A literature review on the therapeutic applicability of cannabidiol in epilepsy, multiple sclerosis and Parkinson's disease

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October 16, 2023

Abstract

Neurodegenerative diseases have complex etiologies, however, neuroinflammation and oxidative stress are important markers in this pathogenesis and, in this sense, cannabinoids, especially CBD, have been identified as potential therapeutics for playing a neuroprotective role. Studies have demonstrated the neuroprotective effect of cannabinoids and derivatives of *Cannabis sativa* L in diseases of the central nervous system due to their interaction with the endocannabinoid system through receptors and other molecular targets. The aim of this review was to provide an overview of the endocannabinoid system and a summary of the clinical and preclinical findings of the therapeutic use of cannabinoids in epilepsy, multiple sclerosis and Parkinson's disease, pointing out interactions with molecular targets and the potential for neuroprotection of CBD. Electronic searches were carried out in international databases, including studies that presented consistent data on this subject. Significant therapeutic effects of CBD were shown for epilepsy and Parkinson's disease, while nabiximols contributed to the reduction of spasticity, being a frequent option for the treatment of multiple sclerosis. Although much has been projected on the therapeutic potential of cannabinoids for neurological disorders, there is a long way to go in the search for strong scientific evidence of their pharmacological effectiveness.

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Abstract

Neurodegenerative diseases have complex etiologies, however, neuroinflammation and oxidative stress are important markers in this pathogenesis and, in this sense, cannabinoids, especially CBD, have been identified as potential therapeutics for playing a neuroprotective role. Studies have demonstrated the neuroprotective effect of cannabinoids and derivatives of *Cannabis sativa* L in diseases of the central nervous system due to their interaction with the endocannabinoid system through receptors and other molecular targets. The aim of this review was to provide an overview of the endocannabinoid system and a summary of the clinical and preclinical findings of the therapeutic use of cannabinoids in epilepsy, multiple sclerosis and Parkinson's disease, pointing out interactions with molecular targets and the potential for neuroprotection of CBD. Electronic searches were carried out in international databases, including studies that presented consistent data on this subject. Significant therapeutic effects of CBD were shown for epilepsy and Parkinson's disease, while nabiximols contributed to the reduction of spasticity, being a frequent option for the treatment of multiple sclerosis. Although much has been projected on the therapeutic potential of cannabinoids for neurological disorders, there is a long way to go in the search for strong scientific evidence of their pharmacological effectiveness.

Keywords: Cannabinoids, endocannabinoid system; epilepsy, multiple sclerosis, Parkinson's disease.

Introduction

Cannabis sativa L. (Magnoliopsida; Cannabaceae) popularly known as hemp, marijuana, cannabis, weed, among other names is a species belonging to the Cannabaceae family [1-6]. All over the world, *Cannabis sativa* L. is an ancient and traditional plant in several cultures, which has been passing through generations, from antiquity to the present day. Although at the beginning of the 20th century it was established as an illegal drug, even with a reduced consumption, it was considered the most consumed recreational drug in the world. Its presence among humans is highlighted in religious rites, for food, psychoactive and especially medicinal use [7, 8].

The constituents of *C. sativa* are formed by nitrogen compounds, amino acids, hydrocarbons, terpenes, and sugars responsible for the toxicological and pharmacological effects [9]. However, it is widely known that the two main ingredients in *Cannabis* are Δ9 -tetrahidrocanabinol (THC) and Cannabidiol (CBD) [10], CBD being the most abundant phytocannabinoid that does not present psychoactive properties, which has shown benefits to human health, mainly due to its molecular interaction with the endocannabinoid system (ES) [11] .

After discovering cannabinoid receptors, mammals were shown to produce endogenous agonists for these receptors (the endocannabinoids), such as anandamide, also known as N-arachidonoylethanolamine (AEA) and 2-arachidonoyl-glycerol (2-AG) [6, 12]. Endocannabinoids are involved in food intake, analgesia, cancer, and addiction [13], but until the discovery of the ES, the receptor identified as "cannabinoid receptor 1 (CB1)" was a "receptor coupled to G" protein without a previously known ligand. The high affinity of THC for the CB1 receptor has increased knowledge about the ES [5]. However, the second cannabinoid receptor (CB2) has low psychoactive activity compared to the CB1 receptor [2-5, 14]. As for CBD, studies have shown that it develops an allosteric binding activity between CB1 and CB2 receptors and that it presents other potential therapeutic targets such as transient receptor potential vanilloid (TRPV), o peroxisome proliferator-actived

receptor γ (PPARγ), o G protein-coupled receptor 55 (GPR55), receptors 5-hydroxytryptamine (5-HT), γ-Aminobutyric acid type A ($GABA_A$) e transient receptor potential cation channel subfamily M (melastatin) member 8 (TRPM8). While the CB2 receptor is mostly found in cells of the immune system, the CB2 receptor is highly common in the central nervous system (CNS), mainly in brain areas [15].

In this way, CBD has been identified as a potent anti-inflammatory and antioxidant that, interacting directly or indirectly with CB1 and CB2 receptors and other molecular targets, mediates neuroprotection. In this sense, it has been investigated as a potential therapy for neurodegenerative diseases [16], considering that throughout the world, due to the increase in people's life expectancy, these diseases have been worrying because they gradually lead to functional loss of motor and /or cognitive and produce high economic and social impacts [16-19].

There are several suggestions about the pathogenesis of neurodegenerative diseases, including the idea that the entire brain begins to be invaded by abnormal protein aggregates that are the result of an abnormal conformation of the peptides β-amyloid, α-synuclein and tau [16, 18, 20, 21]. It is considered that Parkinson's disease, a neurodegenerative disease that generally affects the elderly, presents aggregates of α-synuclein as a triggering factor for neurotoxicity and, consequently, neuronal death. In this process, microglia are activated leading to the production of pro-inflammatory cytokines and mediators of oxidative stress, resulting in the death of dopaminergic neurons in the white matter [22-25].

Also recognized as a neurodegenerative disease, multiple sclerosis affects around 2.8 million people worldwide, including children. It is a very prevalent chronic inflammatory disease of the CNS, with a complex and multifactorial etiology [26, 27]. In multiple sclerosis, there is no consensus that white matter lesions are of inflammatory or neurodegenerative origin, considering that in the early stages of the disease inflammation is rarely observed, thus suggesting that there is a direct involvement of lymphocytes in tissue damage or indirect involvement through the activation of microglia [27, 28]. CBD and THC formulas, in a 1:1 ratio, have been used to treat neuropathic pain and spasticity in multiple sclerosis considering, according to Russo and Guy [29] that beneficial therapeutic effects are increased when these phytocannabinoids are combined in a single product. In this sense, CBD has been seen as responsible for reducing the adverse effects of THC [16].

CBD has been indicated for pediatric epileptic disorders, refractory to medications, and its clinical use was authorized in 2018 by the Food and Drug Administration (FDA). It is known that epileptic disorders are triggered by an imbalance in the excitatory and inhibitory neurotransmission system [30]. On the other hand, epilepsy has currently been recognized as comorbidity in neurodegenerative diseases, consequently increasing longevity. Seeking to control epilepsy in the elderly, for example, would result in the reduction of cognitive deficits, the prevention of mortality from injuries arising from seizures and even from falls, which are frequent in this case [19]. Thus, alone or as an adjuvant, in the near future, CBD may extend its clinical use to secondary neurodegenerative disorders [16].

It is known that cannabis has promoted the modulation of several pathophysiological phenomena due to the interaction between the ES and different preparations, natural (phytocannabinoids) or synthetic (cannabinoids) [31-34]. Thus, this review aimed to provide an overview of the ES and a summary of the clinical and preclinical findings of the therapeutic use of cannabinoids in epilepsy, multiple sclerosis and Parkinson's disease, pointing out the interactions between them and molecular targets. We sought to show the great potential for neuroprotection of CBD and its promise in primary neurodegenerative diseases and secondary to other CNS complications, such as epilepsy.

1.4 The endocannabinoid system

1.4.1 The complexity of the endocannabinoid system - the "endocannabinoidome"

With the advancement of studies, ES has proven to be increasingly complex, since in addition to endocannabinoids of a lipophilic nature, with AEA and 2-AG acting as ligands for CB1 and CB2 receptors, it maintains a relationship with several other mediators such as N- acylethanolamines and 2-acylglycerols, primary amides,

lipoamino acids and N-acyl neurotransmitters, with SE-specific enzymes and metabolic enzymes such as fatty acid amide hydrolase (FAAH), N-acyl-phosphatidyl ethanolamine-specific phospholipase (NAPE-PLD), monoacylglycerol lipase (MAGL), DAGL (sn-1-diacylglycerol lipase) and diacylglycerol lipase β (DAGLβ) and other receptors such as peroxisome proliferator-actived receptor α (PPARα), G protein-coupled receptor 118 (GPR118), G protein-coupled receptor 119 (GPR119), GPR55, TRPV1, PPARγ, T-type Ca2+ channels (Cav3.2), TRPM8, 5-HT1A and $GABA_A$. In this sense, the therapeutic targeting of anabolic or catabolic endocannabinoid enzymes has been hampered by the promiscuity of this system, which interacts with several neuromediators, such as endogenous opioids and GABA, forming a broad alternative network of metabolic pathways and processes [10, 35-37]. Therefore, just as the terms transcriptome, proteome and metabolome emerged, the term "endocannabinoidome" has been used [36, 38-41].

It must be considered that alternative synthesis routes, both for AEA and for 2-AG, have been reported. In the case of AEA, those cited as alternative pathways to "transacylation-phosphodiesterase" are FLC-like/protein tyrosine phosphatase N22 (PTPN22) [42-44], phospholipase A2/lyso-FLD [43, 45] and alpha-beta hydrolase-4/glycerophosphodiesterase GDE1 (Abh4/GDE1) [46]. Furthermore, anandamide can interact with several molecular targets, including the activation of postsynaptic TRPV1 channels at an intracellular site [47]. Such activation may inhibit diacylglycerol lipase α (DAGLα), resulting in a decrease in 2-AG production, thus constituting a regulatory feedback mechanism [43].

Regarding the synthesis of 2-AG, according to Kano et al. [48] other pathways have been proposed including sequential reactions by phospholipase A1 (PLA1) and lysoPI-specific PLC, the conversion of 2-arachidonoyl lysophosphatidic acid into 2 -AG by phosphatase, and the formation of 2-arachidonoyl phosphatidic acid by 1-acyl-2-arachidonoylglycerol.

Both AEA and 2-AG were able to interact with other targets such as GPR55 [43]. As well as reactions involving the arachidonate cascade enzymes, cyclooxygenase-2 (COX-2), originating prostaglandins-ethanolamides (prostamides) and lipoxygenase-12 and -15 (LOX-12-15), also including cytochrome p450 oxygenase enzymes have been mentioned by some authors as exhibiting a catabolic potential for both endocannabinoids [43, 48, 49].

In this context, we briefly illustrate in fig. 1 the complexity of the ES.

Fig. 1. The complexity of the ES

1.4.2 Additional ligands and receptors of the endocannabinoid system

In addition to CB1 and CB2, the ES may include additional ligands and receptors capable of binding to other pharmacological targets. The most studied of the receptors involved in this system are TRPV1, $5HT_{1A}$, PPARγ and PPARα, although some works have addressed the role of two GPRs, GPR55 and G protein-coupled receptor 18 (GPR18) [50-55].

TRPV1 is a cation-permeable ion channel activated by heat, acidic pH, and capsaicin (the pungent compound in the pepper *Capsicum frutescens* pepper). It is a "vanilloid channel" or "transient receptor potential cationic channel, subfamily V, member 1" [56], located in the GABAergic and glutamatergic terminals and in the perikarya of neurons in the hippocampus and cerebellum, being identified as an important target that may represent a potential treatment for some diseases [36, 57-60]. In models of epilepsy, for example, TRPV1 is believed to increase the excitability of central neurons. In this case, studies have shown that from a double blockade of FAAH/TRPV1 there was a mediation of the excitatory effects of anadamide. This strategy induced an increase in AEA, levels, selectively activating the CB1 receptor and inhibiting neuronal activity [56, 61, 62].

In short, TRPV1 has been identified as a receptor with high affinity for endogenous AEA having an opposite action to the CB1 receptor [47], since while the binding of anandamide to the CB1 receptor inhibits neuronal activity, activation of TRPV1 depolarizes neurons and promotes neuronal activity. release of neurotransmitters [50, 63-65].

As for $5HT_{1A}$, they are serotonin receptors coupled to a Gi/o protein and have been related to cannabinoids, including neuroprotective effects [66]. These receptors are considered autosomal and are located on presynaptic membranes and are also found postsynaptically in various areas of the brain [67]. From an*in vivo* study, the hypothesis emerged that $5HT_{1A}$was a mediator that facilitated the neurotransmission of CBD, thus being an agonist of these cannabinoid receptors [68]. However, according to Campos et al [69] this agonist action was not corroborated in other subsequent studies, thus presenting the idea that $5HT_{1A}$-mediated effects of CBD would be caused by allosteric interactions with the receptor binding site and/or interference with intracellular pathways.

The antiaversive pharmacological effects of CBD were observed when CBD was injected systemically and in different areas of the brain, such as the dorsal periaqueductal gray matter, the medial hypothalamus and the medial prefrontal cortex, and in different animal models, including threat stress of predator [70-75]. Based on these and other findings, CBD has been proposed as a positive allosteric modulator for the $5HT_{1A}$ receptor [76-78].

In addition to TRPV1 and $5HT_{1A}$ receptors, investigations with PPARγ and PPARα have been presented in the literature. It is known that PPARα and PPARγ, an important class of nuclear hormone receptors (PPARs), are additional targets of endocannabinoids [79, 80]. Although the data are more significant for some cannabinoids, such as N-oleoylethanolamine (OEA) and N-palmitoylethanolamine (PEA), neuroprotection, anti-inflammatory and analgesic effects have been considered mediated, in part, by their activation to PPARs. However, there are a myriad of factors influencing interactions between cannabinoids and PPARs that need to be elucidated [81-83].

Interestingly, PEA (a compound related to cannabinoids) is currently used to treat pain and inflammation. Like other cannabinoid-related molecules, PEA has a very complex mechanism of action, which includes direct and/or indirect interaction with CB1, TRPV1, PPAR, GPR55 and GPR18, among other receptors [84]. It is known that GPR119, another putative receptor identified, can bind to PEA and also OEA compounds [85].

The list of non-cannabinoid receptors has been advancing. GPR18 and GPR55 have been presented as targets of various phytocannabinoids, synthetic cannabinoids and endocannabinoids [86-89]. Both are related to the modulation of several pathways of signaling of various metabolic disorders, being located mainly dispersed in the central and peripheral systems of the body, such as the brain and vascular system [90].

Moreover, GPR18 interact directly or indirectly with cannabinoids and seem to play an important role in inflammation, acting in the control of immune system activities, such as migration and apoptosis of leukocytes, and also in reducing intraocular pressure in mice. Its expression was evidenced in testes, spleen, peripheral blood leukocytes and lymph nodes [88].

Regarding GPR55, it has been shown to act in the nervous system, being a therapeutic target for Parkinson's disease [91-93], Alzheimer's disease (Medina-Vera et al, 2020), epilepsy (Gaston et al, 2016; Kaplan et al., 2017), in memory and spatial learning [94]. Furthermore, that it exerts antiproliferative effects through inhibition of protein kinase B (PKB) and extracellular signal-regulated kinase (ERK) in which CBD acts as a GPR55 antagonist [90], as well as, that PEA has high affinity for GPR55 as a full agonist [95]. Several interaction actions between endocannabinoids and GPR55 in the CNS have been studied recently, but many mechanisms need to be elucidated in order to obtain scientific evidence [15, 95].

An *in vitro* and *in vivo* study analyzed the affinity of eight compounds, namely, THC, [?]9-tetrahydrocannabinolic acid (THCA), [?]9- tetrahydrocannabivarin (THCV), CBD, cannabidiolic acid (CBDA), cannabidivarin (CBDV), canabigerol (CBG) and cannabichromene (CBC), with CB1 and CB2 receptors. The results demonstrated that many of these phytocannabinoids have a partial agonist activity on CB1 and/or CB2 receptors, and in vivo the interaction of phytocannabinoids often occurs with CB1 receptors [96].

1.5 Therapeutic applications in diseases of the nervous system

1.5.1 Epilepsy

For cases of intractable seizures such as Dravet syndrome, Lennox-Gastaut syndrome and tuberous sclerosis complex, the use of CBD (branded as Epidiolex) was approved in 2018 and 2019 by FDA and the European Medicines Agency, respectively.

Epilepsy is a neurological disorder that affects people of all ages; it is a chronic disorder of the brain characterized by convulsive crises with events of hyperactivation and synchronization of groups of neurons that lead to motor, sensory, autonomic, and behavioral alterations [97]. Roughly 50 million people worldwide have epilepsy, making it one of the most common neurological disorders in the world, and approximately 30% of patients are affected by treatment-resistant epilepsy due to the failure of common antiepileptic therapies [98, 99].

With the advance in the understanding of neurotransmitter systems in recent years, it has been accepted that the break in the balance between excitatory and inhibitory neurotransmitter systems may underlie the triggering of epileptic disorders. However, a precise relationship between such neural systems and the characteristics of epileptiform syndromes has not yet been established [30].

Many epilepsy induction models have been used to study the antiepileptic properties of CBD [100-104]. Broadly, both antiepileptogenic effects with CB1 and CB2 receptor agonists and pro-epileptogenic effects using blockers of these receptors in temporal lobe models of epilepsy have been observed [62, 105-107].

In fact, there is evidence that the ES participates in seizure control mechanisms in developing animals through the CB1 receptor [108]. In preclinical seizure models, the anticonvulsant effect has been related to a pharmacological increase in endocannabinoid levels, and AEA and 2-AG are released after neuronal hyperexcitability to combat glutamate excitotoxicity during seizures [36, 107, 109, 110]. Nonetheless, according to Schlicker and Kathmann [111] and Alger [112], many axon terminals of the CNS express CB1 receptors with the function of inhibiting the release of excitatory and inhibitory neurotransmitters.

A recent review by Bilbao and Spanagel [113] showed that CBD has a significant therapeutic effect (high grade) for epilepsy. Regarding the effects of CBD in epilepsy, it is not yet clear how it exerts its action (a summary of this mechanism was shown in figure 2). However, it has been proposed that the anticonvulsant action of CBD is exerted through several mechanisms independently of CB1 receptors [114], instead including the effects on 5-HT_{1A} receptors, vanilloid TRPV1 receptors, N-metil D-Aspartat receptors (NMDA), GPR55 receptors, Ca^{++} flux regulation, increased adenosine signaling, and interaction with GABAergic receptors [36, 101, 103, 115-122]. In addition to the anticonvulsant potential of CBD [103, 123], a neuroprotective effect has been proposed, restoring hippocampal interneuron functions in a temporal lobe epilepsy model [124-126].

Fig. 2 . Diagram of interactions and therapeutic effects of CBD in epilepsy

It is noteworthy that other compounds derived from Cannabis are being studied, with emphasis on CBDV, which has shown anticonvulsant results, and future analyses may better identify its potential for epilepsy treatment [116, 127, 128]. In summary, several well-designed trials have shown the effectiveness of cannabinoids in controlling epileptic seizures (Table 1). This review presents some studies using CBD, preferably randomized, double-blind, placebo-controlled clinical trials. Serious adverse effects are relatively rare, with somnolence, decreased appetite, and diarrhea being common. However, the use of concomitant medications such as clobazam and sodium valproate has been associated with somnolence and elevated liver enzymes [99, 129, 130].

Currently, CBD can be considered a reasonable treatment for several types of refractory epilepsy, with a favorable profile of adverse events and prolonged and sustained efficacy. However, it is necessary to be careful that these results, which have been demonstrating safety and efficacy, do not extrapolate to other formulations that lack rigorous standards of production and purity; nevertheless, there is more to learn and less to fear with CBD as a treatment for epilepsy [129].

Table 1. Preclinical and clinical evidence using Cannabis derivatives in epilepsy models and patients.

It is important to consider that in addition to pediatric epilepsies, people over 65 years of age can be diagnosed with epilepsy (cryptogenic), underlying seizures resulting mainly from neurodegenerative diseases and also from traumatic brain injury, cerebrovascular diseases and brain tumors. Therefore, in the context of neurodegenerative diseases, epilepsy has been highlighted, including in the search for evaluative procedures for early diagnosis and intervention in elderly people with initial seizures.[19].

1.5.2 Multiple sclerosis

Multiple sclerosis is a chronic, progressive, autoimmune disease caused by inflammation, demyelination, gliosis, and neurodegeneration [131]. It manifests itself clinically through sensory, motor, and psychological symptoms, and via neurological aspects. The most common signs are fatigue (40%), optic neuritis (22%), paresthesia (21%), diplopia (12%), vertigo (5%), and bladder dysfunction (5%). However, other symptoms include cognitive impairment, ataxic gait, spasticity, depression, and internuclear ophthalmoplegia. The region of the CNS that is affected will determine how multiple sclerosis manifests itself, as well as the frequency, severity, progression of the disease's incapacitation, and the sequelae of the relapses [132]. In young adults between 20 and 40 years of age, it appears as the main cause of disability and has a higher incidence in women (2.3:1) [133].

Regarding the pathophysiology, self-reactive leukocytes cross the blood-brain barrier and form active plaques formed by perivascular and parenchymal infiltrates of macrophages, B lymphocytes, and T lymphocytes, which destroy the myelin sheath. The acute inflammatory phase is characterized by partial remyelination by oligodendrocytes in the affected axons [134]. Infiltration of T lymphocytes in the CNS accompanied by oligodendrocyte destruction and axonal damage marks the arrival of the progressive phase of the disease. After the demyelinating event, impulse transmission in the affected axons occurs at 5 to 10% of normal speed. In addition, demyelinated axons generate spontaneous electrical discharges known as Lhermitte's sign [135].

Treatment aims to reduce the occurrence of new outbreaks, slow the progression of neurological damage, and delay the progressive phase of multiple sclerosis, mainly seeking to partially prevent axon destruction arising from the autoimmune inflammatory process. In this sense, CBD use in animal models and patients with multiple sclerosis has been reported (Table 2), with indications for spasticity, pain, relaxation, sleep, anxiety, and tremor [136]. Patients with multiple sclerosis have shown alterations in the expression of CB1 and CB2 receptors and, therefore, therapies with cannabis derivatives have been proposed [36, 126].

Table 2. Preclinical and clinical evidence using Cannabis derivatives in multiple sclerosis models and patients.

Nabiximols have been frequently prescribed as a spray solution for buccal spraying, consisting of THC:CBD (1:1) and trade names Sativex/Mevatyl when prepared synthetically [136-141]. An oral solution that can also be prescribed is dronabinol, being a synthetic enantiomer of THC, under the trade names Marinol/Syndros [142].

Recently, improvements in spasticity and pain linked to multiple sclerosis have been associated with the use of nabiximols. However, despite indicating to be a promising therapy, with good tolerability and safety, nabiximois and dronabinol were not able to significantly improve the symptoms of multiple sclerosis [113, 126, 143-146]. Thus, there is no consensus regarding the possible molecular and cellular mechanisms related to the treatment with these cannabinoids, mainly, how they act to reduce neuroinflammation.

With regard to better elucidating the interaction between THC + CBD and neuroinflammation in experimental autoimmune encephalomyelitis (EAE) models, the work by Al-Ghezi et al. [147] investigated the mechanism by which the THC + CBD combination (10 mg/kg each) suppressed neuroinflammation and showed that these effects were mediated by CB1 and CB2 receptors, since in mice deficient in CB1 and CB2 this effect was reversed, with no reduction in the inflammatory process. In addition, treated animals showed a decrease in the levels of CD4 + T cells infiltrated in the brain and pro-inflammatory molecules (IL-17, INF-γ, TNF-α, IL-1β, IL-6 and TBX21) and on the other hand , an increase in anti-inflammatory phenotype

molecules such as FoxP3, STAT5b, IL-4, IL-10 and TGF-β. We also investigated epigenetic mechanisms through miRNA microarray analysis of brain-derived CD4 + T cells, transfection involving miR-21 and use of Mir21 - / - mice. It was suggested in this study that the combination of THC + CBD suppresses neuroinflammation and attenuates the clinical development of EAE and that this effect is associated with changes in the miRNA profile in cells that infiltrate the brain. In figure 3, a diagram showing interactions and effects of THC:CBD in multiple sclerosis.

Finally, in multiple sclerosis, among other mechanisms, interactions between cannabinoids and receptors need to be better explored, in particular, the pharmacological activation of the CB2 receptor since it has a strong involvement with neuroinflammation, remyelination and neuronal survival.

Fig. 3. Diagram of interactions and therapeutic effects of THC:CBD in multiple sclerosis

1.5.3 Parkinson's disease

Parkinson's disease is the second most prevalent neurodegenerative disease, affecting 5% of the population over 85 years of age. Furthermore, its global burden has more than doubled, making it the fastest growing neurodegenerative disease. Genetic causes also contribute to the etiology of Parkinson's disease, but in smaller proportions, estimated at 5% of all people with the disease. It is known that the combination of these genetic and environmental factors increases the risk of the disease [150].

Symptomatically, it is characterized by motor and non-motor symptoms, which are generally underdiagnosed and untreated [149]; being diagnosed only with the development of motor impairment (e.g. tremor, rigidity and bradykinesia). However, motor features are strongly linked to dopaminergic damage in the nigrostriatal pathway, which occurs only in the intermediate stages of the disease [148]. Staging is based on the appearance of α-synuclein aggregates, and it can take 20 years for motor disorders to appear, highlighting the involvement of other neurotransmission systems and their relationship with early non-motor symptoms, such as mild olfactory and cognitive impairment and depression [149, 151].

Parkinson's disease onset is tightly related to α-synuclein overexpression and/or modification, a protein involved in the synaptic vesicle release. In turn, misfolded α-synuclein forms aggregates called Lewy bodies [152]. Due to an impaired synaptic function, several cellular and physiological mechanisms are affected, resulting in neuroinflammation, oxidative stress, reduced trophic support, and excitotoxicity [153]. Since endocannabinoids regulate synaptic and motor functions through cannabinoid receptors CB1 and CB2, this system is also impacted by striatal rearrangement after dopamine depletion [154-156].

In fact, people with Parkinson's disease have higher AEA levels and altered cannabinoid expression [156-158]. Regarding the CB1 receptor, brain MRI studies demonstrated greater expression in the mesolimbic and mesocortical regions [158, 159]. In contrast, the availability of CB1 and CB2 receptors decreased in the substantia nigra [157, 158]; furthermore, the CB1 receptor appears to be involved in the action of 3,4-dihydroxy-L-phenylalanine (L-DOPA), preventing motor fluctuations that are commonly observed in therapy [160], and the CB2 receptor is increased in glial cells in post-mortem tissues [161].

Based on exposure, pharmacological modulation of the ES may be an interesting approach for Parkinson's disease management. In vitro and in vivo studies on THC effects on Parkinson's disease models have revealed neuroprotective effects that are likely mediated by the CB1 receptor [162-165]. Furthermore, PPARγ appears to play a crucial role, mediating the downregulation of the CB1 receptor and the restoration of mitochondrial content [162, 166, 167].

Recently, in a meta-analysis, it was shown that treatment with CBD promoted a significant improvement in parkinsonian symptoms, however, these benefits were not seen in therapy with nabilone [113]. Thus, modulation between cannabinoid receptors and TRPV may be associated with these results [126, 168, 169].

Beneficial effects of CBD in Parkinson's disease models suggest CB2 but not CB1 receptor involvement [170, 171]. CBD treatment showed neuroprotective effects on the nigrostriatal pathway [163, 170, 172, 173], *in vitro* data suggest that CBD's neuroprotective action is linked to tropomyosin receptor kinase A

activation [174]. Lastly, Gugliandolo et al. [171] reported that the antiapoptotic effect of CBD is mediated by ERK and Akt/mTOR pathways, while ERK activation seemed to be modulated by TRPV1 and CB2 receptors. Finally, recently, Wang et al [175] demonstrated anti-apoptotic effects of dopaminergic neurons and neuroinflammation in which CBD repressed the expression of the inflammasome pathway NLRP3/caspase-1/IL-1β, upregulated Bcl-2 and downregulated Bax and Caspase-3, corroborating its neuroprotective and anti-apoptotic role.

Besides THC and CBD, other cannabis derivatives displayed therapeutic potential in preclinical investigations. There is evidence that THCA, 7 (Z)-methyl p-hydroxycinnamate (ZMHC), Beta-caryophyllene (BCP), and THCV have neuroprotective effects in Parkinson's disease models [165, 172, 173, 176]. Moreover, BCP chronic treatment demonstrated antioxidant and anti-inflammatory effects mediated by the CB2 receptor in a Parkinson's disease model induced by rotenone [176, 177]. In turn, THCV inhibits motor impairment, glutamatergic changes, and microglial activation induced by6-hydroxydopamine (6-OHDA)[172].

In summary, the scientific evidence on therapeutic cannabis use and its derivatives in Parkinson's disease are inconsistent and of poor quality, hindering concrete conclusions of its efficacy to be made. Based on the scientific evidence presented in this review, the therapeutic potential of phytocannabinoids in Parkinson's disease is illustrated in figure 4 and the studies shown in table 3.

Fig. 4. Diagram of interactions and therapeutic potential of phytocannabinoids in Parkinson's disease.

Table 3. Preclinical and clinical evidence using Cannabis derivatives in in Parkinson's disease models and patients

2. Conclusion

In this context of medicinal cannabis as a therapy for diseases of the nervous system, especially neurodegenerative diseases, the highlights have been the cannabinoids, THC and CBD. Several strategies, involving preclinical and clinical research, have reinforced the role of CBD in neuroinflammation, neuroprotection and anti-apoptotic, antiepileptic, as presented in this review. But, evidence on the molecular, cellular and behavioral mechanisms resulting from its interaction with a complex expanded endocannabinoid system requires further studies, particularly in epilepsy, multiple sclerosis, Parkinson's disease, diseases addressed in this review.

Significant therapeutic effects of CBD have been observed for epilepsy and Parkinson's disease, while nabiximois has been a frequent option for the treatment of multiple sclerosis and has been evaluated as a drug that contributes to the reduction of spasticity [113]. Its role as a CB2 receptor inverse agonist, AEA reuptake inhibitor and non-competitive negative allosteric modulator of the CB1 receptor is known [178], but a possible action of CBD in neutralizing the effects of THC has been discussed and it is expected that such interaction mechanisms will be addressed in future studies. In general, in some diseases CBD has shown promising therapeutic benefits, but it is necessary to wait for the evidence to come from more randomized, double-blind, placebo-controlled studies that reach diverse populations.

Much research still needs to be done, requiring preclinical studies that mimic the pathological conditions and double-blind, randomized, placebo-controlled clinical trials so that robust data allow conclusions based on scientific evidence.

Abbreviations

2-AG, 2-arachidonoyl-glycerol; 5-$HT_{1A,}$ serotoninergic receptors of the 5-HT_{1A} type; AEA, anandamide; BCP, β-caryophyllene; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; CBC, cannabichromene; CBD, cannabidiol; CBDA, cannabidiolic acid; CBDV, cannabidivarin; CBG, canabigerol; CNS, Central nervous system; D; DAGLα, diacylglycerol lipase α· DAGL, sn-1-diacylglycerol lipase; DAGLβ, diacylglycerol lipase β· EAE, Experimental autoimmune encephalomyelitis; ERK, protein extracellular signal-regulated kinase; ES, endocannabinoid system; FAAH, fatty acid amide hydrolase; FDA, Food and Drug Administration; FoxP3, Forkhead box P3; $GABA_A$, γ-Aminobutyric acid type A; GPCRs, orphan G protein-coupled recep-

tors; GPR118; G protein-coupled receptor 118; GPR119; G protein-coupled receptor 119; GPR18; G protein-coupled receptor 18; GPR55, G protein-coupled receptor 55; IL-10, Interleukin-10; IL-17, Interleukin-17; IL-1β, Interleukin 1 beta; IL-4, Interleukin-4; IL-6, Interleukin-6; INF-γ, Interferon gamma; MAGL, monoacylglycerol lipase; miRNA, MicroRNA; MS, Multiple sclerosis; NAPE-PLD, N-acyl-phosphatidyl ethanolamine-specific phospholipase; OEA, N-oleoylethanolamine; PEA, N-palmitoylethanolamine; PPARα, peroxisome proliferator-actived receptor α· PPARγ, peroxisome proliferator-actived receptor γ· STAT5b, signal transducer and activator of transcription 5B; TBX21; T-box transcription factor 21; TGF-β, Transforming growth factor beta; THC, Δ^9 -tetrahidrocanabinol; THCA, [?]9-tetrahydrocannabinolic acid; THCV, [?]^9- tetrahydrocannabivarin; TNF-α, Tumor necrosis factor alpha; TRPM8, transient receptor potential cation channel subfamily M (melastatin) member 8; TRPV1, transient receptor potential vanilloid 1.

Author's contributions

Maria de Fátima dos Santos Sampaio: writing, reviewing and figures design. Yara Bezerra de Paiva and Tuane Bazanella Sampaio: writing. Messias Gonzaga Pereira: writing and revised. Norberto Cysne Coimbra: writing, revised and supervised. All authors have read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (Research Grant 2020/15050-7), Fundação de Apoio ao Ensino, Pesquisa e Assistência do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (FAEPA) (Research Grant 374/2022), and Pro-Rectory of the University of São Paulo (USP) Research Grant (NAP-USP-NuPNE; process IaPq2012-156-USP-12.1.25440.01.6). M. de Fátima dos Santos Sampaio is a postdoctoral researcher supported by CNPq (PDJ grant 155489/2018-6). N.C. Coimbra is a researcher from CNPq (PQ1A-level grants 301905/2010-0 and 301341/2015-0; PQ2-level grant 302605/2021-5). Each organisation had no further role in the study design; the collection, analysis, and interpretation of the data; the writing of the report; or the decision to submit the paper for publication. All figures in the manuscript were created with BioRender.com.

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Tables

Table 1. Preclinical and clinical evidence using Cannabis derivatives in epilepsy models and patients.

Table 2. Preclinical and clinical evidence using Cannabis derivatives in multiple sclerosis models and patients.

Table 3. Preclinical and clinical evidence using Cannabis derivatives in in Parkinson's disease models and patients

Legends

Fig. 1. The complexity of the endocannabinoid system. Diagram showing the components of the expanded endocannabinoid system including the biosynthesis and degradation of endocannabinoids in the CNS. In response to demand, AEA and 2-AG are produced, which can cross the synaptic cleft and activate presynaptic CB1 receptors resulting in neurotransmitter inhibition. Biosynthesis and inactivation of AEA endocannabinoids in postsynaptic neurons is done by FAAH and NAPE-PLD. O 2-AG is hydrolyzed in presynaptic neurons by MAGL, also by enzymes DAGLα and DAGLβ. Note the complexity of the endocannabinoid system that interacts with several neuromediators, receptors and new molecular targets. 2-AcGs; 2-acylglycerols; 2-AG, 2-arachidonoyl-glycerol; 5-$HT_{1A,}$ serotoninergic receptors of the 5-HT_{1A} type; AA, arachidonic acid; Abh4, alpha-betahydrolase-4; AEA, anandamide; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; COX-2, cyclooxygenase-2; DAGL, sn-1-diacylglycerol lipase; ETA, ethanolamide; FAAH, fatty acid amide

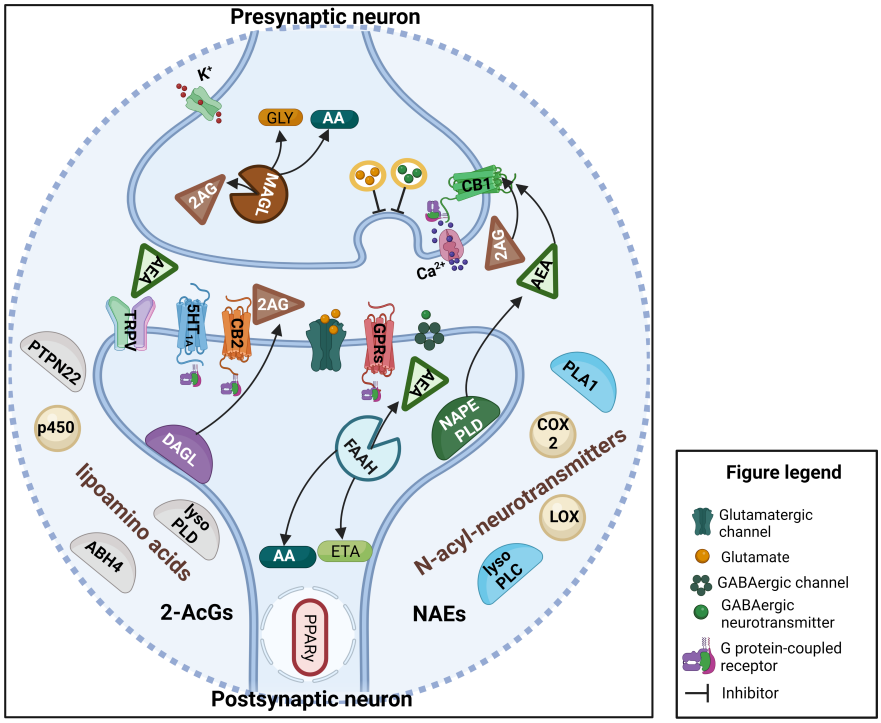
hydrolase; GLY, glycerol; GPRs, G protein-coupled receptors; Lyso PLC, lysoPI-specific PLC; LOX, lipoxygenase; MAGL, monoacylglycerol lipase; NAES; N-acylethanolamines; NAPE-PLD, N-acyl-phosphatidyl ethanolamine-specific phospholipase D; PLA1, phospholipase A1; PPARγ, peroxisome proliferator-actived receptor γ· PTPN22, protein tyrosine phosphatase nonreceptor type 22; TRPV1, transient receptor potential vanilloid 1. (Created with BioRender.com).

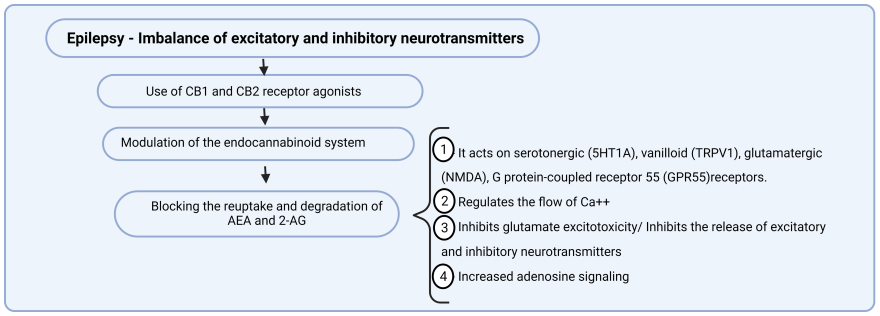
Fig. 2 . Diagram of interactions and therapeutic effects of CBD in epilepsy.

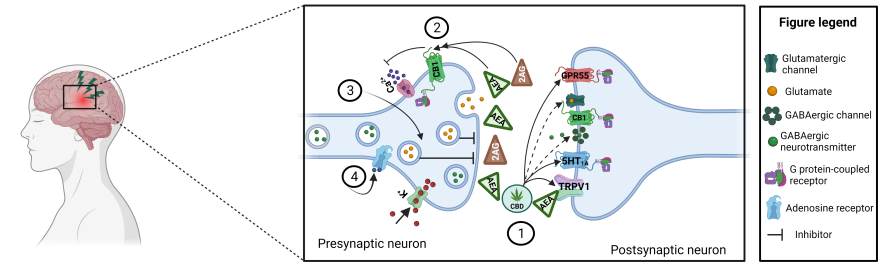
2-AG, 2-arachidonoyl-glycerol; 5-$HT_{1A,}$ serotoninergic receptors of the 5-HT_{1A} type; AEA, anandamide; CB1, cannabinoid receptor 1; CBD, cannabidiol; GPR55, G protein-coupled receptor 55; TRPV1, transient receptor potential vanilloid 1. (Created with BioRender.com).

Fig. 3. Diagram of interactions and therapeutic effects of THC:CBD in multiple sclerosis. A perivascular and parenchymal infiltrate of macrophages, B lymphocytes and T lymphocytes is observed in MS, which cross the blood-brain barrier and destroy the myelin sheath, followed by partial remyelination by oligodendrocytes (acute inflammatory phase) than by infiltration of T lymphocytes, oligodendrocyte destruction and axonal injury will progress to the progressive phase of the disease. Combined THC:CBD therapy has demonstrated pharmacological activation of the CB2 receptor strongly associated with suppression of neuroinflammation and induction of remyelination processes and neuronal survival. Furthermore, the decrease in astrocyte activity leading to inhibition of the neuroinflammatory process was also notable. CBD, cannabidiol; CB1, cannabinoid receptor 1; MS; multiple sclerosis; THC, Δ^9-tetrahidrocanabinol. (Created with BioRender.com).

Fig. 4. Diagram of interactions and therapeutic potential of phytocannabinoids in Parkinson's disease. PD is characterized by dopaminergic damage to the nigrostriatal pathway, dopamine depletion, excitocicity, accumulation of ∝-synuclein and Lewy bodies, reduced trophic support and oxidative stress in the brain region. Cannabis-derived products have been used for the treatment of PD, such as: THC and THCV which have shown neuroprotective effects. In the case of THC, possibly mediated by the CB1 receptor, being also associated with PPARγ, in the negative regulation of the CB1 receptor and the restoration of mitochondrial content. THCV is mediated by the CB1 receptor. CBD has been linked to CB2 and TRPV receptors showing neuroprotective, anti-apoptotic, neuroinflammatory and antioxidant effects. CB2 receptor-mediated anti-inflammatory and antioxidant effects have been demonstrated by BCP. 2-AG, 2-arachidonoyl-glycerol; AEA, anandamide; BCP, β-caryophyllene; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; CBD, cannabidiol; FAAH, fatty acid amide hydrolase; NAPE-PLD, N-acyl-phosphatidyl ethanolamine-specific phospholipase D; PD, Parkinson's disease; PPARγ, peroxisome proliferator-actived receptor γ· THC, Δ^9-tetrahidrocanabinol; THCV, Δ9-tetrahydrocannabivarin; TRPV1, transient receptor potential vanilloid 1. (Created with BioRender.com).







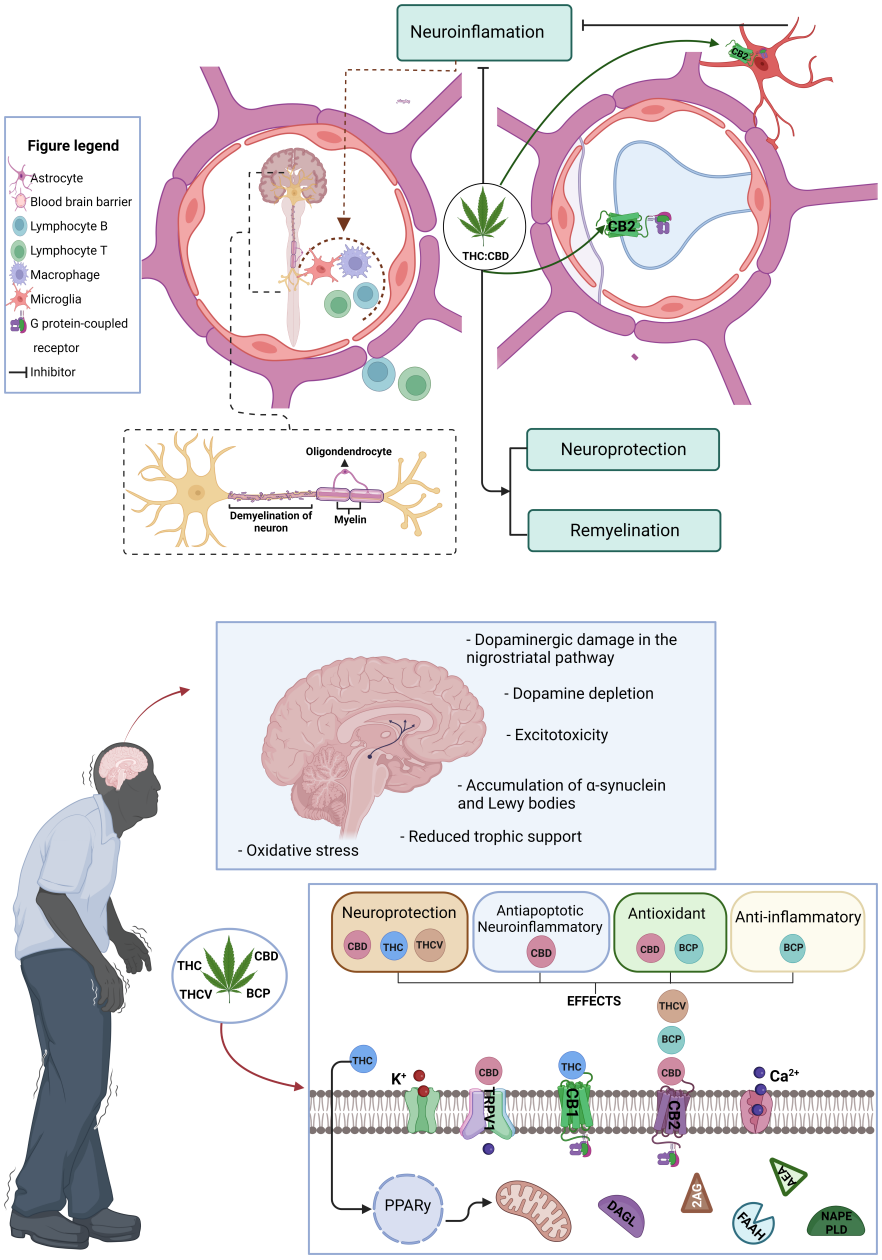


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Table 1 (Epilepsy).doc available at https://authorea.com/users/673796/articles/672479-a-literature-review-on-the-therapeutic-applicability-of-cannabidiol-in-epilepsy-multiple-sclerosis-and-parkinson-s-disease

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