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RESEARCH ARTICLE

Neurological Aspects of Medical Use of Cannabidiol

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Abstract: ***Background***: Cannabidiol (CBD) is among the major secondary metabolites of Cannabis devoid of the delta-9-tetra-hydrocannabinol psychoactive effects. It is a resorcinol-based compound with a broad spectrum of potential therapeutic properties, including neuroprotective effects in numerous pathological conditions. CBD neuroprotection is due to its antioxidant and antiinflammatory activities and the modulation of a large number of brain biological targets (receptors, channels) involved in the development and maintenance of neurodegenerative diseases.

Objective: The aim of the present review was to describe the state of art about the pre-clinical research, the potential use and, when existing, the clinical evidence related to CBD in the neurological field.

Method: Collection of all the pre-clinical and clinical findings carried out investigating the effects of CBD alone, not in combination with other substances, in the neurological arena with the exclusion of studies on neuropsychiatric disorders.

Results: Laboratory and clinical studies on the potential role of CBD in Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), Huntington's disease (HD), amyotrophic lateral sclerosis ALS), cerebral ischemia, were examined.

Conclusion: Pre-clinical evidence largely shows that CBD can produce beneficial effects in AD, PD and MS patients, but its employment for these disorders needs further confirmation from well designed clinical studies. CBD pre-clinical demonstration of antiepileptic activity is supported by recent clinical studies in human epileptic subjects resistant to standard antiepileptic drugs showing its potential use in children and young adults affected by refractory epilepsy. Evidence for use of CBD in PD is still not supported by sufficient data whereas only a few studies including a small number of patients are available.

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1. INTRODUCTION

The plant genus *Cannabis* contains a complex mixture of unique secondary metabolites-phytochemicals (over 60 compounds) so-called cannabinoids of two large chemical types: delta-9-tetra-hydrocannabinol (THC) and cannabidiol (CBD). Cannabinoids are mixed polyketides derived biosynthetically from malonyl-CoA, hexanoyl-CoA units prenylated with geranyl phosphate [1]. THC is the main psychoactive cannabinoid type, whereas CBD is a major component of *Cannabis* but it possesses a highly distinct pharmacological profile with respect to THC. CBD ($C_{21}H_{30}O_2$) is a resorcinol-based compound devoid of the THC psychoactive effects and, on the contrary, is believed able to attenuate the psychotomimetic effects induced by high doses of THC [2, 3]. THC and CBD have the same chemical formula but atoms are differently displayed (Fig. **1**).

CBD was isolated in 1940 from marijuana and hashish. *Marijuana* consists of the desiccated flowers and leaves and stems of the female *Cannabis* plant, containing 3% to 20%

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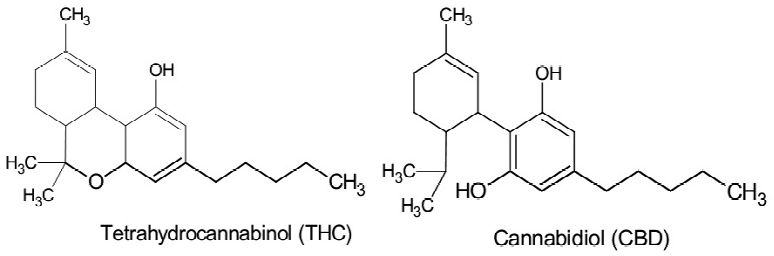

Fig. (1). Chemical structures of Δ 9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

of THC, while industrial hemp has lower concentrations of THC and higher concentrations of CBD, which decreases the psychoactive effects and *hashish* is a concentrated resin from cannabis flowers and leaves or rasped from the surface of the plants and rotated into balls from *Cannabis sativa* var. indica [4, 5]. Its structure was elucidated by Mechoulam in 1963 [6] while its absolute configuration was definitively established later, in 1967 [7].

The mechanism of action of CBD is complex and not fully known since this molecule behaves as a 'multifaceted-target' drug interacting with several non-endocannabinoid systems such as receptors, ion channels, enzymes and transporters [8, 9]. CBD modulates the activity of many cellular effectors, including the receptors CB1 and CB2 [10, 11], GPR55 [12], 5HT1A [13, 14] μ- and δ-opioid [15], peroxisome proliferator-activated receptor gamma (PPARγ) [16, 17], the transient receptor potential subfamily V member 1 (TRPV1) cation channels [18] and fatty acid amide hydrolase (FAAH) [19].

The effects of CBD on intracellular signalling are largely independent of CB1 receptors [20]. While THC acts as a partial agonist of the CB1 and CB2 cannabinoid receptors, CBD does not have significant intrinsic activity over these receptors [21]. On cannabinoid receptors, CBD shows to have high potency as an antagonist [22]. CBD antagonizes CB1/CB2 receptors agonists and inhibits the reuptake of anandamide, the main endogenous cannabinoid. It is also an agonist of the serotonin 5-HT1A, glycine [23] and of the vanilloid receptors TRPV1, TRPV2, TRPA1 [9, 24].

CBD regulates calcium flux in a bidirectional change through control over intracellular calcium stores and it also produces biphasic changes in intracellular calcium levels *via* antagonism of the mitochondrial voltage dependent anion channel 1 [25]. CBD also antagonizes GPR55, working as a counterpart to the canonical CB1R/CB2R signalling pathway [26] and is a competitive inhibitor of adenosine uptake by the equilibrative nucleoside transporter 1 of macrophages and microglial cells, the resident macrophage-like immune cells of the brain [27].

Pharmacokinetic studies have showed that CBD, *in vitro*, inhibits a number of human CYP450 isoforms being a substrate for human cytochrome P (CYP) 450 2C19 and 3A4, a potential substrate for the isoenzymes CYP3A5, CYP2C9, and UDP-glucuronosyltransferase isoforms 1A9, 2B7, and 2B17 [28]. CBD has a large volume of distribution (32 l/kg) and it can be found in many tissues and organs, including the eye and the central nervous system (CNS) [29].

Even not being a psychoactive compound, CBD has anti-inflammatory and antioxidant properties and consequently has been considered as a potential new pharmacological approach for neuroprotection [8]. CBD anti-inflammatory and antioxidant activities can act in a synergistic way since it has been suggested that the antioxidant action ascribed to CBD on the basis of pre-clinical studies in various *in vivo* models of human diseases probably exceeds antioxidant activity expected on the basis of its chemistry alone [3].

Overall, studies suggest that CBD could be a favourable strategy in the neurological arena for the treatment of epilepsy [8], neurodegenerative diseases such as Alzheimer's disease (AD) [30], Huntington's disease (HD) [31] and Parkinson's disease (PD) [32], neonatal brain ischemia [33]. Moreover, it is noteworthy that CBD is not psychoactive but it can readily cross the blood brain barrier and exerts its effects at CNS level [34].

It has been suggested that a clinical endocannabinoid system deficiency underlies many human diseases producing psychiatric disturbances [35, 36] such as mood disorders [37] and also CBD has been recently studied for its potential therapeutic effects in neuropsychiatric disorders such as schizophrenia [38], depression [39] and anxiety [40].

The aim of the present review was to describe the state of art of the pre-clinical research, about the potential use and, when existing, of the clinical evidence related to CBD in the neurological field.

The potential role of CBD for the management of neuropsychiatric diseases have yielded promising positive results [41, 42], however, in this review we consider and discuss only more strictly neurological CBD data about epilepsy, neurodegenerative disorders and neuromuscular diseases. Furthermore, with the aim to focus on CBD properties and to define CBD potential role in the neurological field, in the present article we took in consideration all the pre-clinical and clinical findings in which CBD alone has been investigated, with the exclusion of research carried out with cannabis or THC/CBD herbal preparations.

2. METHOD

All existing pre-clinical and clinical findings carried out investigating the effects of CBD alone, not in combination with other substances, in the neurological arena with the exclusion of studies on neuropsychiatric disorders have been collected.

A bibliographic research was carried out independently by two researchers in the major scientific databases and search engines of peer-reviewed literature on life sciences and biomedical topics (PubMed, Scopus, Embase, Web of Science, Google Scholar) starting from January 1970 to November 2016. Analysis included all articles published on peer-reviewed scientific journals describing clinical trials and applications of CBD in the neurological field excluding studies on neuropsychiatric issues. Articles were excluded if they did not meet the following inclusion criteria: CBD used alone, not in combination with other substances and also articles written only in English language. Consequently, all scientific articles investigating on cannabis preparations or products containing THC or other compounds have been excluded.

3. RESULTS

Pre-clinical and clinical studies on role of CBD in epilepsy, Parkinson's Disease (PD), Alzheimer's Disease (AD), multiple sclerosis (MS), Huntington's disease, amyotrophic lateral sclerosis, cerebral ischemia, were collected and further evaluated.

3.1. CBD pre-clinical and clinical studies on epilepsy

About a third of patients with epilepsy show a treatment-resistant form, associated with severe morbidity and increased mortality. *Cannabis* has been used for centuries for the treatment of epileptic disorders [43], but only in the last decades it has been demonstrated that CBD has anti-seizure activity. This property, together with the lack of psychotropic effects and a good tolerability profile suggests that CBD could have a potential therapeutic role in epilepsy [44]. THC effects on epilepsy are controversial due to the reporting of pro- and anti-convulsant effects [45].

Overall, pre-clinical data obtained through experiments carried out on experimental animal models show that pre-treatment with CBD produces anticonvulsivant effects. It has been reported that pre-treatment with CBD *in vivo* in mice prevents tonic-seizures induced by GABA inhibitors such as picrotoxin, pentylentetrazole (PTZ), bicuculline, isoniazide and by transcorneal electroshock [46]. CBD is able to stop tonic but not clonic seizures in animal models in which seizures are induced by PTZ and maximal electroshock (MES). Thus, suggesting the hypothesis that CBD could act mainly to decrease the spreading of seizures, influencing only partially seizures onset [47, 48]. Due to pharmacokinetic (CBD inhibits several cytochrome P450 isoenzymes) and pharmacodynamic interactions, CBD could have opposite effects when given together with standard antiepileptic drugs to animals subjected to MES, since it increases phenytoin effects and reduces those of clonazepam and ethosuximide [49, 50, 51].

CBD effects have been investigated on seizures induced by PTZ and MES, experimental models causing generalized convulsion. In these experiments, CBD reduced seizures and mortality and both *in vitro* and *in vivo* evidence shows that antiepileptic activity is not dependent from CB1 receptor [52]. Other authors furtherly suggested that CBD antiepileptic activity in PTZ model, but not anti-seizure effects in MES model, could be mediated by big potassium (BK) channels characterized by large conductance for potassium ions (K^+) [53].

In a chronic experimental model of epilepsy induced by PTZ (28 days administration), in rats treated with CBD, were observed both reduction of neuronal death in CA1 and CA3 hippocampal brain areas and hippocampal astrocytic hyperplasia. These effects were associated with decrease of hippocampal expression of N-methyl-d-aspartic acid receptor subunit 1 [54].

Intraperitoneal CBD administration (1-100 mg/kg) before pilocarpine-induced temporal lobe epilepsy reduced tonic-clonic seizures with any influence on mortality, while the same substance (≥ 10 mg/kg) reduced both these two parameters when seizures were induced by penicillin [55]. Protection against seizures induced by CBD has been also related to its antioxidant activity and increase in autophagy at hippocampal cells level in a study in which the pilocarpine-induced epilepsy, a temporal lobe epilepsy model, has been used. Through this model, it has been shown that CBD could enhance the induction of autophagy pathway and antioxidant defence in the chronic phase of epilepsy, which could be considered as a protective mechanisms in a temporal lobe epilepsy [56].

More recently, it has been suggested that CBD could exert its anticonvulsant effects, at least in part, through its actions on voltage-gated sodium channels and resurgent current (an atypical near threshold current predicted to increase neuronal excitability) which has been implicated in multiple disorders of excitability, may be a promising therapeutic target for the treatment of epilepsy syndromes. This hypothesis has been supported by a study examining the effects of CBD on endogenous sodium currents from striatal neurons and reporting CBD inhibition of resurgent and persistent sodium current [57] Pre-clinical research investigating on CBD effects in epilepsy are summarized in Table **1**.

The first human study describing antiepileptic effects of CBD was published in 1980. The study comprised two phases, in the first CBD was given in a double-blind setting 3 mg/kg daily for 30 days to 8 health human volunteers and other 8 volunteers received placebo. In the second phase of the study, 15 patients affected by secondary generalized epilepsy with temporal focus were divided according to a random scheme in two groups and received, following a double-blind schedule, daily 200-300 mg of CBD or placebo for four and a half months. Clinical and laboratory data, electroencephalogram (EEG) and electrocardiogram (ECG) were collected or performed at intervals of 15- or 30-days. During the period treatment the patients continued to take the standard antiepileptic drugs prescribed before the study, although these drugs were no longer controlling the symptoms. CBD was well tolerated and no serious side effects were reported. Results showed that four of seven patients treated with CBD were almost free of epileptic crises and three other patients showed partial improvement [58].

CBD has also received great consideration as a potential therapy for pediatric epileptic syndromes. Experience of children with infantile spasms (IS) and Lennox–Gastaut syndrome (LGS) who have been treated with cannabis preparations enriched with CBD were collected through an online

Table 1. Summary of pre-clinical studies on cannabidiol (CBD) effects in the neurological arena.

Neurological Disease	Cannabidiol Effects	Experimental Model	Dose	Mechanism of Action	References
Epilepsy	Pre-treatment with CBD *in vivo* in mice prevents tonic-seizures induced by gamma-aminobutyric acid (GABA) inhibitors	Mouse	CBD 100-300 mg/kg	The differential effects of CBD suggest that it inhibits seizure spread in the CNS by action on GABA)	[46]
	CBD stops tonic but not clonic seizures in animal models in which seizures are induced by pentylenetetrazol (PTZ) and maximal electroshock (MES).	Mouse	CBD 200 mg kg	Not investigated. CBD could act mainly to decrease the spreading of seizures, influencing only partially seizures onset.	[47]
	CBD exerts anticonvulsant effects with significant decreases in incidence of severe seizures and mortality	Rat	CBD 100 mg/kg	These findings suggest that CBD acts, potentially in a CB1 receptor-independent manner, to inhibit epileptiform activity.	[52]
	CBD produces antiepileptic activity in PTZ model, but not anti-seizure effects in MES model.	Mouse	CBD 100 mg/kg	CBD antiepileptic activity could be mediated by big potassium (BK channels).	[53]
	CBD protects against seizures induced by pilocarpine, a temporal lobe epilepsy model.	Rat	CBD 100 ng	CBD could enhance the induction of autophagy and antioxidant defense, considered as a protective mechanisms in temporal lobe epilepsy.	[56]
Parkinson's Disease (PD)	CBD prevents neuronal damage induced by 6-hydroxydopamine unilateral injection into the nigra pars compacta.	Rat	CBD 3 mg/kg	CBD prevention in rodents is probably due to its antioxidant activity, associated with a CB receptor-undependent mechanism modulating glial responses and inhibition of dopaminergic transmission impairment.	[67]
	CBD may exert protection against cell death and neurite loss induced by the neurotoxin 1-methyl-4-phenylpyridinium on pheochromocytoma-12 (PC-12) cells.	*In vitro*: PC-12 cells, neuroblastomaSH-SY5Y cells.	CBD 1, 5, 10, 25 and 50 μM	CBD neuroprotection may involve activation of tropomyosin receptor kinase A receptors, the increase of the expression of axonal and synaptogenic proteins and CBD nerve growth factor-like effects.	[68]
	CBD administration would attenuate reserpine-induced motor and cognitive impairments *in vivo*, an experimental model for the study of tardive dyskinesia and PD.	Rat	CBD 0.5 and 5 mg/kg	CBD's antioxidant and anti-inflammatory actions are possibly involved in its beneficial effects on the reserpine model.	[71]
Alzheimer's Disease (AD)	CBD produces neuroprotection against β-amyloid when added to cultured neuronal cells.	*In vitro:* PC-12 cells	CBD 10^{-6} to 10^{-4}	Reduction of oxidative stress and blockade of apoptosis.	[77]
	Decrease in β-amyloid production and β-amyloid induced neurodegeneration.	Mouse	CBD 2.5 or 10 mg kg	CBD inhibition of nitrite production and inducible nitric oxide synthase protein expression mediated through the inhibition of phosphorylated form of p38 mitogen-activated protein (MAP) kinase and transcription factor nuclear factor-B activation.	[78]
	Long-term CBD treatment (starting from 2.5 months of age with CBD 20 mg/kg daily for 8 months) in male amyloid β protein precursor × presenilin 1 mice, a transgenic model of AD, prevented social recognition deficit.	Mouse	CBD 20 mg/kg	Impact of CBD on neuroinflammation, cholesterol level, and dietary phytosterol retention.	[79]
Multiple sclerosis (MS)	CBD administration improves clinical symptoms and reduces CNS immune infiltration, microglial activation, and axonal damage in the MS mouse model of myelin oligodendrocyte glycoprotein 35-55-induced experimental autoimmune encephalitis.	Mouse	CBD 5 mg/kg	Suppression of microglial activity and T-cell proliferation by CBD appears to contribute to the beneficial effects.	[82]
	Protective effects of CBD against the damage to oligodendrocyte progenitor (OPC) cells.	*In vitro*: OPC cells	CBD 2.5 and 5 mM	Decrease of caspase 3 induction and reduction of the production of reactive oxygen species at endoplasmic reticulum level.	[85]

(Table 1) Contd….

Neurological Disease	Cannabidiol Effects	Experimental Model	Dose	Mechanism of Action	References
	Protective effects of CBD in experimental Theiler's Murine Encephalomyelitis Virus-induced demyelinating disease. CBD attenuated microglia activation and decreased transmigration of blood leukocytes. Long-lasting ameliorating motor deficits in the chronic phase of the disease.	Mouse	CBD 5 mg/kg	Downregulation of the expression of vascular cell adhesion molecule-1, chemokines (CCL2 and CCL5) and proinflammatory cytokine interleukin-1β. Adenosine A2A receptors participate in some of the antiinflammatory effects of CBD.	[86]
Amyotrophic lateral sclerosis (ALS)	CBD produced modification in genes, pathogenesis, oxidative stress, mitochondrial dysfunction and excitotoxicity, associated with ALS.	*In vitro*: human gingival-derived mesenchymal stromal cells (hGMSCs)	CBD 5 μM	CBD treatment in (hGMSCs) may downregulate genes that induce excitotoxicity.	[96]
Brain ischemia	CBD reduced cell death after oxygen-glucose deprivation in immature mouse brain, an effect accompanied by CBD-induced modulation of glutamate release, cytokine production, and cyclo-oxigenase-2 and inducible nitric oxide synthase expression.	Mouse *In vitro*: oxygen-glucose deprivedslices	CBD 100 μM	Both cannabinoid and adenosine A2A recptors are involved, thus supporting the hypothesis that CBD exerts antinflammatory protective effects.	[100]
	Neuroprotective effects (increase of viable neurons) of CBD in a hypoxic-ischemic brain injury experimental model in newborn pigs induced by interruption of carotid blood flow for 30 minutes and reduction to 10% of the fraction of inspired oxygen.	Newborn pigs	CBD 1 mg/kg	CBD neuroprotective effects were reversed by co-administration either of 5-hydroxytryptamine 1A (5-HT1A) receptor antagonist WAY100635 or CB2 receptor antagonist AM630, suggesting the involvement of CB2 and 5-HT1A receptors.	[14]
	CBD improved spatial learning performance and decreased hippocampal neurodegeneration in mice subjected to bilateral common carotid artery occlusion	Mouse	CBD 10 and 30 mg/kg	Protective effects of on neuronal death induced by ischemia may involve the inhibition of reactive astrogliosis.	[101]
	Intracerebral administration of CBD produced reduction in neurological deficit, area of infarction, brain edema and blood brain barrier permeability in the cerebral ischemia induced by middle cerebral artery occlusion.	Rat	CBD 100 and 200 ng	These positive effects were associated in CBD treated animals with up-regulation of Na+/Ca2+ exchangers 2 and 3.	[102]

survey of parents who gave cannabis enriched with CBD as therapy for their children affected by epilepsy. People participating to the survey included 117 parents of children with highly refractory epilepsy (including 53 subjects with IS or LGS). Average duration of treatment and the average dosage of CBD exposure were 6.8 months and 4.3 mg/kg/day, respectively. Parents' perceived efficacy and tolerability were similar across the subgroups and 85% all parents described a reduction in seizure frequency, and 14% reported that their children were complete seizure freedom. For a high percentage of children, improvement in sleep, alertness, and mood was also reported. Side effects were not common during CBD treatment, with the exception of an increase in appetite (30%). Even though the points of weakness, due to methodological issues (participation bias and lack of blinded procedure) this study confirms the potential role for CBD in the treatment of refractory childhood epilepsy [59].

Add-on therapy with oral CBD to the standard antiepileptic regimen showed beneficial effects reported on the case of a 10-month-age boy with malignant migrating partial seizures. Positive effects were normal growth and significant seizures reduction with the addition of CBD to his standard antiepileptic therapy. Treatment started with CBD 25 mg/mL at 10 mg/kg/day divided twice daily. Dose was increased to goal of 25 mg/kg/day divided twice daily over 15 days with no observed side effects [60].

Children with febrile infection-related epilepsy syndrome (FIRES), after an acute phase with super-refractory status epilepticus, presented progression to a chronic phase with persistent refractory epilepsy. Evolution of this disease is exitus or severe encephalopathy. A study described 7 children who received CBD after no response to all other drugs. CBD was gradually given up to a maximum dose of 25 mg/kg/day. After CBD administration, in most of the patients an improvement in frequency and duration of seizures has been observed [61].

A retrospective multicenter study described the effects of CBD-enriched cannabis (CBD and tetrahydrocannabinol at a ratio of 20:1 dissolved in olive oil) at a dose ranging from 1 to 20 mg/ kg/day for at least three months (average six months) on 74 adolescents and children (aging 1-18 years) with intractable epilepsy resistant to more than 7 antiepileptic drugs and/ or other approaches such as ketogenic diet and/or vagal nerve stimulator implantation. Seizure frequency was assessed by parental report during clinical visits. CBD treatment yielded

a significant positive effect with parental report of reduction in seizure frequency. Improvement in behavior and alertness, language, communication, motor skills and sleep, was also observed. Adverse reactions such as somnolence, fatigue, gastrointestinal disturbances and irritability leading to withdrawal of cannabis use in 5 patients were reported [62].

In another large-scale prospective multicentre open-label trial, patients (aged 1-30 years) with severe, intractable, childhood-onset, treatment resistant epilepsy, were treated with oral CBD (a 99% purified oil-based form of CBD) at doses of 2-5 mg/kg per day, up to a maximum dose of 25 mg/kg or 50 mg/kg per day. Patients were treated with CBD as an add-on treatment to their existing antiepileptic drugs. Motor seizure frequency and adverse events were monitored for 12 weeks. CBD produced an average reduction in monthly motor seizures of 36.5%, similarly to the results obtained with the other antiepileptic drugs used in refractory epilepsy. However, CBD showed a slight not statistically significant greater efficacy in the subgroup of patients affected by Dravet or Lennox–Gastaut Syndromes. Results of this study confirmed the good tolerability of CBD for short term use [63].

Epilepsy is the most common neurologic manifestation of tuberous sclerosis complex (TSC), an autosomal-dominant genetic disorder. About 85% of patients with TSC is affected by epilepsy and in 63% epilepsy is resistant to drugs. CBD efficacy and tolerability has been investigated as an adjunct to current antiepileptic drugs in 56 TSC patients with refractory seizures. Patients were treated with the initial dose of 5 mg/kg/day increased by 5 mg/kg/day every week up to a maximum dose of 50 mg/kg/day. Median weekly seizure frequency was reduced after three months of treatment with CBD. The 50% responder rates during the study were 50%, 50%, 38.9%, 50%, and 50% after 2, 3, 6, 9, and 12 months of therapy, respectively. The authors concluded that CBD may be an effective and well-tolerated treatment option for patients with refractory seizures affected by TSC [64]. Clinical studies on CBD in epilepsy are summarized in Table **2**.

CBD has been shown to produce positive effects in preclinical studies on epilepsy. Results of scientific articles considered in this review indicate that CBD has antiepileptic activity. Several experiments have demonstrated that this cannabis derived compound may reduce seizure frequency and on the basis of a safe good profile could be used in subjects, particularly in children and young adults, affected by treatment-resistant epilepsy. CBD showed beneficial effects in particular in children affected by Dravet or Lennox–Gastaut Syndromes. The mechanisms through which CBD exerts its antiepileptic effects could be the activity on voltage-gated sodium channels and large conductance potassium channels, antioxidant activity, induction of autophagy pathway.

3.2. CBD Pre-Clinical and Clinical Studies on Parkinson's Disease and Alzheimer's Disease

CBD is a non-psychoactive compound of *Cannabis sativa* with antiinflammatory and antioxidant properties. These activities give to CBD a potential role for neuroprotection [65] and a large body of scientific evidence indicates that inflammatory processes are important in the pathophysiology of neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS) [66].

PD is a progressive neurodegenerative disorder clinically characterized by symptoms such as tremor, bradykinesia, rigidity and postural instability and rigidity. These symptoms are produced by brain dopaminergic denervation at the striatum level and progressive death of dopaminergic neurons in the pars compacta of the substantia nigra. Pre-clinical research demonstrated that cannabinoids prevent neuronal damage induced by 6-hydroxydopamine unilateral injection into the nigra pars compacta in rodents probably by its antioxidant activity, possibly associated a CB receptor-independent mechanism having the capability to modulate glial responses, which are relevant to neural survival. It has been also observed that CBD exerts neuroprotective effects by inhibition of dopaminergic transmission impairment by attenuating dopaminergic cell death in experimental hemiparkinsonism, induced by the intranigral administration of 6-hydroxydopamine [67].

It has been shown that CBD may exert protection against the cell death and the neurite loss induced by the neurotoxin 1-methyl-4-phenylpyridinium (MPP+) on PC12 cells. CBD neuroprotection may involve the activation of trkA (a family of tyrosine kinases that regulates synaptic strength and the plasticity in the mammalian nervous system) receptors and the increase of the expression of axonal and synaptogenic proteins. It has been also suggested that nerve growth factor (NGF)-like effects can contribute to CBD neuroprotective activity against the toxicity induced by MPP+, a neurotoxin relevant to development of PD [68].

These effects support the potential neuroprotective role of CBD according to the findings that dysfunction of trophic factors could be involved in the pathogenesis of neurodegenerative diseases [69] and on the light of the evidence that reduction of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and NGF has been found in brain and liquor of PD subjects [70].

More recently, it has been shown that CBD administration would attenuate reserpine-induced motor and cognitive impairments *in vivo* in rats. Repeated administration of reserpine in rodents provokes motor impairments associated with cognitive deficits, for this reason it is used as an experimental model for the study of tardive dyskinesia and PD. *In vivo* experiments showed that CBD (0.5 and 5 mg/kg) attenuates the increase in catalepsy behavior and in oral movements, and improved the reserpine-induced memory deficit in the discriminative avoidance task, but not the reduction in locomotion induced by reserpine [71]. Main pre-clinical data on CBD in PD are summarized in Table **1**.

A first preliminary clinical open pilot study in humans, reported that CBD treatment (100–600 mg/day) for six weeks in five PD patients with dystonic movement disorders, improved dystonia in all patients in a range from 20 to 50%. Mild side-effects were reported including hypotension, dry mouth, psychomotor slowing, lightheadedness and sedation [72].

Successively, it has been observed that CBD at the dose of 160 mg/day could significantly improve the quality of sleep,

Table 2. Summary of clinical studies carried out with cannabidiol (CBD) in the neurological arena.

Disease	Patients' Pathological Characteristics	Study Design	Population	Treatment	Outcome	References
Epilepsy	Secondary generalized epilepsy with temporal focus.	Randomized, controlled, double-blinded study.	N = 15 patients, aging 14-49 years, mean age 24. Two groups treated with CBD (N = 7) or placebo (N = 8).	Two-three capsules/day containing CBD 100 mg for 4 and half months. Patients continued to take the antiepileptic drugs prescribed before the experiment, although they no longer controlled the disease.	4 of the 8 subjects treated with CBD remained almost free of crises throughout the experiment and 3 other CBD patients demonstrated partial improvement. CBD was ineffective in 1 patient. All patients and volunteers tolerated CBD very well and no signs of toxicity or serious side effects were detected.	[58]
	Based on anecdotal reports reported by parents of children affected by highly refractory epilepsy.	Open-label trial.	Survey respondents included 117 parents of children with epilepsy, including 53 with infantile spasms or Lennox-Gastaut syndrome (LGS) who had administered CBD products to their children. Age range of children was 5 months-10 years.	The median duration and the median dosage of CBD exposure were 6.8 months and 4.3 mg/kg/day, respectively.	Eighty-five percent of all parents reported a reduction in seizure frequency and 14% reported complete seizure freedom. Most common reported side effect was increased appetite (30%).	[59]
	Febrile infection-related epilepsy syndrome (FIRES).	Multicenter open study.	7 children from 5 centers with FIRES who had not responded to antiepileptic drugs or other therapies. Age range from 3 years and 11 months to 8 years and 6 months.	CBD was initiated and slowly titrated up to a maximum dose of 25 mg/kg/day.	Treatment with cannabidiol resulted in a marked reduction in seizure burden as defined as a decrease in seizure frequency and/or duration in 6/7 subjects.	[61]
	Pediatric refractory epilepsy.	Retrospective study based on clinical records and phone call visits.	74 patients aging 1-18 years with refractory epilepsy characterized by refractory daily seizures and >7 appropriate antiepileptic drugs and other treatments.	CBD-enriched cannabis oil for more than 3 months. CBD dosage ranged from 1 to 20 mg/kg/d, and it was divided into two groups, 1-10 mg/kg/d and 10-20 mg/kg/d.	Most of the children (66/74; 89%) reported reduction in seizure frequency. Improvement in behavior and alertness, language, communication, motor skills and sleep were observed. Adverse reactions included somnolence, fatigue, gastrointestinal disturbances and irritability.	[62]
	Severe, intractable, childhood-onset, treatment resistant epilepsy.	Multicenter open-label study.	137 patients aging 1-30 years, with intractable childhood onset epilepsy, having four or more countable seizures with a motor component per 4 week period, and receiving stable doses of antiepileptic drugs. 33 patients had Dravet syndrome and 31 patients had LGS. The remaining patients had intractable epilepsies of different causes and typology.	Twelve weeks treatment of CBD 2-5 mg/kg per day divided in twice-daily dosing added to the baseline antiepileptic drug regimen, then up-titrated by 2-5 mg/kg once a week until intolerance or a maximum dose of 25 mg/kg per day was reached.	CBD reduced seizure frequency in children and young adults with highly treatment-resistant epilepsy. Adverse events reported were somnolence, decreased appetite, diarrhoea, fatigue, and convulsion. Serious adverse events were reported in 48 (30%) patients, including one death.	[63]
	Patients with refractory seizures in the setting of tuberous sclerosis complex (TSC).	Expanded-access (compassionate) study.	Of the 56 patients who consented and enrolled in current Institutional Review Boards and Food & Drug Administration approved expanded-access study of CBD under Investigational New Drug 119876, 18 patients have TSC. Eighteen of the 56 enrolled patients carried a diagnosis of TSC. Age range of 18 TSC patients was 2-31 years, mean age was 14 years.	CBD initial dose of 5 mg/kg/day divided in two doses was increased by 5 mg/kg/day every week up to a maximum dose of 50 mg/kg/day for 12 months added to standard therapy.	CBD reduced the median weekly seizure frequency. The most common adverse events were drowsiness, ataxia, and diarrhea.	[64]

(Table 2) Contd….

Disease	Patients' Pathological Characteristics	Study Design	Population	Treatment	Outcome	References
Parkinson's Disease (PD)	Dystonic movement disorders (DMD) and PD.	Open label study.	Five patients with DMD. Patients No. 1, 3 and 5 were taking antidystonic medication but were only partially controlled by these drugs. Patient No. 4 had persistent disabling generalized dystonia despite his current anti-parkinsonism medication. Range age 31-65 years.	CBD was started at 100 mg/day and subsequently increased weekly by 100 mg/day to a maximum of 600 mg/day.	CBD produced dose dependent improvement in dystonia in all patients, ranging from 20 to 50%. CBD side effects were mild and included hypotension, dry mouth, psychomotor slowing, lightheadedness, and sedation. In 2 patients with coexisting Parkinsonian features, CBD at doses over 300 mg/day exacerbated the hypokinesia and resting tremor.	[72]
	Rapid eyes movement sleep bevahiour disorder (RBD).	Case series.	Four patients affected by RBD with age range 59-71 years.	Three patients received CBD 75 mg/day, and one received CBD 300 mg/day for 6 weeks.	CBD produced prompt and substantial reduction in the frequency of RBD-related events without side effects.	[32]
	PD	Randomized, controlled double blinded study.	21 patients with diagnosis of idiopathic PD and use of stable doses of anti-Parkinson medications. Range age 51-82 years; mean age 65.86 years.	CBD (75 mg/day or 300 mg/day) for 6 weeks,	No statistical difference between CBD and placebo in scores obtained with Unified Parkinson's Disease Rating Scale, used to assess PD symptoms, Parkinson's Disease Questionnaire - 39 to assess functioning and well-being; and Udvalg for kliniske undersøgelser side effect rating scale to evaluate possible adverse effects.	[74]

with reported increased total sleep time and lesser sleep fragmentation. Three doses of CBD (40, 80 and 160 mg/day) were shown to decrease dream recall without any adverse effects [73]. On the light of these findings, the effects of CBD at the average dose of 75 mg/day on rapid eyes movements (REM) sleep behaviour disorder (RBD), characterized by a parasomnia with loss of muscle atonia during the REM phase of sleep accompanied with nightmares and active motor behaviour during dreaming, have been described in four patients with Parkinson's disease. All the four patients treated with CBD had immediate and considerable reduction in the frequency of RBD-related events without any side effects [32].

In another study, 21 PD patients without dementia or comorbid psychiatric conditions were divided in three groups of seven subjects each, who were treated with placebo, CBD 75 mg/day or CBD 300 mg/day. No statistically significant differences in Unified Parkinson's Disease Rating Scale (UPDRS) scores, plasma BDNF levels or H(1)-magnetic resonance spectroscopy (MRS) measures of the three groups were found. However, the group treated with placebo and CBD 300 mg/day displayed significantly different mean total scores in the Parkinson's Disease Questionnaire (PDQ-39) ($p = 0.05$). According to the authors, results of the study indicate a potential effect of CBD in improving quality of life in PD patients with no psychiatric comorbidities [74].

CBD anti-inflammatory and antioxidant activities could be used in the treatment of PD. This role is supported by pre-clinical findings and preliminary clinical evidence. Neuroprotection in PD is not associated to a CB receptor mechanism. Rather it is due to the modulation of glia activity related to the survival of neurons, inhibition of dopaminergic transmission, NGF-like effects, activation of trkA receptors. Clinical evidence of the CBD utilization at the range doses 75-600 mg/day shows promising results but needs the performance of larger scale studies. Main clinical findings about CBD in PD are summarized in Table **2**.

AD is characterized by the presence of senile plaques formed by β-amyloid, neurofibrillary tangles, selective neuronal loss, glial activation, associated with progressive cognitive deficit. In the AD, brain damaged neurons and neurites and highly insoluble β-amyloid deposits and neurofibrillary tangles provide obvious stimuli for inflammation [75]. Brain β-amyloid formation due to the cleavage of amyloid precursor protein is considered crucial for the development of this disease. Alteration in neuronal homeostasis together with and oxidative damage cause tangle formation and neuronal loss. CBD produces neuroprotection against the β-amyloid when added to cultured neuronal cells because it may beneficially interfere with several β-amyloid-triggered neurodegenerative pathways. Several mechanisms have been suggested to explain CBD neuroprotection, they are reduction of oxidative stress and blockade of apoptosis [76], capability to induce the ubiquitination of APP protein with consequent decrease in β-amyloid production [77], reduction of β-amyloid-induced neuroinflammation and promotion of neurogenesis through selective activation of peroxisome proliferator-activated receptor-γ (PPARγ) [16], inhibition of inducible nitric oxide synthase (iNOS) and interleukin-1β protein expression and release [78].

In vitro and *in vivo* experiments showed that CBD could reverse cognitive deficits of AD transgenic mice through its anti-oxidant and anti-inflammatory properties. Long-term CBD treatment (starting from 2.5 months of age with CBD 20 mg/kg daily for 8 months) in male AβPPSwe/PS1ΔE9 (AβPP × PS1) mice, a transgenic model of AD, prevented

social recognition deficit that develops in this experimental model. Prevention of the social recognition deficit in mice was not accompanied with any changes in amyloid deposit or oxidative parameters. However, the study showed a slight impact of CBD on neuroinflammation, cholesterol level, and dietary phytosterol retention. The results of this study provide the evidence that CBD may have potential as a prevention treatment for AD with a particular relevance in preventing symptoms of social withdrawal and facial recognition [79]. CBD treatment for a shorter time (20 mg/kg, daily intraperitoneal injections for 3 weeks), also reversed Aβ-induced spatial memory deficits in the same transgenic rodents [80]. Main pre-clinical findings of CBD in AD are summarized in Table **1**.

Clinical evidence of use of CBD alone, not in combination with THC in AD, is not available. A review has been published a few years ago collecting clinical trials on the effects of THC:CBD combination products but the conclusions showed no clear evidence that cannabinoids are effective in the improvement of disturbed behaviour in dementia and/or in the treatment of other symptoms of dementia [81].

The source of data supporting the use of CBD in AD is still essentially consisting in pre-clinical experiments, while clinical studies with CBD in PD patients are only a few and including a small number of involved subjects. However, CBD has demonstrated significant promising effects in pre-clinical models of these disorders suggesting a more deep investigation to clarify the potential clinical utility of CBD.

3.3. CBD Pre-clinical and Clinical Studies on Multiple Sclerosis

CBD has significant immunomodulatory activity and induces anti-inflammatory effects in several *in vivo* experimental animal models of diseases involving T cells (cells playing a central role in cell-mediated immunity) such as collagen-induced arthritis, autoimmune diabetes, and autoimmune hepatitis [82]. Multiple sclerosis (MS), is a neurodegenerative autoimmune disease resulting in progressive paralysis mediated by T cells targeting myelin surrounding the the nerve fibers [83]. It has been shown that CBD administration improves clinical symptoms and reduces CNS immune infiltration, microglial activation, and axonal damage in the MS mouse model of myelin oligodendrocyte glycoprotein (MOG)35-55-induced experimental autoimmune encephalitis (EAE) [84]. Protective effects of CBD against the damage to oligodendrocyte progenitor cells are mediated by decrease of caspase 3 induction and reduction of the production of reactive oxygen species at endoplasmic reticulum level [85].

Protective effects of CBD in MS have been demonstrated also in experimental TMEV (Theiler's Murine Encephalomyelitis Virus)-induced demyelinating disease (IDD). Through the use of TMEV-IDD tool it has been found that CBD attenuates microglia activation and decreases the transmigration of blood leukocytes by the downregulation of the expression of vascular cell adhesion molecule-1 (VCAM-1), chemokines (CCL2 and CCL5) and proinflammatory cytokine interleukin(IL)-1β. Moreover, CBD administration at the time of viral infection exerted also long-lasting ameliorating motor deficits in the chronic phase of the disease [86].

The mechanism through which CBD produces protective effects in experimental MS is not completely known but it has been proved that CBD was able to decrease in mice the function of encephalitogenic Th17 cells as well as the production and the release of IL-6 (controlling Th17 differentiation) and IL-17 from encephalitogenic myelin oligodendrocyte glycoprotein MOG35-55-specific T cells [87, 88]. Moreover, CBD reduced STAT3 phosphorylation modulating Th17-like function of memory TMOG cells and increased the production of anti-inflammatory cytokine IL-10 [89].

Positive effects on the experimental autoimmune encephalomyelitis (EAE) model characterized by reduction of inflammation, demyelination, axonal damage and inflammatory cytokine expression, were obtained by treatment with CBD (5 mg/kg) injection for three consecutive days at the onset of appearance of disease signs [90].

Another study confirmed these findings by using a formulation based on a cream containing 1 % of purified CBD (>98 %), as a daily topical treatment in EAE. The study reported that treatment reduced symptomatic disease score (mean of 5.0 in EAE mice vs 1.5 in EAE + CBD-cream), recovered by paralysis of hind limbs and ameliorated histological features typical of EAE (lymphocytic infiltration and demyelination) in spinal cord tissues [91]. The same group of researchers observed that CBD treatment is able to avoid apoptotic pathway activation through FAS pathway modulation and that CBD interferes with p53-p21 axis, relevant for cell cycle regulation and the DNA damage response. These findings were associated with absence of tissue apobody formation in spinal cord tissues of EAE-mice treated with CBD [92]. Main pre-clinical findings on CBD in MS are summarized in Table **1**. Despite the promising experimental evidence for a CBD positive role in the care of MS, the numerous clinical studies are exclusively centered on the effects of the combination THC:CBD. One of the main reasons is surely the ascertained spasmolytic and analgesic effect warranted by THC.

3.4. CBD Pre-Clinical and Clinical Studies on other Neurodegenerative Diseases

Some beneficial effects of CBD in Huntington's disease (HD), a genetic neurodegenerative disorder with symptoms that are considered as the expression of the progressive dysfunction and neuronal death in corticostriatal circuits, were shown in a non-blinded small study (four patients) [93]. HD is caused by a mutation in the gene encoding the protein huntingtin consisting of a CAG triplet repeat expansion translated into an abnormal polyglutamine tract in the amino-terminal portion of huntingtin, which consequently is toxic for specific striatal and cortical neuronal subpopulations [94]. The effects of CBD at the dose of 10 mg/kg/day for 6 weeks were investigated in 15 neuroleptic-free patients with HD in a randomized-controlled double-blinded cross-over study. Results of this study did not show any positive or toxic effects in comparison to placebo [95].

The effects of CBD on genes associated with the progressive neurodegenerative disease amyotrophic lateral sclerosis (ALS) have been studied by using human gingiva-derived mesenchymal stromal cells (hGMSCs) as an *in vitro* model

system. Results on hGMSCs treated with CBD showed modification in genes associated with pathogenesis, oxidative stress, mitochondrial dysfunction and excitotoxicity in ALS. Authors' conclusions suggest that CBD treated hGMSCs may serve as potential therapeutic approach for ALS patients [96].

3.5. CBD Pre-clinical and Clinical Evidence on Cerebral Ischemia

CBD can influence excitotoxicity following ischemic events. This is due to the fact that this secondary metabolite of *cannabis* plant has a dual role in the regulation of intracellular calcium, whose excessive accumulation is a key process leading to neuronal death or injury. Excitotoxicity and changes of sodium and calcium homeostasis trigger pathophysiologic processes in brain ischemia which can facilitate death of neurons. Normally, in physiological conditions, CBD increases intracellular calcium from intracellular calcium stores and voltage-gated calcium channels, while under high-excitability conditions it maintains calcium homeostasis through mitochondrial Na+/Ca2+ exchanger (NCX) [25], a membrane antiporter that efflux calcium in exchange of sodium influx, that increasing its activity could facilitate neuronal survival in brain ischemia [97].

Cannabinoids have been suggested as promising substances to be used for reduction of hypoxic-ischemic (HI) brain damage in newborns [98]. It has been reported that the CB_1–CB_2 agonist WIN552122 reduces brain damage after HI insults in *in vitro* and *in vivo* models in newborn rats, by modulating excitotoxicity, inflammation, and toxic nitric oxide (NO) production [99].

Mechanisms involved in CBD-induced neuroprotection in HI immature brain have been investigated by using forebrain slices from newborn mice underwent oxygen and glucose deprivation. CBD was investigated alone or with selective antagonists of cannabinoid CB_1 and CB_2, and adenosine A_1 and A_2 receptors. Experiments showed that CBD reduced acute HI brain damage by reducing glutamate and IL-6 concentration, and tumor necrosis factor (TNF) α, cyclooxygenase-2 and inducible nitric oxide synthase expression. CBD effects were reversed by the CB_2 antagonist AM630 and by the A_{2A} antagonist SCH58261. The A_{1A} antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) only inhibited the CBD reduction of glutamate release, while the CB_1 antagonist SR141716 did not modify any effect of CBD. Authors suggestions were that CBD induces neuroprotection in immature brain, and these effects are mediated by CB_2 and adenosine, mainly through A_{2A} receptors [100].

The mechanisms underlying the neuroprotective effects of CBD were investigated *in vivo* by using a hypoxic-ischemic (HI) brain injury experimental model in newborn pigs induced by interruption of carotid blood flow for 30 minutes and reduction to 10% of the fraction of inspired oxygen. Treatment with CBD 1 mg/kg thirty minutes after HI, increased the number of viable neurons and affected in a positive manner the amplitude-integrated EEG background activity as well as prognostic proton-magnetic-resonance-spectroscopy and HI brain damage parameters such as increased glutamate/N-acetylaspartate ratio, oxidative stress and inflammation (increased brain IL-1 levels). CBD neuroprotective effects were reversed by co-administration either of serotonin 5HT1A receptor antagonist WAY100635 or of the CB2 receptor antagonist AM630, suggesting the involvement of CB2 and 5HT1A receptors [14].

In another experiment, mice were subjected to a 17 min of bilateral common carotid artery occlusion (BCCAO) and successively subjected to the Morris water maze test 7 days later. CBD (3, 10, and 30 mg/kg), administered 30 min before and 3, 24, and 48 h after BCCAO, CBD (3-30 mg/kg) improved spatial learning performance and CBD (10 and 30 mg/kg) showed a decrease in hippocampal neurodegeneration after treatment. These results support the idea that protective effect of CBD on neuronal death induced by ischemia may involve the inhibition of reactive astrogliosis [101].

Recently, other results from pre-clinical studies seem to provide further evidence for the potential antiischemic effects of CBD. It has been observed that, as it happens with hypothermia, CBD treatment reduced the glutamate/N-acetyl-aspartate ratio, as well as TNF-α and oxidized protein levels in newborn piglets subjected to hypoxic-ischemic insult [33]. Another very recent experiment of 2016, showed that intracerebral administration of CBD (100 and 200 ng/rat) in the cerebral ischemia induced by middle cerebral artery occlusion, produced a remarkable reduction in neurological deficit, area of infarction, brain edema and blood brain barrier permeability with respect to the vehicle group. These positive effects were associated in CBD treated animals with up-regulation of NCX2 and NCX3 [102].

Hypothermia is a standard treatment for neonatal encephalopathy, but it is not giving always the expected positive results. The combined effect of hypothermia and CBD has been studied in hypoxic-ischemic newborn piglets. Combination of CBD with hypothermia, 30 minutes after the ischemic insult, has showed a higher effect in comparison to the protective effect of the two singular treatments on excitotoxicity, inflammation and oxidative stress, and on cell damage. Thus suggesting that CBD and hypothermia could act complementarily having additive effects on the main factors leading to hypoxic-ischemic brain damage if applied rapidly after the insult [33].

By using the experimental model characterized by bilateral common carotid artery occlusion (BCCAO) in mice, it has also been demonstrated that short-term CBD 10 mg/kg treatment attenuates cognitive and emotional impairments induced by brain ischemia. BCCAO mice showed long-lasting functional deficits characterized by increase in anxiety-like behavior, memory impairments, despair-like behavior. CBD prevented the cognitive and emotional impairments, attenuated hippocampal neurodegeneration and white matter injury, and reduced glial response that were induced by BCCAO, thus improving global functional recovery. In BCCAO ischemic mice treated with CBD an increase in the hippocampal BDNF protein levels, stimulation of neurogenesis and promotion of dendritic restructuring in the hippocampus were also observed [103]. Main pre-clinical findings on CBD in brain ischemia are summarized in Table **1**.

Pre-clinical data indicated that CBD administration after a cerebral ischemic event produced long-lasting neuroprotective effects. In particular CBD was effective in recovering

post-ischemic functional parameters. Neuroprotection observed with CBD is due to a large spectrum of effects such as maintenance of calcium homeostasis and reduction of inflammation mediators formation and indicated that CBD has potential as a new neuroprotective strategy in brain ischemia.

CONCLUSION

CBD has been demonstrated to possess a broad spectrum of therapeutic properties, including neuroprotective effects in numerous pathological conditions. Neuroprotection could be explained with variegate biological properties observed with CBD. It exerts antioxidant and antiinflammatory activities and is able to modulate positively a large number of biological targets in the brain involved in the development and maintenance of neurodegenerative diseases. Pre-clinical evidence largely shows that CBD can produce beneficial effects in AD, PD and MS patients, but its employement for these disorders needs further confirmation through well designed clinical studies. Experimental animal studies also indicate that CBD could be useful as neuroprotective agent in the ischemic event occurring during the neonatal period. Preclinical demonstration of antiepileptic activity is supported but recent studies in human epileptic subjects indicating CBD's potential use in children and young adults affected by refractory epilepsy. Currently, therapeutic continuity by using cannabis or single cannabinoids is more guaranteed by standardized preparations assuring the availability of a homogeneous product of defined stability [104]. Consequently, clinical evidence reporting effectiveness of CBD is increased even if, in the neurological field, it is limited to epilepsy and PD. These findings indicate CBD as a promising potential treatment for refractory epilepsy in children and young adults, as suggested by several clinical studies that need to be confirmed by further clinical research. Evidence for use of CBD in PD is still not supported by sufficient data because only a few studies including a small number of patients are available.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's Disease
ALS	=	Amyotrophic Lateral Sclerosis
BDNF	=	Brain-derived Neurotrophic Factor
CBD	=	Cannabidiol
CNS	=	Central Nervous System
EAE	=	Experimental Autoimmune Encephalitis
HD	=	Huntington's Disease
HI	=	Hypoxic-ischemic
5-HT1A	=	5-Hydroxytryptamine 1A Receptor
MES	=	Maximal Electroshock
MS	=	Multiple Sclerosis
NGF	=	Nerve Growth Factor
PD	=	Parkinson's Disease
PTZ	=	Pentylentetrazole
THC	=	Delta-9-tetra-Hydrocannabinol
TSC	=	Tuberous Sclerosis Complex

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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