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Review

Roles of Cannabidiol in Reversing Proteinopathies

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Abstract: Cannabidiol is a well-known non-psychotropic phytocannabinoid from *Cannabis sativa*, which exerts a broad range of neuropharmacological activities in the central nervous systems. Over the past years, compelling evidence from preclinical and clinical studies support therapeutic potentials of cannabidiol in various neurological disorders, including neurodegenerative diseases. Neurodegenerative diseases are characterized by the accumulation of misfolded or aggregated protein due to the defective protein homeostasis or proteostasis network, termed as proteinopathies. Because of its role in the protein homeostasis network, cannabidiol could be a potent molecule to revert not only age-associated neurodegeneration but also other protein misfolding disorders. In this review, we discuss the potentiality of cannabidiol as a pharmacological modulator of the proteostasis network, highlighting its neuroprotective and aggregates clearing system inducing potentials in the neurodegenerative diseases.

Keywords: Cannabidiol; Alzheimer's disease; Huntington's disease; Multiple sclerosis; Parkinson's disease; Prion disease; Proteinopathies

Introduction

Disruption in protein homeostasis (proteostasis) and protein misfolding are two major drivers in the pathobiology of neurodegenerative diseases (NDDs) including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). NDDs are generally characterized by the presence of protein aggregates either in the nucleus or cytoplasm [1,2], and the region-specific neuronal death with a consequence of motor and cognitive deficits [3,4]. A line of evidence supports the concept that NDDs are proteinopathies, where they share fundamental features of protein aggregate, for example, tau, and amyloid-β in AD, α-synuclein in PD, huntingtin (Htt)

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in HD, etc. [5-7]. Evidence from the recent studies correlates the higher incidence of NDD with the progressive failure of the proteostasis network, which results in proteotoxic stress that reduces both repair and/or clearance of misfolded protein; and thus contributes to pathological aging [8-11]. The proteostasis network is impaired by oxidative stress, which is a pathological condition arising from excess production of reactive oxygen species (ROS) due to starvation, exposure to antibiotics [12], inflammation [13], disease-associated mutations, polymorphisms, energetic deficits and aging [14-17]. Oxidative stress plays vulnerable roles in disrupting proteostasis by causing oxidative damage and neuroinflammation, leading to cell death [17,18].

Accumulating evidence suggests that endocannabinoid systems regulate the functionality of redox homeostasis in different cell types [19,20], thus maintain an equilibrium state between the redox system and pro-oxidant state [21,22]. The endocannabinoid systems, consisting of cannabinoid receptors (CB1 and CB2), are either activated or antagonized by endocannabinoids and phytocannabinoids [23]. Phytocannabinoids, such as cannabidiol (CBD), cannabivarin, delta-9-tetrahydrocannabinol (THC), cannabidivarin, and cannabigerol, have been widely studied for their involvement in endocannabinoid systems [24]. CBD is available in *Cannabis sativa,* categorized as a phytocannabinoid of cannabaece family [25-27], and is one of the fascinating non-psychoactive agents with well-known anti-oxidant and anti-inflammatory properties [28,29].

CBD has shown to provide neuroprotection [30] and thus become a therapeutic option in neurodegenerative disorders like AD, PD, HD, ALS, and MS, where treatment slows down disease progression [31]. Remarkedly, disease-modifying mechanisms of CBD are attributed to its antioxidant, anti-inflammatory, and neuroprotective potentials; the precise mechanisms, however, remain unclear, specifically in the regulation of proteostasis system [32]. In this review, an effort has been made to connect CBD mediated pharmacological effects with proteostasis system, providing a more extensive area for future research on CBD pharmacology, in the management of neurodegenerative disorders.

Cannabidiol chemistry, bioavailability, and toxicity

The plant, *C. sativa,* serves as a primary source of CBD, where CBD is available up to 40% in the organic extraction [33]. CBD from cannabis was first reported in the late 1930s, and purified in 1940; however, structure and stereochemistry were first elucidated in 1960s by Mechoulam et al. [34]. The biosynthesis of CBD is usually triggered by the leading precursor cannabigerolic acid, which is derived from the two phytocannabinoid precursors, divarinic acid and olivetolic acid. Cannabigerolic acid is further converted into cannabichromenic acid, tetrahydrocannabinolic acid, and cannabidiolic acid, where cannabidiolic acid forms CBD [35,36]. Comparatively, CBD is the major non-psychotomimetic compound present in the plant, well-tolerated [37], and has a broad spectrum of potential therapeutic properties, including anxiolytic [38], anticonvulsant [24], anti-inflammatory [39-41], neuroprotective [38,42-45], and immunomodulatory [46]. In combination therapy, CBD alleviates some of the adverse effects of THC, such as cognitive impairment, psychosis, schizophrenia-like effects [47-49].

The pharmacokinetics of CBD is quite complex, and various studies suggest several potential routes of administration. The oral bioavailability of CBD is ranged from 13% to 19% with a substantial first-pass impact, whereas the systemic bioavailability of inhaled CBD was 31% (range 11-45%) for a community of cannabis users. The specification of plasma was identical to Δ 9-THC. At chronically administered oral daily doses of CBD 10 mg/kg/day, the average plasma concentration of CBD was 5.9–11.2 mg/mL [50]. When injected, CBD is absorbed

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rapidly and easily crosses the blood-brain barrier (BBB), owing to its lipophilicity, which in turn provides sustained release of CBD [51]. CBD delivery is controlled by its high lipophilicity, and an approximate volume of distribution ~32 L/kg with prompt dissemination in the fat tissue, brain, and different other organs [52]. CBD is also exceedingly protein-bound, and ~10% is associated with the circulation of red blood cells [53]. It is predominantly metabolized by the liver, as in other cannabinoids, whereby cytochrome P450 (CYP) enzymes, primarily by CYP3A and CYP2C isozymes groups hydroxylating it to 7-OHCBD. This metabolite is then substantially more metabolized in the liver, and the subsequent metabolites are eliminated to feces and slightly less into the urine. The half-life of CBD is 18 to 32 hours in humans, with a clearance of 960–1560 ml/min after the single dosage given in prolonged cannabis users [54]. Without worsening of psychotic symptoms, CBD has well endured in patients with dosages up to 600 mg [55]. No significant CNS impacts or consequences for vital signs or mood changes were identified in a minority of placebo-controlled studies conducted at dosages up to 1,500 mg/day (p.o.) or 30 mg (i.v.) in both intense and persistent administration [56]. For adults, there is a possible hazard of immunosuppression, because CBD has been identified to repress anti-inflammatory factors IL10 and IL8 as well as to induce apoptosis of lymphocytes [55,57]. In humans and other species, cannabidiol exhibits very low toxicity: with an LD_{50} of 212 mg/kg after administered intravenously to rhesus monkeys [58]. The oral LD_{50} has not been reported yet; however, Rosenkrantz has demonstrated, an oral dose of CBD that was 20–50 times higher than intravenous dose was sufficiently high to cause severe toxicity [58]. Besides, a broad range of studies has failed to identify CBD-inducing mutagenic or teratogenic effects [50].

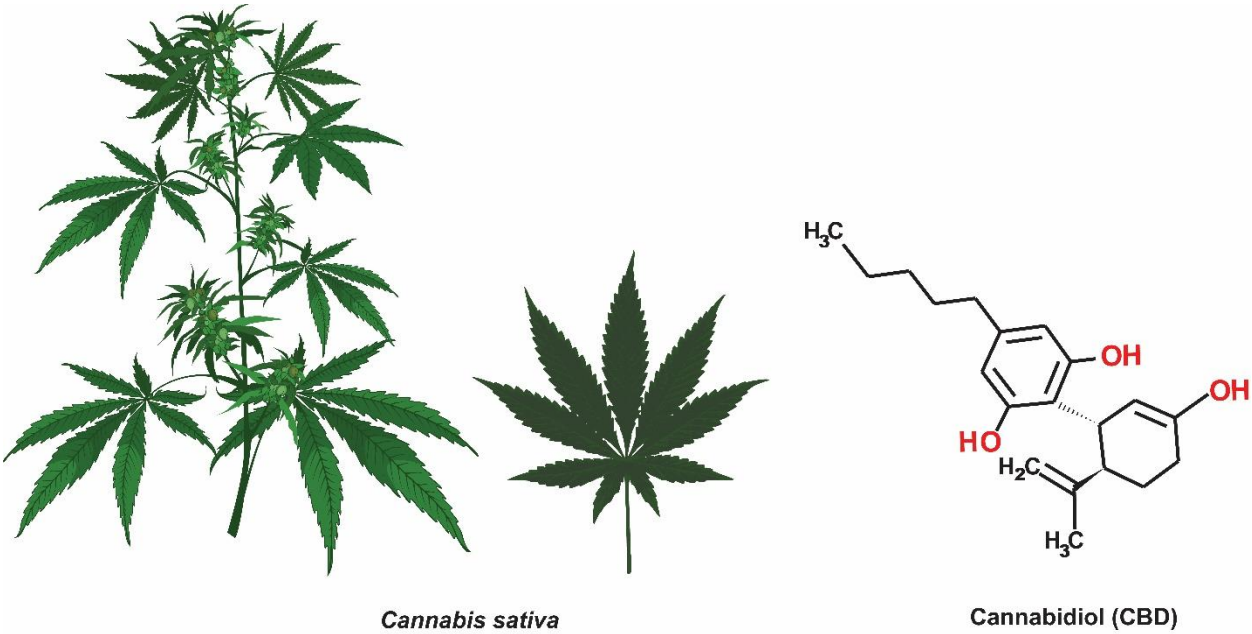

Figure 1. The major source (*Cannabis sativa*) and chemical structure of cannabidiol.

Molecular hallmarks of neurodegeneration

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Disposition of misfolded proteins or protein aggregates in the brain is the main hallmarks of neurodegeneration, where the NDDs are categorized based on the type of protein deposition or by known genetic mechanisms. These disorders, caused by misfolded proteins, are also known as proteinopathies, where the protein conformation is being critically altered [59,60]. For each disease, the clinical manifestation is initiated with the repeated production of a specific protein, which is misfolded, aggregated, and, hence, affects specific neurons [61]. In the basal state, misfolded proteins are either refolded correctly or degraded by the quality control system, like by chaperone proteins [62]. During cellular aging, under proteotoxic stress, or due to mutation, misfolded proteins escape this system, and then aggregated into amorphous assemblies and oligomers, ranging to highly ordered amyloid fibrils and plaques. Once formed, higher-order amyloid aggregates are highly resistant to degradation. Several factors play a critical role in favor of this transition, including post-translational modifications, environmental changes, chemical alterations, in addition to genetic mutations. These factors alter the hydrophobicity or net charge of the protein, which reduces conformational stability and also affect the protein quality control system [63].

Furthermore, cellular insults, like calcium-induced protein misfolding, mitochondrial dysfunction, and inflammation, are also associated with protein aggregation, where mitochondrial dysfunction confers upregulation of ROS/RNS (reactive nitrogen species) in the cells, which leads to cell death [64]. On the other hand, overstimulation of NMDA receptors also caused excessive intracellular calcium accumulation, which promotes ROS/RNS production that impedes quality control mechanisms. Misfolded proteins also activate microglia and astrocytes, causing the release of pro-inflammatory mediators and cytokines that activate several mechanisms, which follows the ROS/RNS generations, mitochondrial dysfunction and neuronal apoptosis [65]. Moreover, excessive aggregation leads to develop a vicious cycle of cell toxicity, where they interact with the membrane systems and establish transmembrane pores, further leading to an influx of calcium [66]. In this regard, CBD could be a fascinating molecule for the particular interest in neurodegenerative disorders, because of having anti-inflammatory, antioxidant, and neuroprotective potentiality. A wealth of literature highlights the therapeutic roles of CBD in models of neurotoxicity and neurodegenerative disorders, which will be discussed in subsequent sections.

CBD regulation in oxidative stress

Oxidative stress (OS) is a pathological condition resulting from an imbalance of pro- and anti-oxidant molecules. [67]. Because of high metabolic demand and huge turnover in brain cells, neurons are particularly highly prone to OS. Prolonged OS causes a depletion of cellular antioxidants enzymes such as superoxide dismutase (SOD), catalases (CAT), glutathione peroxidase (GPx), and non-enzymatic components like glutathione (GSH)), leaving the cellular antioxidant defense system exhausted [68,69]. OS may also lead to inflammation, protein misfolding, mitochondrial dysfunction, impairment of the DNA repair system, glial activation, and ultimately cellular damages, which are critically implicated in the development of neurodegenerative disorders [70,71].

Several studies demonstrate the neuroprotective effects of CBD, owing to its antioxidant activity. A study by Pan *et al.* showed that CBD mitigated cisplatin-induced oxidative/nitrosative stress by downregulating the expression of superoxide-generating enzymes RENOX (NOX4) and NOX1 in mice models [72]. In the Fenton reaction, CBD can transfer electrons under variable voltage potential as well as prevent dihydrorhodamine oxidation similar to the synthetic antioxidant butyled hydroxy toluene (BHT). CBD also protects neurons incubated with *tert-*

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butyl hydroperoxide in a concentration-dependent manner [73]. Moreover, in the glutamate neurotoxicity model, CBD was shown higher neuroprotective efficacy than the popular antioxidants, α-tocopherol (vitamin E), and ascorbate (vitamin C) [73]. Iuvone et al. demonstrated that CBD (10 μM) attenuated apoptosis in PC12 cells by reducing intracellular calcium accumulation, lipid peroxidation, ROS generation, and downregulating caspase-3 level. CBD also demonstrated an antioxidant effect by inhibiting inducible nitric oxide synthase protein expression and nitric oxide production, followed by blocking p38 MAP kinase phosphorylation and the NF-κB activation [74,75]. In the H_2O_2 induced OS model, CBD has shown to protect primary hippocampal neurons, oligodendrocyte progenitor cells, and cerebellar granule cells [76-78]. Juknat and his colleagues have paid an effort to identify underlying molecular mechanisms of CBD mediated antioxidation in BV-2 microglial cells [79]. The study reveals that CBD can modulate redox homeostasis and ROS generation by regulating Nrf2/HO-1 axis and (EpRE/ARE)-Nrf2/ATF4 system, respectively. Similar results were observed in a study with keratinocyte [80]. However, a recent study identified CBD, as a relatively week inducer of Nrf2, although it strongly upregulates HMOX1 by inhibiting BACH1 [81]. Nrf2 is a transcription regulator of various antioxidant factors, whereas HMOX1, one of the targets of Nrf2, is an enzyme that provides antioxidant properties by the rate-limiting reaction in heme catabolism [82].

CBD mediated neuroprotection against neuroinflammation

The phenomenon of neuroinflammation includes a complex reaction of glial activation, related to inflammatory mediators like chemokines or cytokines secretion, and reactive oxygen and nitrogen species generations [83]. Accumulation of misfolded protein or protein aggregates is often triggered by ROS/RNS [76,84], which in turn activates pro-inflammatory responses and thus sustains neuroinflammation [85]. Notably, molecular pathways regulated by CBD, as described in OS, are also implicated in neuroinflammation. As a result, CBD can manage neuroinflammation by not only reducing OS but also by producing anti-inflammatory substances and also regulates pro-inflammatory responses [40,86-89].

Several findings demonstrated that pro-inflammatory responses, including chemokines and cytokines, are mediated through NF-κB signaling, which promotes inflammatory cascade upon the microglial activation [30,90]. NF-κB signaling consequently plays an essential role in neuronal plasticity as well as in the cellular response to brain injury by upregulating cytokines in astrocytes and microglia, especially TNF-α, and IL-6 and many others reviewed elsewhere [91]. The regulation of NF-κB signaling, however, is repressed by the activation of peroxisome proliferator-activated receptor γ (PPAR-γ) [92]. A line of studies demonstrated that CBD reduced the amount of IL-1β, IFN-β, TNF-α, IFN-γ, IL-6, IL-17, NO, and COX-2 through the activation of PPAR-γ [93-98]; while increasing the production of anti-inflammatory cytokines IL-4 and IL-10, and impeding iNOS expression [94]. In the lipopolysaccharide-stimulated animal model, CBD reduced the secretion of pro-inflammatory cytokines (IL-1β and TNF-α), and also other non-cytokine compounds. By inhibiting ROS/NF- κB pathway, CBD can lower glucose uptake in the microglial cell, which is essential for the activation of microglia [86,99], followed by downregulating NADPH oxidase and IκB kinase-2 [86].

Additionally, CBD showed a suppressive role in the immune system, as evidenced by improving innate and adaptive immune responses in a chronic inflammatory model [100]. Ruiz-Valdepeñas et al. represented that CBD reduced leucocyte recruitment and TNF expression in the central nervous system [101]. Furthermore, Juknat et al. found that CBD regulates Th17 proliferation and STAT1 /STAT3 balance, which suppresses microglial cell activation [79] and also reduces inflammatory cytokine IL-6 and IL-17 secretion [102]. Immune regulatory effects of CBD are based on the strong upregulation of $CD4^+$ and $CD25^-$ T cells by inhibitor molecules LAG3 and CD69 [102]. Besides, activation of mitogen-activated protein kinases like p38/MAP-kinases may lead to the upregulation of pro-inflammatory mediators during

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inflammation. Interestingly, CBD can inhibit the p38 phosphorylation, which sequentially reduces the neurotoxic effects with uncontrolled immune reactions [103].

The positive effects of CBD are linked to the expression of brain-derived neurotrophic factor (BDNF) and pro-inflammatory cytokines to interact with intracellular pathways in neuronal survival [33,38]. BDNF is a vital neurotrophin for neuronal development and survival, cognitive function, and also for synaptic plasticity [104]. Barichello et al. found that low brain BDNF levels and augmented proinflammatory cytokines in rats exposed to an experimental model of meningitis were associated with poor cognitive performance. In this regard, CBD therapy minimized these effects [105]. Using rat hippocampus, a study based on amphetamine-induced OS model showed that CBD increased the levels of BDNF as a model to investigate mania [106]. On the other hand, the upregulation of BDNF expression by CBD was also found to be correlated with anti-inflammatory activity, decreasing TNF-α and IL-6 levels in the prefrontal cortex and the hippocampus [42].

In combination therapy, supplementation of CBD with THC suppresses mi-RNA mediated neuroinflammation [107,108]. This conjugated therapy reduces Th1 and Th2 expression and neuroinflammation in murine experimental autoimmune encephalomyelitis (EAE) model system, which was mediated through CB1 and CB2 receptors. Again, CBD therapy combination with THC has been reported to reduce CD4+ T cell proliferation in the brain and pro-inflammatory cytokines IL-1β, IL-6, INF-γ, IL-17, TNF-α, and TBX21 and enhanced the production of anti-inflammatory molecules like as STAT5b, FoxP3, TGF-β, IL-4, and IL-10. The miRNA microarray data revealed that THC+CBD upregulated miR-706-5p and miR-7116 whereas, suppressed miR-21a-5p, miR-31-5p, miR-122-5p, miR-146a-5p, miR-150-5p, miR-155-5p, and miR-27b-5p [109]. The pathway analysis revealed that most of the downregulated miRNA's targeted cell cycle-arrest and apoptosis molecules, such as CCNG1, CDKN2A, and BCL2L11 and anti-inflammatory molecules such as FoxP3 and SOCS1 [109].

Studies suggested that CBD has no or little effect on endocannabinoid receptors. However, depending on the concentration, CBD can act as both agonist or antagonist to the various receptors, including ionotropic (TRP) as well as voltage-gated sodium channel, nuclear (PPAR) receptors, and also cannabinoid receptors (CB1 and CB2), albeit [110-112]. In this way, CBD regulates redox balance, and collectively provides an anti-inflammatory effect by reducing OS [113]. For a detailed understanding, readers are referred to a comprehensive review [114]. Besides, based on our discussion, we provide an illustration, highlighting CBD mechanism of action in OS and inflammation mediated through PPAR-γ receptor (Figure 2).

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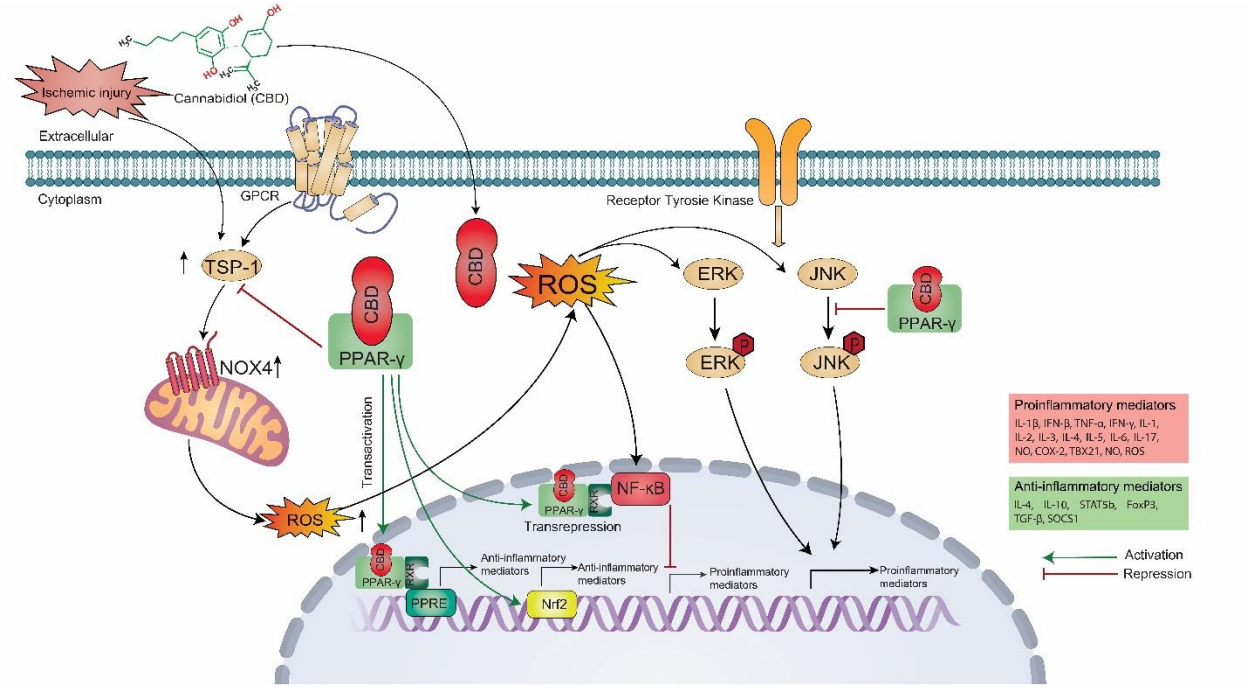

Figure 2. Potential mechanisms of CBD as a PPAR-γ agonist to attenuate oxidative stress and inflammation. During oxygen deprivation, ROS generated through the upregulation of NOX4 in a TSP-1 dependent manner [115]. In that case, CBD binds and activates PPAR-γ, which in turn inhibits TSP-1 expression and signaling. PPAR-γ activation by CBD also enhances antioxidant gene transcription by regulating transcription factor PPRE. Furthermore, PPAR-γ activation transrepress NF-κB, and reduce proinflammatory cytokine secretion. CBD-PPAR-γ also inhibits JNK phosphorylation, resulting in decreased inflammatory response and oxidative stress. In addition, PPAR-γ activation also induces transcription factor, NRF2, which reduces the inflammatory damage by enhancing expression of anti-inflammatory molecules. Here, green arrow represents activation of signaling and close red arrow represents inhibition of signaling. CBD, Cannabidiol; ROS, Reactive oxygen species; NOX4, Nicotinamide adenine dinucleotide phosphate oxidase 4; TSP-1, Thrombospondin-1; PPAR-γ, Peroxisome proliferator-activated receptor γ; PPRE, Peroxisome-proliferator-responsive element; NF-κB, Nuclear factor-kappa B; JNK, Jun N-terminal kinases; NRF2, Nuclear factor erythroid 2–related factor 2.

CBD Protects calcium-induced protein misfolding

Calcium (Ca^{2+}) ions are the critical factor in intracellular signaling by regulating second messengers in the systems and used as a cofactor for some enzymes as well as bone formation. Although Ca^{2+} is prominent in cell physiology, its imbalance severely disrupts protein conformation [116]. Growing evidence supports the concept that the accumulation of excessive Ca^{2+} in the cell induces OS, which promotes protein aggregation, leading to cell death. Oxidative reactive species, such as ROS/RNS modify misfolded proteins to be highly oxidized and cross-linked, leaving them more prone to aggregates. These aggregated forms act as endogenous proteasomal inhibitors [70]. Consequently, reduced activity of the proteasomal system, the primary machinery for the removal of oxidized and misfolded protein leads to further accumulation of protein aggregate [117-121]. These protein aggregates can interact with the lipid bilayer of the cell membranes, causing membrane disruption or pore formation [122,123], which eventually disrupts ion homeostasis [124,125]. Furthermore, studies also showed an interaction between protein aggregates

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with cellular receptors, including mGluR5s, causing gain or loss of function in the signaling platform, resulting in the upregulation of NMDAR (N-methyl-D-aspartic acid receptor) dependent Ca^{2+} response [124]. NMDAR is one of the ionotropic glutamate receptors dealing with the Ca^{2+} regulation, along with Na^{+} and K^{+} in the cytoplasm [126,127]. However, overstimulation of NMDAR exaggerates the massive influx of Ca^{2+}, which leads to energy loss with depolarization of mitochondrial Ca^{2+}, and neuronal apoptosis by the activation of caspase pathways [128]. An excessive influx of Ca^{2+} gives rise to the production of ROS successively with the rising oxygen tension [129].

Several studies showed that CBD has anticonvulsant activity [130-132], focusing its effect on NMDAR regulation (Figure 3). Indeed, Azza B.El-Remessy et al. found that CBD decreased nitrite/nitrate, lipid peroxides, and nitrotyrosine expression, which subsequently protects neurons from NMDA induced injury [133]. Moreover, CBD was shown to inhibit glutamate release in the brain hypoxia model by acting on both CB2 and adenosine receptors but mainly on A_{2A} receptor [134]. Linge et al. found a correlation between CBD mediated glutamate signaling and serotonergic systems, where glutamate regulation is maintained by 5-HT_{1A} receptor-dependent mechanism [24]. Strikingly, Gobira et al. found that activation of mTOR by CBD is associated with a subsequent reduction in glutamate release [135]. However, substantial evidence indicates that CBD behaves as an antagonist for chaperone protein σ1R, which is a viable target to treat neuropathic pain by reducing the influence of glutamate NMDARs [136-139]. The σ1R antagonist also inhibits G protein-coupled receptors (GPCRs), which subsequently reduce the actions of NMDARs [140,141]. They produce secondary messengers, control homeostasis of calcium by triggering PKA, which is responsible for the activation of the calcium channels [142].

A variety of GPCRs such as CB1 and CB2, orphan GPCRs such as GPR6, GPR3, GPR18, GPR12, and GPR55, along with adenosine, serotonin, and opioid receptors are found to be modulated by CBD [143]. Along with GPCRs, Voltage-gated calcium channels (VGCC) increases calcium influx due to constant hyperpolarization and activation of NMDAR [144], and these are implicated in the aging and neurodegeneration [145]. The higher concentration of calcium ions affects Calcineurin (CaN) and CaMKII signaling pathways and results in memory deficits and stimulation of long term depression in AD [146-148]. Evidence represented by Ross et al. have shown that CBD acts as VGCC antagonist, and was able to fully inhibit T-type voltage-gated calcium channels (VGCCs), expressed from CaV3 gene [149]. Furthermore, CBD is also demonstrated to suppress L-type VGCC with IC_{50} of 0.1μM, where the effect was not mediated in a voltage-dependent manner [150]

Additionally, CBD also balances intracellular Ca^{2+} level, as the study found that CBD act as a transient receptor potential cation channel subfamily V1 (TRPV1) stimulant in HEK-TRPV1 cells, lacking any subtractive effects [151]. TRPV1 can act both as ion channel and receptor, and more prolonged activation of TRPV1 reduced pain through desensitization. TRPV1 can be activated upon any pain stimuli [152]. Some recent studies have indicated that TRPV1's channel unlocks upon activation, allowing ions to pass through the membrane from one side to another. Calcium passes over the pore systemically into the cell and activates various calcium-dependent pathways that finally lead to desensitization of the channel resulting in a reduction of inflammation pain [152-154]. Similarly, CBD exerts anti-hyperalgesic effects that may result from underlying peripheral and spinal activation via TRPV1 desensitization [155]. In vivo study shows that CBD derived TRPV1 agonistic activity can act as anti-inflammatory agents [154,156].

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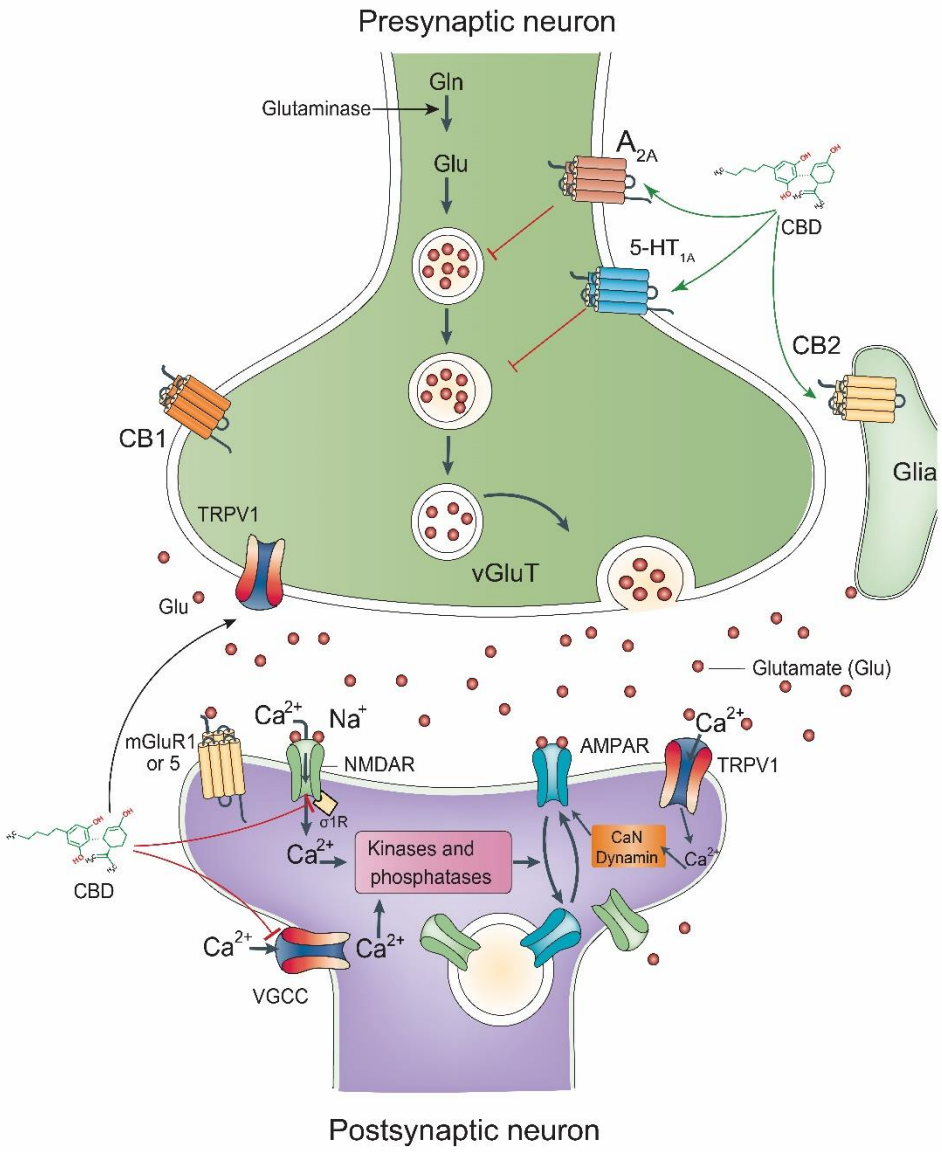

Figure 3. Effect of CBD on Ca^{2+} dynamics in the synapse. In the presynaptic terminal, glutamine is converted to glutamic acid by glutaminase enzyme, and packaged to synaptic vesicles through vesicular glutamate transporters (vGluTs). The agonistic activity of A_{2A} R in the presynaptic terminal enhances glutamates release, whereas CBD is reported to acts as an antagonist and thus blocks glutamate release. CBD also indirectly regulate glutamate secretion by 5-HT_{1A} receptor [157]. Upon the release, glutamates bind with NMDAR, AMPARs and mGluR1/5 receptors, which causes Ca^{2+} influx, and activates intracellular messenger cascades. The σ1R directly interacts with the cytosolic C-terminal region of the NMDA receptor, and regulate NMDAR activation. CBD inhibits the regulatory interaction between σ1R with NMDAR, and shows an opposite effect of NMDAR overactivity. Furthermore, CBD also acts as an antagonist of VGCC and TRPV1 antagonist and thus regulate intracellular calcium levels. CBD, Cannabidiol; $A_{2A,}$ Adenosine 2A receptor; 5-$HT_{1A,}$ Serotonin-1A receptor; NMDAR, N-methyl-D-aspartate receptor; AMPARs, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; and mGluR1/5, metabotropic glutamate receptors 1/5; VGCC,

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Voltage-gated calcium channels; TRPV1, Transient receptor potential cation channel subfamily V member 1.

CBD regulates proteostasis

Proteostasis is known as the protein homeostasis network that regulates all aspects of the cellular proteome, from protein synthesis to degradation. As a part of this network, there are several signaling pathways, which are usually activated in response to misfolded protein and protein aggregation, are also known as quality control systems [158]. Once a protein is misfolded, chaperone control systems assist protein folding and disaggregation; however, if escaped, clearance systems are activated, leading aggregates into proteolytic degradation [10]. The clearance system is consisting of two main types of machinery, including the ubiquitin-proteasome system (UPS) and autophagy, where UPS functions in cytoplasm and nucleus, while autophagy only in the cytoplasm [159]. The degradation is directed by unfolded protein response (UPR), that follows either UPS or autophagy, which can be in the form of macroautophagy, including mitophagy, microautophagy, and chaperone-mediated autophagy (CMA) [160].

During the unfolded protein response, misfolded peptides are recruited by GRP78; eventually, ERS, IRE1α, PERK, and ATF6 dissociate from the luminal domains of UPR^{ER} sensors, which promotes parallel downstream signalings to reduce protein load by activating protein degradation and transport pathway. Lim et al. identified that CBD can alter ER morphology and initiate signaling cascades of PERK, ATF6, and IRE1, and thus elicits an endoplasmic reticulum (ER) stress response, which is not mediated by cannabinoid receptor [161]. In oligodendrocyte progenitor cells, CBD (1 μM) decreased phosphorylation of eiF2α, enhanced Bcl-2 expression, and thus protected against OS, and similarly, those effects were not mediated through CB1, CB2, TRPV1 or PPAR-γ receptors [76]. Moreover, a study on cadmium (Cd)-treated differentiated neuronal cells, showed that CBD (1 μM) increased GRP78 upregulation and thus prevented Cd mediated ROS generation. Accordingly, CBD ameliorated Cd-induced neuronal injury, as well as prevent the cellular distribution of the cytochrome C, while down-regulated BAX [84]. CBD enhanced phosphorylation of PERK-chop and thus upregulated DR5 [162], where DR5/TRAIL-R2 signaling regulated UPR mediated cell death [163]. More recent studies showed that CBD regulated noxa ROS signaling pathway, resulting in the upregulation of IRE1α, PERK, Bip, GRP94, and CHOP in a dose-and time-dependent manner [164]. Moreover, due to the upregulation of CHOP, CBD can regulate Smac, which inhibits XIAP, and thus plays a role against mitochondrial damage [165].

The autophagy is considered as the non-selective system, where aggregates are degraded by the lysosome, while UPS is target-specific protein for lysosomal degradation using ubiquitins like cargo-recognition molecules and chaperons [166-168]. In this aspect, CBD is also reported to induce autophagy, appeared in several studies. The report represented by Shrivastava et al. showed that CBD could regulate autophagy by inhibiting AKT and mTOR signaling pathway by downregulating cyclin D1 and reducing the phosphorylation of mTOR and 4EBP1 (Figure 4) [169]. Similarly, CBD was also shown to induce autophagy in vivo, and prevented alcohol-mediated autophagy inhibition, while downregulating JNK MAPK pathway and OS [170]. Supporting this finding, Giacoppo and colleagues observed that CBD regulated in PI3K/Akt/mTOR pathway Encephalomyelitis (EAE) MS model and also promotes neuroprotection by inhibiting JNK and p38 MAP kinases [171]. Hossein Zadeh et al. showed that repeated treatment of 0.100 ng CBD as an intracerebroventricular injection in epileptic rats induce several autophagy markers such as conjugation of Atg5/12, Atg7, Atg12, and LC3II/LC3I expression, especially in hippocampal cells, confirming protective effect in epilepsy followed by autophagy pathway [172]. A study using Glioma stem-like cells suggested that induction of autophagy by CBD was triggered by activating transient receptor potential vanilloid-2 (TRPV2) [173,174], and thus increased response to radiosensitivity [175].

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Although the precise mechanisms of CBD remain to be further investigated, it is unlikely that activation of autophagy is mediated through CB1 receptor [176], which is localized in lysosomal compartments [177]. However, a very recent study showed that CBD could potentially inhibit BACH1 [81], which acts as a repressor of p62 expression, a component that involved in selective autophagy [178].

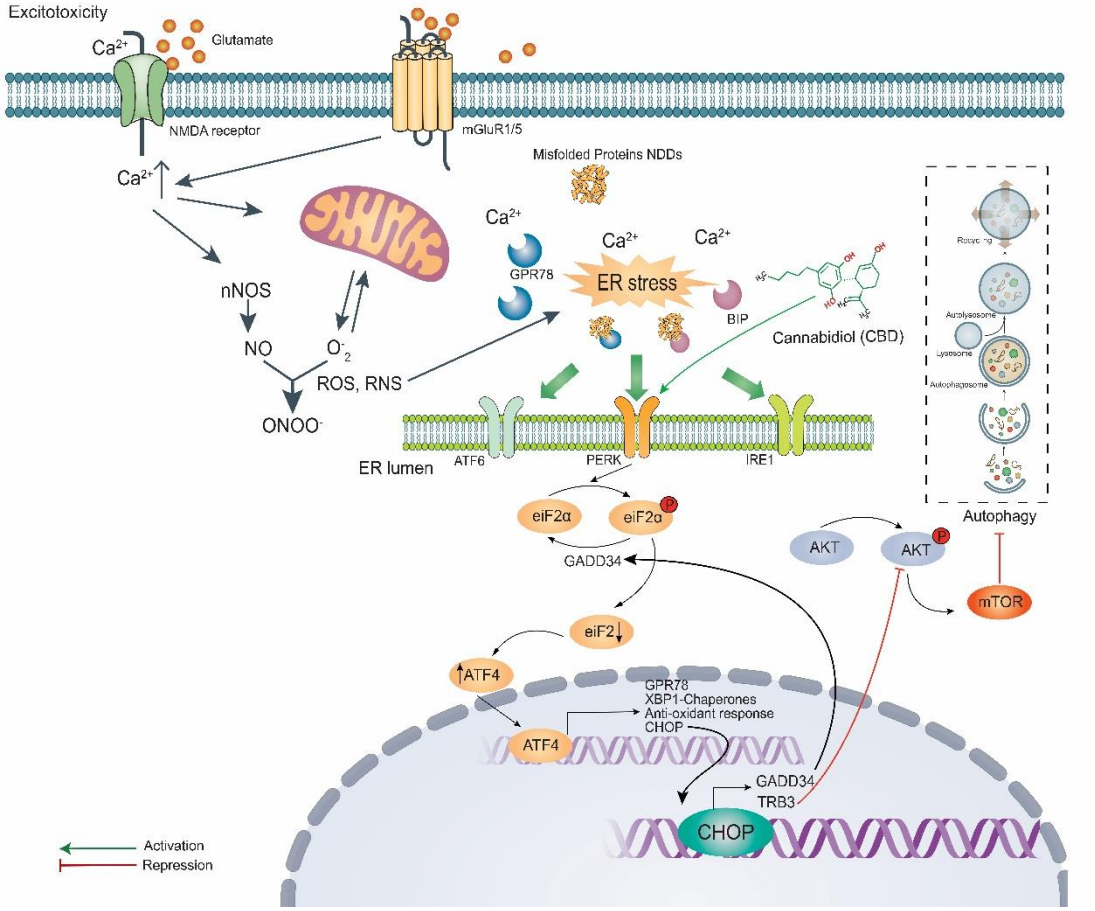

Figure 4. Proposed mechanism of CBD effects in the ER stress-related signaling pathway. In excitatory toxicity, the excessive glutamates overactive NMDAR function, which leads to Ca2+ influx, in turn, cause NO production. The ER stress is mediated by NO as well as by misfolded proteins, where misfolded protein bind to BIP and GPR78 and activates UPR, which comprises PERK, IRE1, and ATF6 pathways. Among them, CBD may regulate the PERK signaling pathway, and by doing so, it upregulates ATF4 mediated genes transcription, including CHOP and GRP78. The CHOP, which is a transcription factor, enhances TRB3 and GADD34 expressions. TRB3 inhibits AKT phosphorylation that subsequently inhibits mTORC1, and thereby promotes autophagy. The CHOP mediated gene transcription also promotes apoptosis in prolonged ER stress, when protein misfolding is not resolved, whereas, GADD34 acts as a negative regulator of eIF2α phosphorylation and hence halts pro-apoptotic signaling pathways. UPR, unfolded protein response; ER stress, endoplasmic reticulum stress, NMDAR, N-methyl-D-aspartate receptor; NO, Nitric oxide; GRP78/BIP, Immunoglobulin heavy-chain-binding protein; PERK, PRKR-like ER kinase; eIF2α, eukaryotic translation initiation factor 2α, ATF6, activating transcription factor 6α; ATF4, activating transcription factor 4, CHOP, C/EBP homologous protein; GADD34, growth arrest and DNA damage-inducible protein 34.

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Cannabidiol as a treatment of neurodegenerative disorders

Huntington's disease (HD)

Huntington Disease is a lethal, progressive neurodegenerative disorder, featured by motor impairment, cognitive deficits, and behavioral shortages that occur due to mutation of the huntingtin proteins [179]. The major pathogenic mechanisms underlying the neuronal dysfunction and death in HD include transcriptional dysregulation, altered proteostasis, mitochondrial dysfunction [180]. Impaired huntingtin proteins are also responsible for enhancing OS, dopamine toxicity, metabolic impairment, excitotoxicity, apoptosis, and autophagy [181]. The oxidative and inflammatory death of neurons can be reduced by activating anti-inflammatory PPAR-γ signaling [182]. For preclinical studies, there are many compounds such as histone deacetylase inhibitors, coenzyme Q10, minocycline, unsaturated fatty acids that have been tested to inhibit HD. However, the finding was not significant [183]. The application of CBD alone or, in combination with Δ9-THC (tetrahydrocannabinol), showed much efficiency in the preclinical evaluation of several experimental models of HD [184,185]. Abdel-Salam et al. found that CBD reduced neuroinflammation and microglial cell activation in HD models [186]. Da Silva et al. suggested that CBD has iron-induced anti-apoptotic effects on cognitive decline model system [187]. CBD also decreased the expression of HD biomarkers such as GPR3, GPR6, and GPR12, acting as an inverse agonist [188,189], while in another experiment, CBD showed neuroprotective activity in a rat model of HD [190]. A licensed drug Sativex® (a combination of Δ(9)-THC and CBD) showed positive effects against HD [191]. Valdeolivas et al. also found that Sativex® treatment reduced basal ganglial metabolism in R6/2 transgenic HD mice model [192]. Another study conducted by Moreno et al., however, claimed that treatment with sativex® in HD patients showed no changes in biomarkers of HD and no symptomatic adverse effects [193].

Alzheimer's disease (AD)

Alzheimer's disease (AD) is a chronic, neurodegenerative disorder which is characterized by the intra-neuronal neurofibrillary tangles, extracellular senile plaques, and neuronal atrophy [194]. Senile plaques are surrounded by dystrophic neurites, microglia, and astrocytes [195]. In AD, it is prominent to clear the aggregation of β-amyloid, and here microglia plays a vital role in the clearance of Aβ [196,197]. Evidence showed that CBD has a potential impact on AD-associated pathology [74,198]. Giuseppe Esposito et al. demonstrated that CBD promotes hippocampal neurogenesis through the association with PPAR-γ, prevented reactive gliosis, reduced Aβ induced inflammation by lowering pro-inflammatory cytokines and thus neurodegeneration in an AD rat model [40]. These neuroprotective roles of CBD against Aβ-induced toxicity are known to be attributed to its antioxidant and anti-inflammatory activities. An in-vivo experiment conducted by Watt & Karl showed that CBD ameliorated the cognitive deficits in a double transgenic AD mouse [199]. Some studies demonstrated that CBD enhanced APP ubiquitination, which subsequently decreased Aβ plaques by inhibiting the hyperphosphorylation of tau [200]. It was correlated with the decreased expression of Wnt signaling inhibitor p-GSK-3β. It is also evident that CBD decreases mitochondrial dysfunction and the production of reactive oxygen species through the activation of PPAR-γ and suppressing pro-inflammatory signaling in AD [201]. Singh & Abraham proposed that CBD inhibits reactive gliosis occurred by Aβ, which is an effective technique to slow down the growth of AD [202]. The activation of CB2 decreases the microglia activity and the production of inflammatory cytokines [203]. Harris et al. suggested that through the clearance of Aβ, CB2 agonists could lower Aβ plaque, whereas CBD act as an agonist [204]. Moreover, the toxicity of Aβ diminishes PI3K/Akt signaling, and interestingly, CBD down regulates GSK-3β expression and promotes PI3K/Akt signaling [171,200]. CBD also reduces the expression of β- and γ-secretase enzyme, which eventually decreases Aβ production [200].

Parkinson's disease

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Parkinson's disease (PD) is a progressive neurodegenerative disorder that is characterized by the lack of dopamine, deposition of α-synuclein, and the gradual loss of dopaminergic neurons [205,206]. The symptoms of PD in the early stages are shaking, gait abnormality, spasticity, and slow thinking capacity. The pathogenesis of PD is associated with neuroinflammation and oxidative damage to the neurons [207]. In PD rodent models, CBD influenced the levels of SOD mRNA, increased the expression of antioxidant zinc homeostasis gene, and reduced OS [76,208,209]. A series of the study verified the activity of CBD in PD patients, where they showed CBD ameliorate the quality of life, reduced sleep disorder, provide antidepressant and anxiolytic activity [210,211]. The effects of CBD in PD have also been validated in animal models such as 6-hydroxydopamine-lesioned PD rats in which the antioxidant properties of CBD protected the eventual degeneration of nigrostriatal dopaminergic neurons [209,212,213]. Lotan et al. suggested that CBD lowered gliosis, free radicals, amyloid, tau deposition, iNOS, oxidized-GSH, and influenced autophagy, and complex IV in PD mouse model preclinical study [214]. In an experimental trial, the administration of CBD reduced the tremor amplitude in PD patients [215], and CBD could be a promising drug to treat non-motor symptoms of PD [216]. Fernanda F. Peres et al. showed that CBD could reduce reserpine-induced motor and cognitive impairment in AD model rats [217].

Furthermore, previous results from several clinical trials suggested that CBD is beneficial while conjugating with Δ(9)-THC in alleviating symptoms linked to PD like dystonia but not in symptoms such as tremor [218-220]. Again, the promising neuroprotective effects of CBD have been observed in vitro studies on PD models [221]. Santos et al. reported the CBD-mediated neuroprotection against MPP^+-induced neurotoxicity in PC12 that involved induction of neurite differentiation, expression of synaptic (synaptophysin and synapsin I) and axonal (GAP-43) proteins and the activation of tropomyosin receptor kinase A (TrkA) receptors [221].

Multiple sclerosis (MS)

Multiple sclerosis (MS) is an inflammatory demyelinating disease, which destroys the spinal cord and brain nerve cells of the CNS [222], and considered to affect the young and middle-aged individuals [223]. It impedes signal transmission with the following symptoms; trouble with sensation or coordination, blindness in one eye, double vision, muscle weakness, and bladder dysfunction [224,225]. The downregulation of PI3K/AKT/mTOR pathway is known to be associated with the pathogenesis of MS [226]. However, several studies suggested that MS disease has complicated pathophysiology, and immunotherapy was not so responsive in the progressive stages of MS [227-229]. The previous study indicated that the use of cannabis reduces MS symptoms [230]. The cannabis-based compounds such as CBD was used to alleviate pain and spasticity in MS [231,232]. In an EAE model of MS, Elliott et al., found that CBD reduced T cell penetration, IFNγ, and IL-17 and increased MDSCs (myeloid-derived suppressor cells) with attenuation of EAE [233]. Kozela et al. found that the pathogenic activity of Th17 cells was decreased after CBD treatment [102].

Moreover, CBD reduced microglial activity, leukocyte homing, and inflammation in TMEV-IDD and EAE model. Besides, CBD reduced blood leukocyte migration by reducing VCAM-1, CCL2 and CCL5, TNFα/IL-1β, and microglial activation [39]. Giacoppo et al. observed that phosphorylation of PI3K, Akt, and mTOR was significantly increased together with BDNF expression and reduced the expression of proinflammatory cytokine IFN-γ and IL-17 after CBD treatment. CBD was also acted as an antagonist to JNK and p38 MAP kinases [171]. Indeed, THC combination with CBD as an oromucosal spray (Sativex®) was established as a potential therapeutic agent for mitigating MS symptoms [234]. The combination of THC: CBD oromucosal spray was able to decline MS spasticity [235].

Furthermore, the CBD/THC transdermal treatment (Sativex R) has been proven to be useful to relieve pain associated with MS in a new study of cannabis-based therapy for neuropathic pain [236]. Further research reported that the CBD/THC combination is capable of reducing sleep and pain disorders and is

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broadly accepted in patients with MS-related chronic neuropathic pain [237]. Croxford al., reported that CBD could be more effective in neuroprotection that in immunosuppression. Moreover, a substantial reduction of urinary pressure, a decrease of bladder control, volume, and excessive urination frequency have been demonstrated in combining THC/CBD treatment [238]. Overall, the pharmacological properties of THC/CBD may provide an overview of its clinical efficacy and tolerability in spasticity and other MS-related symptoms [239].

Prion Diseases

Prion diseases occur due to the abnormal assembly of the protease-resistant prion protein (PrPres) aggregates on the surface of many cells forming clump in the brain, causing brain damage, which split the typical tissue structure. As vacuole forms in the neurons, some holes are formed in the tissue like spongy architecture [240,241]. The PrPres aggregates cause extensive ER stress, which subsequently disrupts Ca^{2+} homeostasis. The maintenance of Ca^{2+} homeostasis is an essential event for continuing neuronal signaling Ca^{2+} released in the cytoplasm when cells are exposed to the misfolded prion proteins [242-244]. Mecha et al. found that CBD attenuated ER stress and induced an anti-apoptotic pathway [76]. Cannabinoids, including CBD, have shown to protect against brain injury. PrPres assembly was inhibited by the treatment of CBD in mouse and sheep scrapie-infected cells. Peripheral CBD injection restricted PrPres cerebral accumulation and increased the lifespan of the infected mice after intraperitoneal infection [241].

Additionally, it has been found that neurons trigger microglial cell migration in response to PrPres exposure [245]. CBD reduced neurotoxic impacts of PrPres, and microglial cell migration is activated by affected PrPres in a concentration-dependent manner [241]. Thus, during the prion infection, CBD may tend to prevent neurons in the diverse stages of the neurodegenerative treatment against the multiple molecular and cellular influences. As a corollary, CBD could be a favorable drug showing anti-prion properties, which to be used in prion disease, but it requires high concentration of CBD to achieve its survival efficacy [241].

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a progressive and lethal neurodegenerative disease, which affects both lower and upper motor neurons, resulting in spasticity, weakness, and, lastly, death due to respiratory collapse [246,247]. Although the pathobiology of ALS much remains unknown, like other NDDs, the pathogenic mechanisms, including OS, inflammation, excitotoxicity, mitochondrial dysfunction, and protein misfolding, are also known to be involved in ALS [28,248]. Having antioxidant, anti-inflammatory, and neuroprotective potentials, CBD has shown to attenuate ALS pathology in various experimental evidence [28,249].

As an in vitro ALS model, treatment of human gingiva-derived mesenchymal stromal cells with CBD modulated the expression of genes associated with ALS pathologies, such as OS, mitochondrial dysfunction, and excitotoxicity [250]. CBD upregulated the expression of Nrf2, mitochondrial respiration maintenance genes, i.e., SDHC1, NDUFC2, and NDUFV3, and downregulated cell death-inducing genes, i.e., CABIN1, PPP3CC, HTRA2, and TARBP2. The evidence that the expression of CB2 receptors has been reported in activated microglia from the spinal cord of human ALS patients suggests the possibility that CBD, a CB2 agonist, may provide therapeutic impacts in ALS at the clinical level. A recent phase 2 trial (CANALS study) demonstrated that THC: CBD was able to lessen the spasticity in ALS [251]. Finally, treatment satisfaction by the patients has studied in which 84% of patients experienced positive effects on

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THC: CBD treatment in ALS [252]. A randomized, double-blind, placebo-controlled trial evaluating the efficacy of CBD oil (CBD:THC = 25:<2) has shown to slow the ALS progression [253].s

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Table 1: Pre-clinical and clinical evidence of CBD in the treatment of Neurodegenerative disorders

Disease	Drug combination	Experimental model (in vivo/ in vitro)	Dose	Cellular findings	Molecular pharmacology	References
Huntington Disease		Adult wistar rat model	10 mg/kg	• ↑ anti-apoptotic action	• ↓ caspase 9, APAF1, Caspase 3 and cleaved PARP levels	[187]
		Affymetrix GeneChip microarray samples of caudate nucleus, frontal cortex and cerebellum			• ↓ GPR3, GPR6, and GPR12 expression	[188]
		Male Sprague–Dawley rats	5 mg/kg	• Protect against oxidative stress • ↓ GABAergic injury	• ↓ mRNA level of SOD-1, SOD-2	[190]
	THC	R6/2 mice HD model	4.5 mg/kg	• ↓ basal ganglial metabolism		[192]
	THC	Human (age: 18-35years)	10mg of THC, 600mg of CBD	• ↓ blood oxygenation level– dependent signal		[193]
	THC	HD patients, older than 18 years	12 sprays/day; 2.5 mg CBD per spray	• no changes in biomarkers of HD		[254]

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Alzheimer's disease		PC12 neuronal cells		• ↓ tau hyperphosphorylation	• ↑ Wnt/β-catenin pathway • ↓ p-GSK3β	[74]
		Mice inoculated with human Aβ42 peptide	2.5, 10 mg/kg	• Protect against oxidative stress • ↓ reactive glisosis	• ↓ iNOS • ↓ IL-1β expression	[198]
		Adult male Sprague-Dawley rat model		• ↓ Aβ induced inflammation • ↓ reactive gliosis	• ↑ of PPAR-γ • ↓ NO, TNFα, and IL-1β expression	[40]
		PC12 neuronal cells		• Protect against oxidative stress • ↓ Aβ neurotoxicity	• ↓ ROS production • ↓ lipid peroxidation, caspase 3 level	[75]
		SH-SY5YAPP+ Cells		• ↑ APP ubiquination • ↑ cell viability	• ↑ PPAR-γ activation	[255]
		Gingiva derived mesenchymal stem cells	5 μM	• ↓ tau hyperphosphorylation • ↓ Aβ production	• ↑ PI3K/Akt signaling cascade • ↓ GSK3β, CDK5, DYRK1A, CAMK2A,and the MAPKs (MAPK1, MAPK12, and MAPK14) expression	[200]
		Mice intraventricularly injected with fibrillar Aβ	20 mg/kg	• ↓ microglial activation		[256]
	THC	Young APPxPS1 transgenic mice	10 mL/kg (0.75 mg/kg each)	• ↓ Aβ42 peptide levels • ↓ astrogliosis and microgliosis	• ↑ Mapk3 and Wnt16 sig-705naling pathways • ↓ ERK1 phosphorylation	[257]
	THC	Aged APPxPS1 transgenic mice	10 mL/kg (0.75 mg/kg each)	• ↓ cognitive deficits • ↓ glial reactivity	• ↓ GluR2/3 expression • ↑ GABA-A Rα1 expression	[258]

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	THC	Transgenic tauopathy mouse model	4.63 mg/kg (CBD: 1.5 mg/kg)	• Protect against oxidative stress • ↓ astrogliosis and microgliosis	• ↓ iNOS level • ↑ complex IV expression	[259]
Parkinson's disease		6-OHDA/rat	3 mg/kg	• ↓ oxidative stress • ↓ glial cell activation	• ↓ ROS • ↑ mRNA levels of Cu, Zn-SOD	[209]
		6-OHDA/rat	3 mg/kg	• ↑ dopaminergic transmission	• ↓ mRNA levels of tyrosine hydroxylase	[212]
		In vitro retinoic acid (RA)-differentiated neuroblastoma SH-SY5Y cells with the toxin MPP+	10 μM	• ↓ loss of cell viability	• ↑ ERK and AKT/mTOR pathway • Downregulate PARP-1 levels	[215]
		Reserpine-induced Mice model	0.5-5 mg/kg	• ↓ catalepsy, memory deficits	• ↑ 5-HT1A receptor activation	[217]
		Human (age: >45 years); placebo controlled trials	75 mg/kg and 300 mg/kg; 6 week	• ↓ REM related sleep behavior disorder • ↑ antidepressant and anxiolytic activity		[210]
		Male swiss mice	30, 60 mg/kg	• ↓ catalepsy	• ↓ c-Fos protein expression • ↑ 5-HT1A receptor activation	[260].
		PC12 and SH-SY5Y cell	1, 5, 10, 25 and 50μM	• ↑ cell viability	• ↑ TrkA receptors • ↑ GAP-43, synaptophysin and synapsin I expression	[221]
		Experimental autoimmune	215 mg/kg	• ↓ disability and disability progression • ↓ pain and spasticity	• ↓ TNF-α production • ↑ BDNF gene expression	[261]

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Multiple Sclerosis disease		encephalomyelitis (EAE)-induced Rat model				
		Experimental autoimmune encephalomyelitis (EAE)-induced Mice model	20 mg/kg	• ↑ myeloid-derived suppressor cell • ↓ cellular infiltration and tissue damage	• ↓ T cell penetration • ↓ IFNγ and IL-17 levels	[233]
		in vitromodel of stimulated TMOGcells co-cultured with spleen-derived CD19+B cells and other accessory CD4+cells	5 μM	• ↓ TH17-driven autoimmunity • ↓ pro-inflammatory avtivity	• ↑ of CD69 and LAG3 levels • ↓ CD25 and CD69 levels • ↑ EGR2 transcription • Reduce Akt activation	[102]
		TMEV-IDD susceptible Mice model	5 mg/kg	• ↓ leukocyte transmigration • ↓ microglial activation	• ↓ VCAM-1, CCL2 and CCL5 expression • ↓ IL-1β levels	[39]
		Experimental autoimmune encephalomyelitis (EAE)-induced Mice model	10 mg/kg	• ↑ neuronal survival • ↓ inflammation • ↓ JNK and p38 MAP kinases	• ↓ PI3K/Akt/mTOR pathway • ↑ BNDF level • ↑ PPAR-γ • Decrease IFNγ and IL-17 levels	[171]
	THC	Human (age: >50 years); placebo controlled trials		• ↓ pain and spasticity		[235]
	THC	Human (age: ≥18years); placebo-controlled trials		• ↓ neuropathic pain		[236]

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	THC	Human (age: 18-65 years)	2.5 mg of each per spray	• ↓ pain, spasticity • ↑ quality of sleep • ↓ excessive urination frequency		[262]
Prion disease		mice and sheep scrapie-infected cells	5 μM	• ↓ PrPres accumulation • ↓ PrPre-induced microglial cell migration	• ↓ NMDA receptor action	[241]
Amyotrophic lateral sclerosis (ALS)		human gingiva-derived mesenchymal stromal cells (hGMSCs)		• Control oxidative stress • Control mitochondrial dysunction	• ↑ NFE2L2, TRAP1 gene expression • ↑ SDHC1, NDUFC2, and NDUFV3 gene expression • ↓ CABIN1, PPP3CC, HTRA2, and TARBP2 gene expression	[250]
	THC	Human (age:18-80 years); placebo-controlled trials	100 μL (2·7 mgTHC and 2·5 mg CBD)	• ↓ spasticity	• ↓ presynaptic Ca^{2+}influx • ↓ glutamatergic neurotransmitters release	[251]

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Concluding remarks and future perspectives

OS and neuroinflammation affect the integrity of the proteostasis network and thereby play a pivotal role in the pathogenesis of neurodegenerative diseases by affecting the integrity of the proteostasis network. Because of the involvement of the endocannabinoid systems in OS modulation, CBD may count as an interesting molecule, as it is has shown to provide antioxidant and anti-inflammatory effects in various preclinical models. However, the precise mechanisms of CBD is remained to elucidate, especially in the activation of protein aggregates clearance systems.

Although multidirectional studies provide clear evidence of CBD mediated autophagy induction, however, neuronal system-based studies are limited, and the molecular pharmacology is also poorly understood. Furthermore, studies showed that autophagy as a double edge sword might induce either death or survival mechanism, suggesting the need for future study, as the phenomenon of the activation and activating receptors are unlike with different cell types.

Recently, Scott et al. showed that CBD treatment modulated HSPs expression, notably upregulated HSP70 and HSP90 in glioma cell lines [263]. Substantial evidence highlighted the critical roles of HSP70 and HSP90 in the quality control and clearance of the misfolded and aggregated proteins by the ubiquitin-proteasome system and chaperone machinery [264]. Additional observation by Rodríguez-Muñoz et al. stated that CBD act as an antagonist of σ1R, which has been identified as a master regulator of proteostasis system [265]. The antagonist of σ1R is responsible for the induction of unfolded protein response and autophagy in dose dependent manner [266], and also modulate HSP70 regulations [267]. Furthermore, CBD promoted cytosolic degradation of BACH1, which, according to another study, is mediated through the ubiquitin-proteasome system [268]. Thus these findings provide a clue that CBD can regulate both the ubiquitin-proteasome system and chaperone machinery. Maintenance of intracellular Ca^{2+} homeostasis is an essential function of ER, if disturb, stress in ER induced that endorsed misfolded protein accumulation. Since CBD regulates both glutamate release and NMDAR activation, it can protect neurons from glutamate excitotoxicity and ER stress-mediated injuries. Although several comprehensive reviews [30,95,97,114] suggest that CBD regulation in OS and inflammations is likely to mediate by CB1, CB2, TRPV1 or PPAR-γ receptors, but none of the receptors is reported to implicate when studies showed CBD effect in mitigating OS in ER stress response [269]. Furthermore, the molecular insights into the activation and regulation of PERK, IRE1, and ATF6 pathways are still unclear. Thus understanding the ROS regulation by CBD is still far away and deserves more studies, especially in neuronal models.

As represented in Table 1, CBD and its combination with THC provide therapeutic benefits for various neurodegenerative disorders. However, most of the findings were based on short term effects, and the preclinical studies barely used transgenic models, and future studies should, therefore, be designed to analyze long term effects analysis, as well as using transgenic mouse models. Although studies discussed in this review suggest therapeutic benefits of combination therapy with CBD, care must be taken when choosing drug combination, as the study showed induction of serum ALT and AST, and also inactivation of cytochrome P450 3A and P450 2C in CBD therapy [270]. Furthermore, combination therapy may facilitate the drug interaction that could be antagonistic to reduce the pharmacological efficacy of the compounds.

Finally, this review suggests a "proof of principle" of CBD regulation in proteostasis network, especially in the activation of protein clearance systems, that would offer a therapeutic window in protein aggregates clearance and thus to reverse proteinopathies. The discussed studies in this communication are promising; however, they provide preliminary data. Therefore, we suggest advanced research to investigate the CBD effect in protein aggregates clearance on the various disease model of neurodegeneration.

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