REVIEW

CNS Neuroscience & Therapeutics

Cannabidiol: A Promising Drug for Neurodegenerative Disorders?

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Neurodegenerative diseases represent, nowadays, one of the main causes of death in the industrialized country. They are characterized by a loss of neurons in particular regions of the nervous system. It is believed that this nerve cell loss underlies the subsequent decline in cognitive and motor function that patients experience in these diseases. A range of mutant genes and environmental toxins have been implicated in the cause of neurodegenerative disorders but the mechanism remains largely unknown. At present, inflammation, a common denominator among the diverse list of neurodegenerative diseases, has been implicated as a critical mechanism that is responsible for the progressive nature of neurodegeneration. Since, at present, there are few therapies for the wide range of neurodegenerative diseases, scientists are still in search of new therapeutic approaches to the problem. An early contribution of neuroprotective and antiinflammatory strategies for these disorders seems particularly desirable because isolated treatments cannot be effective. In this contest, marijuana derivatives have attracted special interest, although these compounds have always raised several practical and ethical problems for their potential abuse. Nevertheless, among *Cannabis* compounds, cannabidiol (CBD), which lacks any unwanted psychotropic effect, may represent a very promising agent with the highest prospect for therapeutic use.

Introduction

In the present article, the current literature regarding CBD use in preclinical and clinical studies has been revised, underlying the potential of CBD in the prevention of the main neurodegenerative disorders and the clinical management of symptoms related to these pathologies. Although the range of its clinical effect is impressive; however, to date, the molecular mechanisms through which CBD exerts its action remain elusive. As a result, this phytocannabinoid may represent a lead compound for the development of therapeutics that are able to exert neuroprotection as well as to operate against neuroinflammatory component of neurodegenerative disorders.

Neurodegenerative Disorders

Neurodegenerative diseases, from Greek νευρο-, *néuro-*, "nerval" and Latin *dēgenerāre*, "to decline", are characterized by a slow progressive neuronal loss in specific brain areas, which leads to the observed clinical manifestations [1]. Although they have different etiologies, most of them share similar histomorphological features, such as neuronal loss, gliosis, and the presence of aggregates of misfolded or aberrant proteins [2,3]. Neurodegenerative diseases are characterized by cognitive, motor, and/or behavioral dysfunctions. This clinical heterogeneity is in large part attributable to pathological variability and the characteristic topographic pattern of central nervous system (CNS) involvement, displayed by each particular disease entity, the latter being determined by the selective vulnerability of brain cells to the disease process. Neurodegenerative diseases may be crudely divided into two major groups according to phenotypic features: conditions causing problems with movements, or conditions affecting memory and related to dementia [2]. Neurodegenerative disorders usually extend over a decade. Neurodegeneration begins long before patients experience any symptoms, which are noticed only when many cells are irreversibly damaged and cease to function, so

that the actual onset of disease precedes clinical manifestations by many years.

The mechanism that drives chronic progression of neurodegenerative diseases remains elusive. Clearly, if a driving force persists actively, therapeutic strategies aimed at neurorescue, replacement, or regeneration might underperform. Recently, neuroinflammation, a prominent feature shared by various neurodegenerative diseases, has been increasingly implicated in the mechanisms that are responsible for such disorders, so that it is now regarded as a double-edged sword [4]. In fact, without neuroinflammation, removal of offending materials and recovery from injuries become impossible, whereas an uncontrolled neuroinflammation can become devastating, since overactivated microglia and astrocytes produce a myriad of neurotoxic substances that are responsible for a vicious self-propagating cycle that drives to chronic progression of neurodegenerative diseases [5,6]. The classical division between degenerative and inflammatory CNS disorders is vanishing, as accumulating evidence shows that inflammatory processes are important in the pathophysiology of primarily degenerative disorders, and neurodegeneration complicates primarily inflammatory diseases of the brain and spinal cord. In fact, Alzheimer disease (AD), Parkinson disease (PD), and amyotrophic lateral sclerosis (ALS) are among the best examples of neurodegenerative disorders that are precociously associated with intense inflammation, whereas multiple sclerosis (MS) is an inflammatory disease in which neurodegeneration may occur as a very early event [7,8]

Such evidence imposes reconsideration of the perceived relationship between neuroinflammation and neurodegeneration, suggesting that one is not simply a culmination of the other, since they may occur in parallel. On the basis of these considerations, an early combination of antiinflammatory and neuroprotective strategies, irrespective of the nature of the primary insult, appears as a rationale and desirable approach, since focusing on only one process might also worsen the other. Therefore, in view of the emerging role of the activated glia in contributing to neurodegeneration, in recent years, the importance to finely tune a protracted glial overactivation as a novel disease-modifying approach to counteract neurodegenerative disorders has been highlighted and it offers hope for a successful therapy.

Because of the vicious cycle and the disappointing failure of the present treatments, drugs with multiple actions, addressed at both inflammatory and noninflammatory mechanisms, may represent the most promising therapeutic strategies for neurodegenerative diseases. Along this line, a unique opportunity to improve neuroinflammation and neurodegeneration simultaneously could be offered by pharmacological agents affecting the endocannabinoids system (ECS) [9,10]. In the last few years, *Cannabis* derivatives have attracted much attention.

Cannabinoids or, Even Better, Cannabidiol?

The anecdotal use of *Cannabis* for therapeutical aim dates back to about 5000 years, although the introduction of its derivatives in the Western medicine belongs to the nineteenth century, reaching a peak of interest in 1960s, when Δ^9- tetrahydrocannabinol (Δ^9-THC), the main psychotropic component of marijuana, was identified and synthesized [11].

At present, "cannabinoids" (CBs) can be separated into three different groups: endogenous (endocannabinoids), synthetic, and phytocannabinoids. The latter group includes terpenophenolic substances extracted from *Cannabis sativa*, such as Δ^9-THC and cannabidiol (CBD). Two membrane receptors for CBs, both coupled to G_i protein, and named CB_1 and CB_2, have been identified so far [12]. It is now commonly accepted that CB_1 receptors are located primarily in the central and peripheral neurons, whereas CB_2 receptors are most abundant in cells of the immune system [13]. However, CB_1 receptors are also expressed by some nonneuronal cells, including immune cells, whereas CB_2 has been recognized on some neuronal cells, either within or outside the brain, even if its role remains to be better clarified [14,15]. Moreover, two orphan G protein-coupled receptors, GPR119 and GPR55, possibly activated by multiple different CB ligands, have been recently proposed as novel CB receptors [16].

Cannabis pharmacology is constantly growing up, and therapeutic properties of CB receptor agonists and antagonists have been suggested for the treatment of different human disorders by preclinical and clinical observations in which interactions at CB_1 and/or CB_2 sites appear to affect molecular mechanisms that are responsible for disease onset or progression [17]. Along this line, a particular interest was raised by the discovery that these agents may be protective in some CNS disorders. In fact, CB receptors are present in the senile plaques from postmortem human brain, together with markers of microglial activation, as well as in AD patients, although the number of CB_1-positive neurons has been found to be drastically reduced [18]. Moreover, it has been reported that CB_1 agonism was able to prevent tau hyperphosphorylation in cultured neurons [19] and antagonize cellular changes and behavioral consequences in β-amyloid-induced rodents [18,20]. On the contrary, CB_2 antagonists resulted to be protective in *in vivo* experiments by downregulating reactive gliosis occurring in

β-amyloid-injected animals [21]. The protective role of CBs has been recognized not only in AD models but also in other experimental paradigms of neurodegenerative disorders, such as 1-Methyl 4-Phenil 1,2,3,6 Tetrahydro-Piridine (MPTP) and HIV-1/Tat protein neurotoxicity [22,23]. Finally, there are growing evidence that CB_1, and possibly CB_2, receptor interactions could affect neuropathology and disease progression in rodent model of both MS [24] and ALS [25,26].

Despite the emerging evidence regarding putative therapeutical activities of CBs, their effective introduction in the clinical use is still controversial and strongly limited by unavoidable psychotropic effects, exhibited by many of them. In this scenario, CBD, which constitutes up to 40% of the *Cannabis* extract, may represent the most promising candidate for clinical utilization due to its remarkable lack of any cognitive and psychoactive actions, in addition to its excellent tolerability profile in humans [27].

Because of its very low toxicity in humans, a large number of trials have been performed to assess the clinical efficacy of CBD in different pathologies. Most of these trials have been executed utilizing Sativex® (GW Pharmaceuticals, Salisbury, UK), the only commercially available preparation containing CBD/Δ^9-THC. Four different formulations of Sativex® are currently under investigation: high THC extract (Tetranabinex®; GW Pharmaceuticals), THC:CBD (narrow ratio), THC:CBD (broad ratio), and high CBD extract (Nabidiolex®; GW Pharmaceuticals) [28]. Three Sativex® delivery systems exist: oromucosal spray, sublingual tablets, and inhalated (but not smoked) dosage forms.

In 2005, the oromucosal spray administration of Sativex® has been agreed to for MS symptoms treatment [29].

It has been established that coadministration of CBD and Δ^9-THC may modify the pharmacological effect of the latter, potentiating some of its reputed benefits, whereas attenuating some of its negative effects [30–32].

CBD Pharmacology

CBD is a natural compound isolated across the 1930s and 1940s from marijuana, but its structure and absolute configuration were fully elucidated only in the 1960s by Mechoulam et al. [33].

(−)CBD isomer is the major nonpsychotropic constituent naturally present in *Cannabis sativa.* Molecular pharmacology of CDB is not well defined, and little is known about a possible CBD-dependent signaling pathway. At first glance, at the chemical structure, it is easy to recognize CBD antioxidant properties due to the presence of two hydroxilic groups [33]. Since its antioxidant properties cannot account for the wide spectrum of biological effects displayed in both preclinical and clinical investigations, several studies have been carried on in order to identify other mechanisms through which CBD exerts its actions. Up to date, no evidence has been provided that, at least, the natural isomer fully binds to any known receptor site, so that such an interaction might be regarded as responsible for some or all the biological effects observed. In fact, CBD, even if it belongs to the CB "family", exhibits only a weak ability to remove ^{3}[H]CP55940, a not selective ligand for CB receptors from both CB_1 and CB_2 receptor sites, being required for this effect concentrations in the micromolar range [34,35]. However, recently, evidence has emerged pointing out that, despite its low affinity for CB receptors, CBD could work as an inverse agonist at CB_2 receptor, at concentration values in low nanomolar range, in both mouse whole-brain membranes and membranes from CHO cells transfected with hCB_2 receptors [36]. In any case, even if the relevance of CBD interactions at CB receptors still remains controversial, its influence on the endocannabinoid signaling system appears convincingly demonstrated. Indeed, although CBD does not seems to clearly operate at CB receptors; however, it has been observed that it is able to potentiate the endocannabinoid signaling system, working at different levels. Indeed, CBD increases anandamide (AEA, the first endocannabinoid identified) levels by inhibiting its reuptake and degradation, blunting both the expression and the activity of fatty acid amide hydrolase (FAAH) [37,38], the enzyme involved in the breakdown of AEA. It should be noted, however, that the concentrations of CBD required for the inhibition of AEA reuptake and hydrolysis are quite high (>20 μM) [37]. Moreover, further interactions between CBD and ECS have been reported to occur in the hippocampal tissue. Indeed, by enhancing the levels of endocannabinoids, either by exogenous application or by a stimulated upregulation, CBD-induced calcium responses appeared strongly decreased. In this case, CBD responses, observed both in the neurons and in the glia, were not dependent on classical CB receptor [39] but potentially mediated through an uncharacterized postsynaptic CB-like receptor coupled to a Gq/11 protein.

Moreover, CBD and its (+) enantiomer interact with the transient potential vanilloid receptor type-1 (TPVR-1), with an EC_{50} estimated between 3.2 and 3.5 μM and a maximal effect similar to that exhibited by the natural agonist capsaicin, both *in vitro* [37] and in a rat model of acute inflammation [40]. Looking for sites possibly responsible for CBD activity, it has been reported the ability of CBD to interact at the 5-HT_{1A} serotonin receptor [41],

as well as to allosterically modulate μ and δ opioid receptors in rat cerebral cortex membrane homogenates [42]. Finally, CBD has been observed to significantly antagonize the orphan receptor GPR55 [16].

To date, although CBD pharmacodynamic remains, in many aspects, still unclear, yet, its pharmacokinetics appears better defined. Once orally given, in consequence of a marked first-pass effect, CBD bioavailability ranges between values of 13 and 19%, making for this reason the intravenous administration preferable [43]. Once injected, CBD is rapidly distributed and easily passes the blood–brain barrier (BBB), considering its lipophilicity, which in turn provides CBD a prolonged elimination [43].

Metabolism of CBD showed biotransformation routes typically observed for phytocannabinoids [44,45]. Although different metabolic pathways have been observed in different animal species, including human, overall CBD metabolism displays common features. Indeed, CBD undergoes multiple hydroxylations, oxidations to carboxylic acids, beta-oxidation, conjugation, and epoxidation [45,46]. Finally, CBD is preferentially excreted from urine, both in the free state and as its glucuronide, with a half-life of 9 h [47].

Encouraged by the lack of any unwanted psychotropic effects, and in view of its potential therapeutic use, efforts have been made to delineate its toxicological profile. In this regard, CBD has been found to exert a very low toxicity, both in human and in other species, exhibiting an LD_{50} of 212 mg/kg when intravenously injected into rhesus monkey [48]. Moreover, CBD does not display teratogenic as well as mutagenic activities [49]. However, CBD appears to impair hepatic drug metabolism of same drugs in different animal species [50] through the inactivation of specific cytochrome P450s belonging to the 2C and 3A subfamilies. These interactions deserve to be taken into the right account in case of CBD coadministration.

CBD: Mechanism of Cell Protection and Antiischemic Effect

CBD exhibits a wide spectrum of interesting biological effects either *in vitro* or *in vivo*. A special attention merits the ability of CBD to regulate both cell cycle and cell survival fate. The antiproliferative effects of CBD, described in leukemia, breast cancer, and glioma [51,52], together with its property to induce tumor regression and inhibition of glioma cell invasion observed in rats [53], support a key role of CBD in the control of tumor development and progression.

A similar proapoptotic potential was also exhibited by CBD in primary cells of the immune system [54]. All this, in concert with a strong inhibition of neutrophil chemotaxis and proliferation [55], would be considered, at least in part, as the basis of its great efficacy as an antiinflammatory drug, described both in models of acute and chronic inflammation [56].

Further effects of CBD on immune cells include the modulation of tumour necrosis factor (TNF)-α, interleukin (IL)-1, and interferon (IFN)-γ by mononuclear cells [57,58] and the suppression of chemokine production by human B cells [59].

The antiinflammatory effects of CBD have not been restricted to the control of the peripheral inflammatory process since interesting results have also been observed in the prevention of the neuroinflammation [60], an effect that may justify the emerging role, described for CBD, as a potential neuroprotective agent.

The nonpsychoactive marijuana-constituent CBD was found to prevent both glutamate neurotoxicity and radical oxygen species (ROS)-induced cell death. Neuroprotection was unaffected by CB receptor antagonism, suggesting CBD as a useful therapeutic effect, independent of psychoactive effects mediated by receptor interactions. CBD was able to antagonize glutamate toxicity in cortical neurons with potency, regardless of whether the insult was operated through N-methyl-D-aspartate (NMDA), 2-amino-3-(4-butyl-3-hydroxyisoxazol-5-yl)propionic acid (AMPA), or kainate receptors, pointing out that CBD antagonizes all three receptors with similar affinity or, more likely, that its site of action remains downstream of initial receptor activation [61]. In an *in vitro* model of neurodegeneration, the neuroprotective effect of CBD involved the attenuation of the excessive production of peroxynitrites induced by glutamate, thus preventing apoptosis [62]. In addition, CBD was found to possess antioxidant properties, since it attenuated ROS-induced neurotoxicity, being more protective than either ascorbate or α-tocopherol [61,63].

Pre- and posttreatments with CBD were reported to significantly diminish the infarct size in a mouse model of brain ischemia. This effect was not inhibited by CB receptor antagonism. CBD also suppressed the decrease in cerebral blood flow (CBF) due to the failure of cerebral microcirculation after reperfusion, as well as it blunted metalloperoxidase activity after reperfusion for up to 3 days, showing potent and long-lasting neuroprotectant and antiiflammatory effects mediated through a CB-independent mechanism [64,65].

Interestingly, these CBD neuroprotective effects were inhibited by the 5-HT_{1A} antagonist, W100135, but not by the TPVR-1 antagonist, capszepine. Furthermore, the

increased CBF induced by CBD was in part decreased by 5-HT_{1A} antagonism, pointing out that CBD may exert a neuroprotective effect toward brain ischemia, at least in part, via 5-HT_{1A} receptor [66].

Finally, in order to identify the mechanisms involved in CBD neuroprotective actions, it cannot be excluded that this phytocannabinoid operates its beneficial effects also through the uncloned postsynaptic CB-like receptor coupled to Gq/11, since mice deficient in this site were found to display an impaired ability to activate neuroprotective mechanisms [67].

CBD and Experimental Model of ADs

The substantial and well-documented antioxidant, antiinflammatory, and neuroprotective properties of CBD have prompted researchers to test its effects in models of neurotoxicity and neurodegenerative disorders. In this context, very promising results have been achieved in the control of β-amyloid-induced toxicity. Although, to date, it is not fully elucidated if β-amyloid plaque deposition and the neurofibrillary tangles, found in postmortem brain of AD patients, are the cause or the consequence of the disease; however, the pivotal role of β-amyloid in inducing neuronal damage and mediating neuroinflammation is evident. In investigations aimed at exploring CBD effects on β-amyloid-induced neurotoxicity, this phytocannabinoid was found to be able to protect differentiated PC12 neuronal cells from the detrimental action induced by peptide exposure through a combination of its antioxidant, antiinflammatory, and antiapoptotic properties [64,68,69]. Indeed, CBD antioxidant effects account mainly for the survival of cultured neurons, with a potency higher than that exhibited by α-tocopherol [63], also attenuating β-amyloid-induced molecular changes possibly through additional mechanisms that are not displayed by classical antioxidants [69]. In fact, CBD resulted in being able to weaken β-amyloid-induced GSK-3β activation, the key enzyme of *wingless gene* (WNT)/β-catenin pathway, thus preventing tau protein hyperphosphorylation and the consequent neurofibrillary tangle formation [69].

It has also been demonstrated that CBD decreased phosphorylation of the stress-activated protein kinase, P38 mitogen activated protein kinase (MAPK), thus preventing the translocation of nuclear factor (NF)-κB into the nucleus and the subsequent transcription of important proinflammatory genes, including those encoding for inducible nitric oxide synthase (iNOS) protein [68].

The beneficial effects of CBD were also confirmed in a mouse model of AD-related neuroinflammation induced by the intrahippocampal injection of the human Aβ (1–42) fragment, where CBD inhibited reactive gliosis by attenuating glial cell activation and proinflammatory mediator release in a dose-dependent manner [70].

These encouraging results emphasize the relevance of CBD as a novel, very promising pharmacological tool capable of mitigating β-amyloid-evoked neuroinflammatory and neurodegenerative responses.

CBD and Control of Movement Disorders: ALS and Parkinson and Huntington Disease

Anecdotal evidence has supported the notion that CBD can exert beneficial role, alone or in combination with Δ^9-THC, in different neurodegenerative disease, such as PD and Huntington's disease (HD), two chronic disorders provoked by degenerative processes implicating specific nuclei of the basal ganglia, responsible for abnormal regulation of movements. Both disorders have been scantly investigated from the clinical point of view, whereas, at preclinical level, accumulated findings appear more exhaustive and convincing for a possible medical utilization of CBD to improve symptoms and/or delay disease progression. According to recent preclinical findings, plant-derived CBs were able to prevent neuronal damage induced by 6-hydroxydopamine unilateral injection into the nigra pars compacta [71]. This effect appeared to not involve CB receptor mediation, whereas, more likely, it might implicate the antioxidant activity, possibly combined with the capability to modulate glial responses, relevant to neural survival. In rodents with hemiparkinsonism, induced by the intranigral administration of 6-hydroxydopamine, neuroprotective effects exerted by CBD antagonized dopaminergic transmission impairment by attenuating dopaminergic cell death, rather than by increasing the functional turnover of the surviving neurons [71]. Early human reports showed a dose-related improvement (ranging from 20 to 50%) in parkinsonian patients treated with oral doses of CBD (100–600 mg/day over a 6-week period) [72]. On the contrary, in a more recent controlled trial, a mixture of Δ^9-THC/CBD (2.5 mg/1.25 mg per capsule) failed to exhibit any beneficial effect either on parkinsonism or on levodopa-induced dyskinesias [73]. Unfortunately, no subsequent trials were performed to elucidate such controversial findings. Certainly, in comparison to the relevance of rodent results, the limited clinical evidence suggests performance of human studies to verify for good the possible future clinical use of CBD in PD.

Similarly, founded on anecdotal accounts and results of preliminary clinical reports, CBD was regarded as a compound with therapeutical potential also against hyperkinetic disorders. Indeed, CBD was found to

reduce apomorphine-induced turning behavior in 6-hydroxydopamine-injected rats, an animal model of hyperkinetic movement disorders, whereas, on the contrary, it was able to potentiate hypokinesia generated by tetrabenazine [74]. More recently, it was demonstrated that CBD prevents in striatal neurons the toxicity of 3-nitropropionic acid, a mitochondrial toxin that is able to induce some biochemical alterations similar to those occurring in HD [75].

CBD was investigated to prove its efficacy in HD, alone or as an add-on drug to the approved therapy with neuroleptics [76]. CBD, at an average daily dose of 10 mg/kg/day for 6 weeks, was neither symptomatically effective nor toxic compared with placebo in neuroleptic-free patients with HD. Considering the negative results on both the therapeutic and the safety measures, there is a question about the dose as well as the duration of the trial. Since such findings cannot be considered conclusive, further clinical investigations, utilizing CBD alone or in combination with Δ9-THC, have to be carried out to estimate the actual antihyperkinetic value of these molecules in a clinical setting.

ALS is a fatal neurodegenerative disease that is characterized by selective loss, implicating motoneurons in the cortex, brainstem, and spinal cord. Since recent studies substantiate the relevance of neuroinflammation and oxidative stress in the pathophysiology of ALS [77], then it is possible to suggest that CBD, because of its antiinflammatory and antioxidative properties, could be a promising tool to treat disturbances and prolong survival in ALS patients. This is strongly supported by the report that Δ^9-THC was able to slow progression and prolong survival in a mouse transgenic model of ALS, and that similar results were obtained when cannabinol was utilized [78]. Furthermore, these results have to be weighed up with the anecdotal reports that recreational smoking of marijuana does ameliorate symptomatology in ALS subjects.

CBD and MS

MS is considered the leading cause of neurological disability among young and middle-aged people in the northern industrialized countries. MS is considered to be an autoimmune, demyelinating disease that has a complex pathophysiology [79]. There is now clear evidence that: (i) The immune response drives lesion formation and relapsing-remitting clinical attacks. (ii) The progressive stages of MS result from neurodegenerative processes, which do not appear to respond to immunotherapy [80–83]. (iii) These, distinct but related, disease elements both produce nerve/loss that results in altered neurotransmission which leads to the development of a number of signs of the disease, such as spasticity, pain, and bladder dysfunction [79]. The inability of available medicines to control such symptoms has prompted people with MS to self-medicate and perceive benefit by taking *Cannabis* [84]. They also perceived an effect on relapsing disease suggestive of immunosuppressive capabilities [84]. This latter aspect is hard to predict, and disease activity may naturally slow down at a time when residual symptoms are becoming increasingly apparent and people may be taking *Cannabis* for symptom control [79,82]. Although the ability of some CBs to exhibit immunosuppressive potential has been shown by several studies in MS models [85–88], current *Cannabis* trials in MS for symptom control have, so far, failed to demonstrate a significant reduction of relapse, indicative of immunosuppressive properties in humans [89]. Recently, accumulating evidence from preclinical observations supports the notion that CBs may be of more relevance in neuroprotection that in immunosuppression [90], and this is currently being investigated in trials of a long-term administration of THC/CBD in progressive MS. Conversely, CBs have been reported to exert a marked symptom control in MS.

Cannabis has long been proposed as a muscle relaxant drug, with the first report of chronic motor handicaps remarkably improved following marijuana smoking described almost 30 years ago [91].

Since then, extensive preclinical findings have reinforced the notion deduced from the anecdotal observations that *Cannabis* derivatives may have a role in relieving symptoms in MS subjects. [92], offering the rationale for performing randomized, controlled trials of *Cannabis*-based medicine in MS-associated symptomatology.

The clinical trials focused on Sativex® efficacy in the treatment of symptoms of MS, notably spasticity and neuropathic pain. Beneficial results in placebo-controlled trials were obtained when Sativex® was administered as an add-on therapy in these indications, supporting the view that Sativex® is efficacious and well tolerated in the treatment of these symptoms [93]. Additional trials confirmed that the CBD/THC combination is able to reduce pain and sleep disturbance in patients with MS-related central neuropathic pain and that this treatment is mostly well tolerated [94].

Finally, a recent meta-analysis of *Cannabis*-based treatment for neuropathic pain has concluded that the CBD/THC buccal spray (Sativex®) was effective in alleviating MS-related pain [95].

For bladder dysfunctions occurring in MS patients, anecdotal reports have suggested that *Cannabis* derivatives may mitigate lower urinary tract symptoms. More specifically, the results of a pilot study, utilizing THC/CBD combination, have demonstrated a significant decrease in urinary urgency and a reduction in the number and volume of incontinence episodes, as well as a reduction

in the frequency of nocturia. The daily total voided and catheterized volume and urinary incontinence pad weights were also significantly decreased, whereas patients reported significant improvements in spasticity, the quality of sleep, and the level of pain (measured by patient self-assessment) [96]. Large, multicenter, randomized, placebo-controlled trials are underway, although no results are available at the moment. All these data taken together suggest that although, until few years ago, there was little consensus in the scientific literature regarding phytocannabinoid utilization in current neurological therapy, presently, the majority of studies focusing on this topic are oriented to suggest CBD, alone or in combination, as a useful option in the treatment of MS, at least in a subset of individuals.

CBD and Prion Diseases

Prion diseases are transmissible neurodegenerative disorders that are characterized by the accumulation in the CNS of the protease-resistant prion protein (PrPres), a structurally misfolded isoform of its physiological counterpart PrPsen. Both neuropathogenesis and prion infectivity are related to PrPres formation [97]. CBD inhibited PrPres accumulation in both mouse and sheep scrapie-infected cells. Moreover, after intraperitoneal infection with murine scrapie, peripheral injection of CBD limited cerebral accumulation of PrPres and significantly increased the survival time of the infected mice. CBD inhibited the neurotoxic effects of PrPres and affected PrPres-induced microglial cell migration in a concentration-dependent manner [97]. Therefore, CBD may protect neurons against the multiple molecular and cellular factors involved in the different steps of the neurodegenerative process, which takes place during prion infection. This evidence, together with CBD's ability to specifically target the brain and its lack of toxic side effects, makes CBD a promising drug, also to be used in Prion diseases, although the high concentration of CBD needed to obtain the survival effect and the absence of an effect if CBD is administered after infection have to be taken into the right account, considering, at the moment, the lack of an early diagnosis of this diseases in humans.

Conclusions

The present review summarized a growing number of evidences, indicating an emerging role for CBD in the prevention and management of the main neurodegenerative disorders. CBD, in fact, resulted in being able to protect neuronal and nonneural cells against several detrimental insults, such as β-amyloid or 6-hydroxydopamine and glutamate [62,70,71], which are considered to be the basis of disorders such as AD and PD. The protective effects of CBD have been, moreover, evidenced in several animal models of neurodegeneration, and very interestingly, important clinical trials have confirmed the potential pharmacological activity of CBD in the management of clinical symptoms and the slow-down of the progression of a variety of pathologies, including AD, MS, PD, and ASL. Unfortunately, despite CBD promising therapeutic value, the actual mechanism responsible for its action still remains to be fully elucidated. In fact, although its antioxidant structure is evident, if truth be told, it would be limited to restrict all CBD actions to a simple antioxidant mechanism, since CBD has revealed to possess not only an effectiveness higher than that of the classical antioxidant compounds but also some special activity unfamiliar to them [98]. In fact, in almost all the clinical studies performed, CBD has strongly enhanced the effects of THC, underlining that at least some biological and clinical action is stoutly linked to the enhancement of endocannabinoid and endovanilloid signaling system.

Until now, the best results with CBD were reached by the use of Sativex®, a combination of THC and CBD, thanks to the mutual benefit capitalized by one from the other active marijuana components. The medical literature on the topic seems to reinforce the view that CBD achieves synergy with THC [99,100], consisting of potentiation of benefits, antagonism of adverse effects, summation (entourage effects), and pharmacokinetics advantages (CBD suppression of 11-hydroxylation of THC).

The great therapeutic value of CBD, either given alone or in association with THC, derives from the consideration that it represents a rare, if not unique, compound that is capable of affording neuroprotection by the combination of different types of properties (e.g., antiglutamatergic effects, antiinflammatory action, and antioxidant effects) that almost cover all spectra of neurotoxic mechanisms that operate in neurodegenerative disorders (excitotoxicity, inflammatory events, oxidative injury, etc.).

The reported data here, taken together with the evidence of the CBD's almost absolute absence of side effects, including psychotropicity, suggest its great efficacy and open new horizons for the treatment of the main neurodegenerative disorders. However, in the near future, further clinical trials, well designed, carefully executed, and powered for efficacy, are crucial to definitively assess the clinical values of CBD, alone or in combination, in the management of neurodegenerative diseases, also in comparison to the other therapeutic approaches. This will allow the promising expectations to move from the present promising, although limited, results toward incontrovertible evidence.

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Conflict of Interest

All authors disclose any potential conflicts of interest, including all relevant financial interests (e.g. employment, significant share ownership, patent rights, consultancy, research funding) in any company or institution that might benefit from the publication.

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