMed, Virtual Health Library (VHL), and Scientific Electronic Library Online (SciELO). The search included articles published in Portuguese and English.

The inclusion criteria were studies that addressed the mechanisms of action of CBD, its anti-inflammatory and analgesic properties, and its specific application in PD. Both pre-clinical

and clinical studies involving the use of CBD in experimental models or patients with PD were considered. Excluded were studies that did not explicitly mention the administration of CBD or that focused on other therapies without emphasis on CBD.

The selection of studies was conducted in three stages. Initially, three independent reviewers assessed the article titles, excluding those that clearly did not meet the inclusion criteria. Next, the abstracts of the selected articles were analyzed for a more detailed screening. Finally, the full texts of the eligible articles were thoroughly reviewed to ensure they met the established criteria. Throughout the process, the reviewers followed a strict protocol to avoid selection bias and ensure the inclusion of only relevant studies.

Data extracted from the included articles encompassed information on study design, samples used, dosages of CBD administered, methods of efficacy assessment, and key findings. The evidence was synthesized and discussed with a focus on the potential therapeutic applications of CBD for PD, as well as the limitations of existing studies and areas requiring further investigation.

3. RESULTS AND DISCUSSION

The main findings on the topic have been synthesized and are presented in Table 1. This table gathers essential information from the selected studies, including the objectives, employed methodologies, and findings. It provides a comprehensive overview of the effects and mechanisms of action of cannabidiol (CBD) in the treatment of Parkinson's disease, highlighting the different contexts in which CBD has been investigated and the conclusions drawn.

Given the multiplicity of mechanisms through which CBD acts in the body, several pathways relevant to the treatment of Parkinson's disease (PD) can be analyzed. Since 1996, numerous studies have indicated the potential involvement of apoptosis in PD. It has recently been demonstrated that cannabinoids can control the decision between cell survival and death, inhibiting apoptosis [16].

Neurotoxin-based models are useful for understanding the mechanisms underlying the neurobiology and dopaminergic neuronal loss in PD. The most common neurotoxins used in experimental models of nigrostriatal degeneration, such as 6-hydroxydopamine [6-OHDA], MPTP, and MPP+, induce apoptosis and reproduce the pathophysiological characteristics responsible for the motor deficiencies seen in PD. These models are thus used in studies investigating the neuroprotective effects of CBD [17,18]

It has been found that cannabinoids provide neuroprotection in both acute and chronic cases of neurodegeneration related to these neurotoxins. In an experiment involving the injection of [6-OHDA] in mice followed by the administration of cannabidiol, there was a significant reduction in the magnitude of dopamine depletion [19]. One detail that should be highlighted is the chemical architecture of this compound, the chemical structure of Cannabidiol shows the arrangement of atoms and the chemical bonds that connect them. The formula contains an aromatic benzene ring, attached to a side chain with a hydroxyl group (OH) and an aliphatic chain as can be observed in Figure 1.

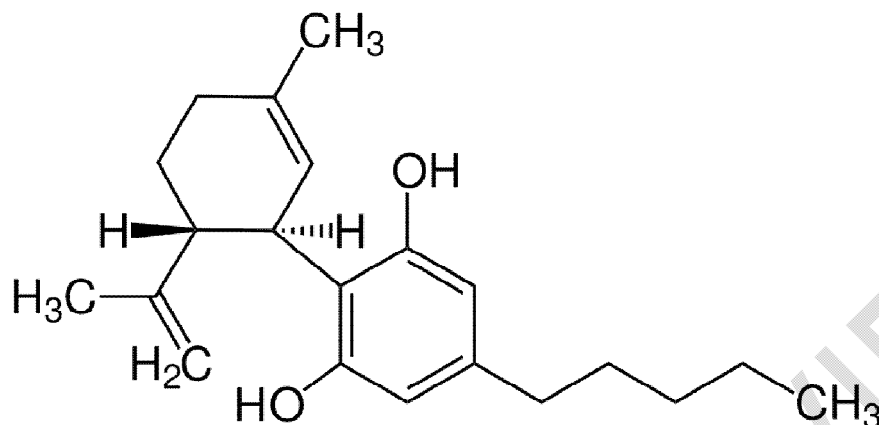


Fig. 1. Structural Formula of Cannabidiol (CBD)

This effect appeared irreversible, as there was no recurrence of neurodegeneration induced by 6-hydroxydopamine after stopping daily administration. The authors suggest that this result may be due to the antioxidant or anti-inflammatory actions of cannabinoid [20]. Similarly, in another study, CBD exhibited a protective role against cell death in MPP⁺-induced toxicity, associated with the formation of reactive oxygen species [21]. Data from research involving MPTP-induced neurotoxicity suggest that the selective activation of CB1 receptors by exogenous or endogenous cannabinoids can provide neuroprotection, as they are capable of modulating the inflammatory response. A body of evidence indicates an active role of neuroinflammation in the pathophysiology of progressive neurodegenerative diseases, including PD.

A neuroinflammatory cycle is triggered by excessive activation of glial cells, making these components a viable target for discovering new therapeutic approaches. Among the actions of CBD, its anti-inflammatory capability stands out. Although CBD is non-psychoactive, its lipophilicity allows it to easily cross the blood-brain barrier and exert beneficial effects on the brain [22].

Three studies demonstrate this effect: the first study examines the potential of two cannabis extracts, concluding that the anti-inflammatory properties are mediated by effects on arachidonic acid metabolism, an inflammatory mediator precursor. These extracts inhibit cyclooxygenase and lipoxygenase, as well as phospholipase activity, thus preventing the synthesis and mobilization of prostaglandins. The activity of these substrates appears complex, affecting at least three key enzymes in the arachidonic acid cascade [23]

In the second study, it was found that non-psychoactive CBD significantly suppressed the release of cytokines (IL-1, TNF, IFN), and at high concentrations, it could completely block the synthesis or release of IFN, specifically. Finally, the last study suggests a promising option for simultaneously improving neuroinflammation and neurodegeneration through pharmacological agents affecting the endocannabinoid system (ECS) [21]. It investigates the efficacy of cannabidiol and its ability to antagonize cannabinoid receptor agonists, contributing to its anti-inflammatory properties [24]

These compounds are also part of a complex endogenous neural signaling system in humans, the endocannabinoid system. The ECS consists of cannabinoid receptors, type 1

(CB1) and type 2 (CB2), present in central and peripheral immune cells, endogenous ligands known as endocannabinoids, and a set of degradation enzymes [25]. As demonstrated in research, cannabidiol acts as a potent agent for the cannabinoid receptor, activating the neuroprotective actions of these receptors, with neuroprotective activities occurring through various mechanisms [26].

In a study, it was found that endogenous activation of CB1 receptors in the principal neurons of the forebrain promotes neuronal survival during excitotoxicity [27, 28]

Additionally, some in vivo studies have tested the efficacy of CBD treatment for Parkinson's disease in certain groups of people. One study selected 21 patients from a sample of 119 patients monitored in a clinic, dividing them into three groups of seven individuals each. The groups were treated with placebo, cannabidiol (CBD) 75 mg/day, or CBD 300 mg/day. Overall, significant improvements in functioning and well-being measures were found in PD patients treated with CBD 300 mg/day compared to the placebo group [8]. Another study found that cannabis not only improved motor scores but also alleviated pain symptoms in PD patients, along with a dissociative effect on heat and cold pain thresholds [29].

Furthermore, CBD has demonstrated effectiveness in treating levodopa-induced dyskinesia (LID), often described as more debilitating than PD itself. LID is a major limiting factor in levodopa therapy, preventing the administration of adequate drug doses. Dyskinesias can manifest as choreiform movements, dystonia, tics, and myoclonias[30]. A study using mice involved unilateral striatal lesions induced by 6-hydroxydopamine, followed by levodopa administration for 21 days, resulting in LID. Subsequently, the animals were treated with CBD (intraperitoneally) before levodopa for three days, either alone or in combination with TRPV-1, CB1 cannabinoid receptors, or peroxisome proliferator-activated receptor-gamma (PPAR γ). It was observed that CBD, along with a TRPV-1 antagonist, reduced dyskinesia by acting on CB1 receptors [31].

The findings presented by Patricio *et al.* (2020) reinforce the therapeutic potential of cannabidiol (CBD) as a neuroprotective and neuromodulatory approach in Parkinson's Disease (PD). The review conducted by the authors highlights that CBD, by interacting with the endocannabinoid system, can mitigate central pathological processes in PD, such as neuroinflammation and oxidative stress. Moreover, the data suggest that CBD has the potential to improve both motor and non-motor symptoms, offering a promising alternative to traditional therapies, which are often associated with undesirable side effects. These findings underscore the need for further clinical studies to explore the use of CBD in therapeutic protocols for PD, particularly in the early stages of the disease, where neuroprotective intervention could have a more significant impact on the progressive course of the pathology [32]

Giuliano *et al.* (2021) observed that CBD conferred neuronal protection and reduced motor symptoms in an animal model of PD, reinforcing the hypothesis that the compound may act on multiple molecular and cellular targets involved in neurodegeneration [33]. Nascimento *et al.* (2020) complement this view by reporting that CBD increased the nociceptive threshold in preclinical models, indicating additional therapeutic potential for managing pain associated with PD [34]. On the other hand, the study by Leehey *et al.* (2020) in PD patients revealed that CBD was well-tolerated in a dose-escalation study, without significant adverse effects, although the direct clinical benefits still require further evaluation [35]. Together, these findings support the idea that CBD is a multifaceted substance that may offer benefits both in symptom modulation and neuronal protection in PD patients, while also highlighting the need for larger, controlled clinical studies to establish its long-term efficacy and safety.

The findings of this study corroborate the growing evidence that cannabidiol (CBD) possesses neuroprotective and anti-inflammatory properties that may be particularly beneficial in the treatment of Parkinson's Disease (PD). For example, studies in animal models have demonstrated that CBD can reduce neuroinflammation and neuronal death by modulating microglial cell activity and regulating the release of pro-inflammatory cytokines [33,35]. These mechanisms are crucial for attenuating the progression of PD, suggesting that CBD could serve as an effective intervention in the early stages of the disease. Additionally, clinical trials in humans have shown that CBD is well-tolerated with a favorable safety profile, although further investigations are still needed to fully understand its clinical efficacy and to optimize dosages for different stages of PD [24,32].

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Table 1. Summary of Key Studies on the Effects and Mechanisms of Cannabidiol (CBD) in Parkinson's Disease

Author/Year	Title	Objectives	Methodology	Findings
IsabelLastres-Becker(2005)	Cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro: relevance for Parkinson's disease	To evaluate the in vivo effects of D9-THC and CBD on neurodegeneration progression in rats unilaterally lesioned with 6-hydroxydopamine.	Male rats were housed in a room with controlled photoperiod and temperature, with free access to food and water. The experiment involved unilateral injection of 6-hydroxydopamine followed by treatment with D9-THC and CBD. The animals were euthanized, and their brains were removed and processed.	Daily administration of D9-THC for 2 weeks after 6-hydroxydopamine injection in the medial forebrain produced a significant decrease in dopamine depletion caused by the substance. The effect of D9-THC appeared to be irreversible, as stopping the cannabinoid administration did not lead to the reinitiation of 6-hydroxydopamine-induced neurodegeneration. The same neuroprotective effect was observed with CBD.
NeifeAparecidaGuinaim Santos (2015)	Neuroprotection by cannabidiol against MPP+ toxicity in PC12 cells involves TrkA receptors, upregulation of axonal and synaptic proteins, and neuritogenesis, potentially relevant for	To assess the neurotrophic potential of CBD as a neuroprotective mechanism and its involvement in the NGF pathway.	PC12 and SH-SY5Y cells were obtained from the American Type Culture Collection (ATCC, Rockville, MD). MPP+ induced toxicity, with some cells treated with 1µM CBD and incubated at 37°C for 72 hours,	CBD protects against cell death and neurite loss induced by the neurotoxin MPP+ in PC12 cells, suggesting a protective effect similar to NGF, contributing to its neuroprotective activity.

	Parkinson's disease		while untreated cells served as control.	
Marcos HortesN Chagas (2014)	Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial	To evaluate the effects of CBD in PD, including neurological evaluations of motor skills, functional symptoms, psychiatric evaluation, and complementary exams (brain-derived neurotrophic factor levels and H1-MRS)	A sample of 119 patients consecutively evaluated at a specialized movement disorder clinic; 21 patients with PD without dementia or psychiatric comorbidities were selected. Participants were divided into three groups of seven each, treated with placebo, cannabidiol (CBD) 75 mg/day, or CBD 300 mg/day. One week before and in the last week of treatment, participants were evaluated for (i) motor and general symptoms score (UPDRS); (ii) well-being and quality of life (PDQ-39); and (iii) possible neuroprotective effects (BDNF and H1-MRS).	Significant improvements were observed in functioning and well-being measures in patients with PD treated with CBD 300 mg/day compared to a placebo group. No differences were found between groups in other measures. The findings suggest a possible effect of CBD in improving quality of life measures in patients with PD without psychiatric comorbidities.
A. Thomas (2007)	Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro	To investigate whether these properties of cannabidiol extend to CB1 receptors expressed in mouse brain and	The [³⁵ S]GTPγS binding assay was used to determine the efficacy of cannabidiol and its ability to antagonize	The study found that cannabidiol can act as an inverse agonist at the human CB2 receptor. Additionally, it acts as a

		human CB2 receptors transfected into CHO cells.	cannabinoid receptor agonists (CP55940 and R-(+)-WIN55212) at CB1 receptors in the mouse brain and human CB2 receptor.	potent antagonist of cannabinoid receptor agonists in mouse brain tissue and CHO cells transfected with human CB2 receptors, contributing to its anti-inflammatory effect.
Teresa Luvone (2007)	CB1 receptor stimulation provides neuroprotection in MPTP-induced neurotoxicity by attenuating S100B upregulation in vitro	To elucidate the involvement of S100B in MPTP-induced neurotoxicity, its molecular mechanism, and the role of cannabinoids and ECS in controlling S100B toxicity.	C6 cells were treated with 1-methyl-4-phenyl 1,2,3,6 tetrahydropyridine (MPTP) and co-cultured with differentiated PC12 cells. They were then treated with arachidonyl-2-chloroethylamide, a CB1 agonist.	Neuronal damage due to MPTP exposure appeared closely related to increased density and release of the protein S100B. The selective CB1 receptor agonist protected PC12 cells from apoptosis.
Maurício dos Santos-Pereira (2016)	Co-administration of cannabidiol and capsazepine reduces L-DOPA-induced dyskinesia in mice: Possible mechanism of action	To investigate if CBD and CBD combined with CPZ can alleviate LID (L-DOPA-induced dyskinesia) in hemiparkinsonian patients.	The study used 6-hydroxydopamine in C57/BL6 mice to replicate the pattern of cell death present in PD patients. Mice with unilateral striatal lesions were given levodopa for 21 days, developing abnormal involuntary movements (AIMs). Subsequently, the animals were treated with CBD (intraperitoneally)	The study indicates that CBD, combined with a TRPV-1 antagonist, reduces LID by acting on CB1 and PPAR γ receptors and reducing the expression of inflammatory markers such as cyclooxygenase-2 and nuclear factor kappaB.

before levodopa for three days, either alone or in combination with antagonists of the transient receptor potential vanilloid 1 (TRPV-1), cannabinoid type 1 (CB1), or peroxisome proliferator-activated receptor gamma (PPAR γ).

Bernhard Watzl (2007)

Components of cannabis stimulate peripheral blood mononuclear cell secretion of interferon gamma and suppress interleukin-1 alpha in vitro

To investigate the in vitro effects of psychoactive and non-psychoactive cannabis components on leukocyte secretion of immunoregulatory cytokines interleukin-1 alpha (IL-1), tumor necrosis factor alpha (TNF), interferon gamma (IFN), and interleukin-2 (IL-2).

Delta-9-psychoactive tetrahydrocannabinol (THC) and non-psychoactive cannabidiol (CBD) were added to cultures of human peripheral blood mononuclear cells (PBMC) activated by mitogens, and concentrations of IL-1, TNF, IFN, and IL-2 in the culture were measured using the ELISA system.

The study results demonstrate that in vitro, psychoactive and non-psychoactive cannabis components are immunomodulatory and can potentially alter cytokine secretion by human PBMC. Non-psychoactive CBD had a stronger suppressive effect on the release of cytokines (IL-1, TNF, IFN) than THC. CBD suppressed the secretion of IL-1, TNF, and IFN, while THC suppressed only IFN release.

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4. CONCLUSION

Despite the emerging evidence on the therapeutic activities of cannabinoids (CBs), their effective introduction and clinical use remain controversial and are significantly limited by potential psychotropic effects. In this context, cannabidiol (CBD), which can constitute up to 40% of Cannabis extract, stands out as a promising candidate for clinical use due to its benign cognitive and psychoactive properties, as well as its excellent tolerability profile in humans. CBD offers a viable alternative with fewer associated risks, enhancing its therapeutic potential in various medical conditions.

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