Biomedicine & Pharmacotherapy 186 (2025) 118044

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Cannabinoid Receptor 2 (CB2R) as potential target for the pharmacological treatment of neurodegenerative diseases

Ramona Meanti [a], Elena Bresciani [a], Laura Rizzi [a,*], Laura Molteni [a], Silvia Coco [a], Robert J. Omeljaniuk [b], Antonio Torsello [a]

[a] School of Medicine and Surgery, University of Milano-Bicocca, Via Cadore 48, Monza 20900, Italy
[b] Department of Biology, Lakehead University, 955 Oliver Rd, Thunder Bay, Ontario P7B 5E1, Canada

ARTICLE INFO

Keywords:
Cannabinoid receptor 2
NeuroHIV
Alzheimer's disease
Parkinson's disease
Amyotrophic Lateral Sclerosis
Multiple Sclerosis
Huntington's Disease

ABSTRACT

The endocannabinoid system (ECS) is a ubiquitous physiological system that plays a crucial role in maintaining CNS homeostasis and regulating its functions. It includes cannabinoid receptors (CBRs), endogenous cannabinoids (eCBs), and the enzymes responsible for their synthesis and degradation. In recent years, growing evidence has highlighted the therapeutic potential of the ECS and CBRs, in a wide range of severe diseases and pathological conditions, including Alzheimer's and Parkinson's diseases, Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Huntington's Disease, HIV-1 associated neurocognitive disorders, neuropathic pain and migraine. Targeting the cannabinoid type 2 receptor (CB2R) has gained attention due to its ability to (i) mitigate neuroinflammatory responses, (ii) regulate mitochondrial function and (iii) provide trophic support, all without eliciting the psychotropic actions associated with CB1R activation. This review aims to explore the potential of CB2R modulation as a strategy for the prevention and treatment of neurologic disorders, exploring both preclinical and clinical findings.

1. Introduction

The endocannabinoid system (ECS), discovered in 1988 by Allyn Howlett and William A. Devane, is a key physiological system that regulates various processes crucial for human health [1].

ECS consists of three main components including (i) endogenous endocannabinoids (eCBs), namely anandamide (AEA), 2-arachidonoylglycerol (2-AG), virodhamine (O-AEA), N-arachidonoyldopamine (NADA), N-oleoylethanolamide (OEA) and N-palmitoylethanolamide (PEA) (Table 1), (ii) cannabinoid receptors (mainly CB1R and CB2R, but also the recently found orphan receptor GPR55) and (iii) various enzymes required for synthesizing and degrading eCBs [2–4]. More recently, nuclear receptors such as peroxisome proliferation-activated receptors (PPARs) have been recognized as interacting with the ECS [5]. Additionally, the non-selective cation channel type 1 vanilloid receptor (TRPV1) [6] has also been identified as an endocannabinoid receptor.

CB receptors (CBRs) are implicated in various physiological processes and have gained attention as promising therapeutic targets for several diseases. Interestingly, CB1R and CB2R are phylogenetically ancient and different studies suggest that CBRs occur in mammals, birds, amphibians, fish, sea urchins, molluscs, leeches and *Hydra vulgaris* [16].

CBRs are widely expressed in several tissues:

- CB1R, initially identified in rats [1], is encoded by the gene *Cnr1* and consists of 472 amino acids. CB1R is the most abundant in the central nervous system (CNS), in adipocytes and the pituitary gland.
- CB2R, discovered in 1993, consists of 360 amino acids and is encoded by the gene *Cnr2*. Although initially thought to be restricted to peripheral tissues (it was originally named the 'peripheral cannabinoid receptor'), mainly expressed in intestinal and lymphoid tissue [17]; however, recent research has revealed that the CB2R is also expressed in the CNS, where its role in neurodegenerative diseases is under active investigation [18].

Both receptors belong to the A class of G-protein-coupled receptors (GPCR) sharing about 44 % of sequence homology and 68 % of homology in their transmembrane domains. The main differences concern

* Correspondence to: School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy.
E-mail addresses: ramona.meanti@unimib.it (R. Meanti), elena.bresciani@unimib.it (E. Bresciani), laura.rizzi@unimib.it (L. Rizzi), laura.molteni@unimib.it (L. Molteni), silvia.coco@unimib.it (S. Coco), romeljan@lakeheadu.ca (R.J. Omeljaniuk), antonio.torsello@unimib.it (A. Torsello).

https://doi.org/10.1016/j.biopha.2025.118044
Received 28 December 2024; Received in revised form 25 March 2025; Accepted 3 April 2025

Table 1
Endogenous endocannabinoids and biological activities in relation to binding to specific receptors.

eCBs Name	Activity Agonist/ Antagonist	Effects	References
N-arachidonoyl-ethanolamide/ Anandamide (AEA)	TRPV1 - < CB1 - < < CB2	- Treatment of inflammatory, respiratory and cardiovascular disorders - Antiproliferative action - Regulation of autoimmune disease	[7] [8] [9]
2-arachidonic glycerol (2-AG)	CB1-CB2	- Modulation of pain	[10]
O-arachidonoyl ethanolamine/ Virodhamine (O-AEA)	CB2 CB1	- Regulation of inflammation	[11] [12]
N-arachidonoyldopamine (NADA)	CB1	- Role in nociception and inflammation	[13]
N-oleoylethanolamide (OEA)	TRPV1-PPARα GPR119	- Inhibition of food intake - Reduction of body weight - Modulation of lipid and glucose metabolism	[14]
N-Palmitoylethanolamide (PEA)	PPARα GPR55 GPR119	- Anti-inflammatory actions	[15]

the N-terminal domain, the second extracellular loop (ECL2), and the C-terminal domain [19]. The CB1R and CB2R are primarily coupled to inhibitory Gαi/o proteins, but may also interact with stimulatory G proteins such as Gαs and Gαq/11 depending on the cell or tissue type [20]. GPCR activation typically leads to phosphorylation of G protein receptor kinases (GRKs), which in turn recruit β-arrestins 1 and 2, thereby triggering receptor desensitization and internalization [21,22].

Besides the classical signal pathways, both receptors exhibit non-canonical signalling; for instance, CB2R activation in endothelial cells and insulinoma β-cells results in calcium level increases mediated by a PLC pathway [6,23]. Evidence suggests that CB1R and CB2R can form heterodimers, which may affect their signalling properties; for example, CB2R antagonists have been shown to block CB1R-mediated effects, and vice versa [24]. Additionally, the CB2R can form heterodimers with other receptors such as the C-X-C Motif Chemokine Receptor 4 (CXCR4) [25].

Although extensive research is still required, recent investigation of ECS activity has shown therapeutic promise in a wide range of different diseases and pathological conditions, ranging from mood and anxiety disorders, motor disorders such as Parkinson's and Huntington's Disease, neuropathic pain, multiple sclerosis and spinal cord injury, cancer, atherosclerosis, and many other conditions [26,27].

2. Differential expression of CB2R in the neural cells

CB2R is differentially expressed in various neuronal cell types, with notable variations across the CNS. Recent evidence has revealed significant expression of CB2R in CNS cells, particularly in microglia and neurons.

2.1. CB2R Expression in Microglia

CB2R was originally considered the "peripheral receptor", due to its high expression in the immune system and spleen [22,28]. However, advancements in molecular biology techniques allowed for the detection of CB2R in the brain, both at mRNA and protein levels [29,30]. Initial evidence of CB2R expression in the CNS emerged from studies on microglia, the brain resident immune cells [31–33]. Microglial CB2R expression varies upon cell activation state; it is low or undetectable in resting microglia, but significantly increases upon activation [28,31,32,34,35]. Since CB2R primarily mediates the immunosuppressive and anti-inflammatory effects of ECS [36], its activation is thought to modulate neuroinflammation by promoting a switch in microglial phenotype from a pro-inflammatory state to a protective one [37]. In activated microglia, CB2R stimulation leads to increased production of endocannabinoids such as 2-AG and AEA, which enhances the anti-inflammatory response through downstream CB1R and CB2R signalling cascades [27,32]. This dynamic regulation of CB2R underscores its functional significance in neuroinflammation and highlights its potential as a therapeutic target.

Notably, microglia not only express CB2R but also synthesize and degrade eCBs. Microglia express biosynthetic enzymes like NAPE-PLD, DAGLα, and DAGLβ and degrading enzymes like FAAH and MAGL, which hydrolyze 2-AG and AEA into arachidonic acid and ethanolamine, respectively [22,28,30,31,33,34,38–41]. Under neuroinflammatory conditions, microglia can produce approximately 20 times more eCBs than neurons and other glial cells *in vitro*, making them the main cellular source of eCBs in these conditions [32]. This ability highlights CB2R as a promising therapeutic target for neuroinflammatory conditions, where its activation may help restore the balance between the beneficial and harmful effects of inflammation, ultimately promoting neuroprotection and functional recovery [42–46].

2.2. Role of CB2R in neuronal cells

Beyond inflammation control, CB2R modulates neuronal activity, impacting neuronal excitability, synaptic transmission and plasticity, neurotransmitter release, ionic currents and membrane potential. Electrophysiological studies demonstrated that CB2R activation reduces neuronal excitability in various brain regions [47,48], modulating also neurotransmitter release. CB2R neuroprotective effects vary within a region- and in a cell type-specific manner, impacting neurons, astrocytes, microglia, and oligodendrocytes, thus influencing neurodegeneration, protection, and repair.

In vitro studies have shown that CB2R activation reduces the release of neurotransmitter, such as GABA, glutamate and dopamine in the nucleus accumbens [49–51]. In contrast, CB2R activation increased dopamine and serotonin levels in a rodent model of Parkinson's disease and reduced ischemia-induced glutamate release in the hippocampus [52]. Several studies have also shown that CB2R activation regulates calcium influx [47,53] and interacts with ion channels such as GIRKs and HCN channels [47,54]. Moreover, CB2R influences synaptic plasticity by regulating long-lasting hyperpolarization in hippocampal CA3 pyramidal neurons and cortical interneurons [55].

Several findings highlight CB2R's potential in treating neurodegenerative disorders like Parkinson's and Alzheimer's by preventing neuronal apoptosis and degeneration. In models of AD, PD, and ischemia, CB2R agonists such as WIN55,212–2 and beta-caryophyllene reduced oxidative stress, prevented neuronal apoptosis, and modulated neuroinflammatory pathways [56–58]. In AD models, chronic CB2R activation protected long-term potentiation (LTP) in hippocampal neurons [59].

Overall, CB2R represents a promising target for developing treatments for oxidative stress-related neurological and inflammatory disorders.

2.3. CB2R Expression in Neurons

CB2R expression in neurons remains controversial due to limitations in detection specificity. To date, both CB2R mRNA and protein have been detected in several brain regions and cell types under physiological conditions [29,60].

Techniques like Reverse Transcription-quantitative real-time Polymerase Chain Reaction (RT-qPCR) and *in situ* hybridization (ISH) have consistently demonstrated the presence of CB2R mRNA in the neocortex, amygdala, nucleus accumbens, ventral tegmental area (VTA), globus pallidus, brainstem, hippocampus, cerebellum, hypothalamus and retina [29,60–62].

Using RT-qPCR and a highly sensitive *in situ* hybridization technique (RNAscope), Li and colleagues [28] showed that CB2R mRNA is expressed in both glutamatergic and GABAergic hippocampal neurons in mice, with no significant age-related changes from one week of age to adulthood. Moreover, consistent with previous results, they did not detect CB2R mRNA in microglia of healthy animals [28].

2.4. Improving Specificity and Sensitivity in CB2R Protein Detection

Different studies have also reported the presence of CB2R protein in the same regions where CB2R mRNA is detected, including the hippocampus, VTA, brainstem, retina, cerebellum, amygdala and hypothalamus [29]. However, limitations in antibody specificity and sensitivity cause challenges in reliable detection of CB2R protein [28,29,62].

The use of CB2R-knockout ($CB2R^{-/-}$) mice could represent a promising model for investigation of solution to investigate CB2R specificity in the brain [28,60,63]. The first $CB2R^{-/-}$ mice, developed by Buckley and colleagues [64], have been used to map CB2R tissue functions, assessing its involvement in different physiological processes and diseases, and verifying the specificity of CB2R agonists, antagonists and antibodies [63]. Studies have confirmed CB2R expression in different brain regions of wild-type mice, but not in the corresponding regions of $CB2R^{-/-}$ mice, highlighting the specificity of CB2R in the brain [18,63].

2.5. CB1R-CB2R Cross-Talk in Neural Cells

The cross-talk between CB1 and CB2 receptors (CB1R-CB2R) in neural cells represents a complex interplay that modulates various physiological and pathological processes, including neuroprotection, neuroinflammation, and synaptic plasticity.

The mode of this interaction is not unique but there are several mechanisms to explain CB1R-CB2R cross-talk:

1. CB1R-CB2R Heterodimerization. Studies have shown that CB1R and CB2R can form functional heterodimers in neural cells. This direct receptor-receptor interaction modulates intracellular signalling, influencing pathways such as Akt phosphorylation and neurite outgrowth [24,65].
2. Intracellular Signalling Convergence. Despite CB1R and CB2R coupling to different G-proteins (CB1R mainly to Gi/o and CB2R primarily to Gi), their downstream pathways often overlap, influencing ERK/MAPK, PI3K/Akt, and NF-κB signalling. These interactions fine-tune responses related to cell survival, inflammation, and oxidative stress [24].
3. Ligand-Dependent Modulation. Endocannabinoids such as 2-AG and AEA can activate both CB1R and CB2R, leading to context-dependent effects. For example, CB1R activation promotes neuroprotection, whereas CB2R activation primarily modulates neuroinflammatory responses [62].
4. Interaction with Other Receptor Systems. CB1R and CB2R cross-talk with other receptor systems, such as somatostatin receptors (SSTRs). Activation of either SSTRs or CB1R leads to neuroprotective effects by modulating cell survival pathways, particularly ERK1/2, against quinolinic acid-induced excitotoxicity [66].

From the point of view of functional implications, the CB1R-CB2R crosstalk affects neurogenesis in key neurogenic niches, such as the subventricular zone (SVZ) and the dentate gyrus (DG). This interplay regulates proliferation, differentiation, and migration of neural progenitor cells [67]. Moreover, the interaction between CB1R and CB2R plays a crucial role in neuroprotection and neuroimmune modulation, and presents a significant therapeutic potential for neurodegenerative and neuroinflammatory diseases [65,68].

Collectively, these findings suggest CB2R as a promising therapeutic target for modulating neuroinflammation. However, it is essential to note that ECS components in microglia vary depending on the specific type of pathology. Therefore, to optimize future possible therapies, further studies are needed in order to define more explicitly how microglia and the ECS interact in different developmental stages of each CNS disorder.

3. CB2R as a therapeutic target

The endocannabinoid system (ECS) exerts multiple physiological and pathophysiological effects, thereby making its components promising drug targets for various conditions [3,69–71]. Among these effects, CB2R has gained significant attention due to its antioxidant, anti-inflammatory, immunomodulatory and anti-apoptotic properties demonstrated in the absence of the adverse psychotropic effects typically associated with CB1R activation [72].

The development of agonists and antagonists targeting CB1R and CB2R has become a dynamic field of research; while CB1R agonists show potential in treating pain, inflammation, multiple sclerosis, and neurodegenerative diseases, CB1R antagonists may be beneficial for treating obesity-related metabolic disorders, mental health issues, liver fibrosis, and nicotine addiction [73]. Similarly, CB2R agonists are being investigated for treating inflammatory and neuropathic pain, neuroinflammation, and neurodegenerative pathologies, and modulating immune system responses [20]. Unlike CB1R, targeting CB2R offers therapeutic benefits without psychotropic effects, making it an attractive target in conditions requiring long-term treatment.

Despite these advances, a critical issue to address is the development of ligands that selectively target CB2R over CB1R, as many current compounds lack receptor specificity [20]. To address this issue, recent advancements in molecular modeling, including modern molecular dynamics simulations and computational approaches, have been helpful in predicting binding affinities and identifying receptor-subtype-specific compounds. These methods provide new insights into drug-receptor interactions at the atomic level, offering valuable data for the design of selective CB1R and CB2R ligands. Moreover, analyzing the free energy of ligand-residue interactions allowed the identification of specific binding sites, helping to design modulators that are potent, selective, and functionally specific for each receptor subtype [74].

In conclusion, while CB2R represents a promising therapeutic target for a wide range of conditions, further research into its structure and the development of receptor-specific ligands are critical steps toward realizing its full therapeutic potential.

4. Targeting the endocannabinoid system for the treatment of neurodegenerative diseases

The ECS could slow neurodegenerative disease progression through its anti-inflammatory, neuroprotective, and anti-apoptotic effects, which are of particular interest in conditions characterized by chronic neuroinflammation and immune activation. The following sections discuss ECS activities in specific conditions, highlighting their therapeutic potential across a spectrum of neurodegenerative and psychiatric disorders.

4.1. NeuroHIV

The term HIV-1 associated neurocognitive disorders (HAND) was introduced in 2007 [75] and refers to a range of cognitive disorders that include mainly three subtypes: (i) HIV-associated dementia (HAD), (ii) minor neurocognitive disorders (MND), and (iii) asymptomatic neurocognitive impairments (ANI) [76]. In the past, the occurrence of

neurocognitive disorders, particularly HAD and HIV encephalitis (HIVE) was high in HIV patients, as emerged at autopsy [76,77]. Although the introduction of combined antiretroviral therapy (cART), has significantly reduced the incidence of severe HAD and HIVE [78], the prevalence of the milder forms of HAND still remains high. By impairing executive functions, HAND can impact the quality of life, memory consolidation, decision-making ability, attention and mood [79]. The persistence of HAND can be traced to two factors: (i) cART does not fully eradicate HIV [80] allowing the virus to remain latent in various cells including microglial cells, triggering neuroinflammation [81], and (ii) cART drugs have limited penetration into the CNS [82]. Upon HIV infection, microglial cells secrete several inflammatory factors, including the viral trans-activating protein Tat, which causes the release of chemokines, cytokines, and a chemotactic response that recruit uninfected microglia, expanding the neuroinflammatory process.

CB2R, expressed at low levels in microglia and neurons, is dynamically upregulated in response to CNS inflammation [83,84]. Studies on white matter from HIV patients with HIVE have revealed increased expression of CB2R in microglia, astrocytes, and perivascular macrophages [85]. Accordingly, in the cortical tissue of SIV-infected rhesus macaques, CB2R upregulation was reported in perivascular monocytes/macrophages and microglia [86]. This upregulation may represent an anti-inflammatory response, which is common in various neuronal insults, including those induced by bacterial or viral inflammatory mediators and neurotoxins [87].

Interestingly, several *in vitro* studies suggest that CB2R upregulation could regulate microglial activity, shifting it to an anti-inflammatory, pro-healing state and promoting its migration to the site of the injury [84]. In contrast, CB2R agonists can inhibit microglial migration in response to harmful stimuli, such as (i) viral products [53], (ii) synapse loss induced by HIV-1 envelope glycoprotein 120 (gp120) [88,89] and (iii) activation of the NLRP3 inflammasome [90] potentially blunting neuroinflammation. Thus, CB2R may represent a promising therapeutic target in multiple neuropathological conditions. Since CB2R is endowed with neuroprotective effects and lacks psychotropic effects, many efforts have been made to develop ligands for CB2R, including synthetic cannabinoids and β-caryophyllene (BCP) a natural cannabinoid ligand, abundant in cannabis and non-cannabis plants, including spices and other edible plants [91].

Despite promising preclinical findings, the clinical use of CB2R agonists remains limited [92]; to illustrate, only a single pilot study has tested the effects of oral cannabinoids in HIV patients, and demonstrated a favorable safety profile and anti-inflammatory properties [93].

4.2. Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of age-related dementia and represents a major challenge in public health. Over the past few decades, the prevalence of AD has increased exponentially, affecting millions of individuals worldwide and significantly impacting the lives of patients and their families [94]. AD is characterized by a progressive cognitive decline, severely impairing memory, abstract thinking, communication and executive function. At the neuropathological level, the disease is defined by two hallmarks including extracellular beta-amyloid (Aβ) plaques, which result from altered amyloid precursor protein (APP) processing, and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein [95]. These pathological markers play a pivotal role in the definitive diagnosis of AD and are closely associated with the progression of symptoms [94]. Another key feature of AD is glial activation, intimately linked to neuroinflammation, which recent discoveries have highlighted as a critical factor in disease progression [96]. Recent studies emphasized earlier involvement of the immune system, prompting a re-evaluation of the role of microglial cells. As a result, innovative therapies aim to slow degeneration by targeting not only neurons but also glial cells, particularly microglia and astrocytes, due to their key role in neuroinflammation in AD and other neurodegenerative diseases.

The lack of effective pharmacological treatment for AD has encouraged research to explore novel therapeutic avenues, including the intriguing field of cannabinoids. Alterations in the ECS have been observed in AD [97], and eCBs have gathered increasing interest for their potential involvement in this condition [98–100]. Preliminary studies have indicated that eCBs, such as cannabidiol (CBD) and delta-9-tetrahydrocannabinol (Δ9-THC) could possess neuroprotective and anti-inflammatory effects that might slow the progression of AD [101,102]. Although the role of the ECS in AD remains contraversial, a case-report study has shown that microdoses of a cannabis extract ameliorated mnemonic and non-mnemonic AD symptoms, as assessed by the Mini-Mental State Examination and Alzheimer's Disease Assessment Scale-Cognitive Subscale [103].

In AD patients, the expression of CB2R is upregulated in microglia of neuritic plaques in regions such as the hippocampus and entorhinal cortex [99,104]. This suggests that CB2R could be involved in the inflammatory processes associated with AD. Administration of CB2R agonists seems to reduce microglial activation and the release of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, triggered by exposure to Aβ fibrils, both *in vitro* and *in vivo* [99,105–107]. Notably, post-mortem examination of brains from AD patients have revealed an up-regulation of CB2R in cells connected to Aβ-enriched neuritic plaques [87,99,108], further implicating CB2R in the inflammatory response.

Moreover, given the multifactorial nature of AD, exploring therapeutic combinations that target CB2R alongside other modalities, such as immunomodulatory or conventional treatments, may enhance efficacy. For instance, combining CB2R agonists with drugs that modulate neurotransmission or reduce amyloid-beta (Aβ) accumulation could slow disease progression more effectively.

While the CB2R remains the main target, future research should investigate the role of other ECS components, such as CB1 receptors or enzymes like FAAH and MAGL, with the intent to modulate neuroinflammation and neuroprotection in AD.

It is important to note that research in this area is still in its early stages. However, while cellular and animal models have provided support for the role of the ECS in AD, clinical studies aimed at exploring cannabinoid-based therapies to address behavioral disturbances in AD, such as night-time agitation, eating behavior, and aggressiveness, have shown only limited success [109,110]. Nonetheless, the safety and efficacy of such treatments need to be further explored in larger clinical studies in order to understand their full therapeutic potential.

4.3. Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease in the elderly population, following AD [111]. This disorder affects the basal ganglia, characterized by the progressive degeneration of dopaminergic neurons within the substantia nigra (SN) of the midbrain. Given the need for new, non-invasive treatments for PD, cannabinoids, such as cannabidiol (CBD) and delta-9-tetrahydrocannabinol (Δ9-THC) may offer therapeutic potential due to the prominent modulatory role played by the cannabinoid signaling system in the basal ganglia [112]. Although cannabinoids should never be considered a first-line treatment, they could serve as adjuvant therapy in specific situations. For instance, they could slow the deterioration of the brain's dopaminergic systems, for which no current treatment exists.

The ECS plays a prominent role in modulating neurotransmitter secretion within the basal ganglia, influencing both healthy and pathological conditions. Components of the ECS are abundant in basal ganglia structures and the activation and/or inhibition of this system is associated with important motor responses that are maintained and even enhanced under conditions of malfunction and/or degeneration.

Despite the increasing amount of research on cannabinoids and their

effects in PD, clinical data on their efficacy and safety in PD patients remains lacking. One study found that cannabis, CBD, and nabilone (a synthetic form of THC) consistently improved motor symptoms compared to placebo. All treatments also alleviated various non-motor symptoms, particularly with cannabis reducing pain intensity, and CBD blunting neuropsychiatric symptoms in a dose-dependent manner. Adverse effects were usually mild, with CBD showing rare side effects, except at very high doses. These findings suggest that cannabinoids could be safely used to treat motor symptoms in PD and some non-motor symptoms, though large-scale randomized control trials (RCTs) would be required to confirm their overall efficacy and safety [113].

In a systematic review of 569 papers on PD and cannabinoid treatment, only seven randomized trials were identified, and the results did not support the efficacy of cannabinoids in treating motor signs of PD. Therefore the authors conclude that there is insufficient data to support the administration of cannabinoids to PD patients [114].

Although levodopa remains the most effective medication available for managing PD motor symptoms, other treatments may be considered first to avoid levodopa-related motor complications. Different case series and a single case report described that cannabinoids might have potential beneficial effects on PD motor symptoms such as akinesia, tremor or dyskinesia. However, the results of RCTs evaluating cannabinoids for PD motor symptoms have been not encouraging. So far, four RCTs involving 49 PD patients have been published, testing CBD, THC/CBD, nabilone, and rimonabant. Three of these RCTs failed to show significant effects of cannabinoids on parkinsonian motor symptoms or levodopa-induced dyskinesia (LID) when used as add-on therapy [115].

Concerning clinical research, only one of the four RCTs showed an effect on motor symptoms with alleviation of LID [115,116]. Despite strong preclinical evidence supporting cannabinoid-based therapies, the clinical potential of cannabinoid-based medicines for PD has been little explored, highlighting the need for alternative treatments to classic dopaminergic replacement therapy for motor symptoms and neuroprotective strategies in PD.

4.4. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disease characterized by the progressive degeneration of both upper and lower motor neurons, leading to irreversible paralysis of skeletal muscles, ultimately resulting in respiratory failure.

ALS is classified into two main forms: (i) sporadic (sALS) which is the more common form, accounting for 90–95 % of cases, with a poorly understood genetic inheritance component, and (ii) the familial type (fALS, 5–10 %), which is typically associated with autosomal dominant inheritance, though rarely to recessive and X-linked transmission [117]. Despite this distinction, the pathogenetic mechanisms underlying both forms share significant overlaps and are not easily classified. The pathophysiology of both fALS and sALS is multifactorial, involving (i) neurofilament accumulation, (ii) excitotoxicity, (iii) mitochondrial dysfunction and dysregulation, (iv) impaired axonal transport, (v) intracellular protein aggregates, and (vi) genetic mutations, though many of these processes remain incompletely understood.

Current treatment options for ALS are limited, with only a few drugs (riluzole, edaravone) approved to slow or ameliorate some symptoms. The marketing authorization of ursodoxicoltaurine (Relyvio/Albrioza, AMX0035) has been voluntary discontinued by the producer. However, none of these therapies can halt the disease progression, and other interventions remain symptomatic and palliative treatments [117,118]. This therapeutic gap has driven research into the potential role of cannabinoids in modulating ALS-associated pathological events [119].

Elevations in mRNA and protein levels of AEA and 2-AG, along with a parallel increase in CB2R expression, have been observed in the spinal cord of SOD1 mutant [120–123] and TDP43 transgenic mice [124,125]. Similar findings have also been reported in the spinal cord of a canine neurodegenerative model resembling ALS [126], and in postmortem tissues obtained from ALS patients, including spinal cords and primary motor cortex [127]. In particular, the up-regulation of CB2R occur predominantly in activated astrocytes and microglial cells. Since both are primarily recruited to sites of injury in the spinal grey and white matter, as well as at motor neuron lesions, this mechanism could be a protective response [124]. This hypothesis is supported by different studies showing that ECBs can reduce microglial activation and the release of pro-inflammatory cytokines via the CB2R [119].

Concerning the mechanisms underlying these effects, plant-derived cannabinoids like Δ9-THC seems to reduce oxidative and excitotoxic damage in spinal cord cultures *in vitro*, likely through the reduction of pro-inflammatory cytokines and the upregulation of brain-derived neurotrophic factor (BDNF) [128,129]. Furthermore, experimental studies have demonstrated that cannabinoids, such as the non-selective cannabinoid agonist WIN55,212–2 and the CB2R-selective agonist AM-1241, can extend survival in ALS animal models [89,90,98].

Although the number of clinical trials remains limited, the results obtained so far are promising. A randomized, double-blind crossover trial of oral Δ9-THC administration (5 mg twice daily for 2 weeks) in a small number of ALS patients showed that the treatment was well tolerated, though no significant effects on cramp frequency and intensity was observed [130]. Supporting evidence from two other clinical studies also confirmed the tolerability of cannabinoids in ALS patients [131].

Additionally, following the approval of nabizimols (Sativex) for treating spasticity in multiple sclerosis, four clinical studies are currently exploring the potential of cannabinoids as disease-modifying therapies in ALS (NCT01776970; NCT03690791; NCT04997954; NCT03944447). One of these trials has obtained promising results, showing an acceptable profile of safety and tolerability and positive effects on ALS-associated spasticity [132].

From this perspective, targeting the endocannabinoid system, particularly the CB2R to modulate pathogenic processes at the molecular and cellular levels offer a potential approach to address the current lack of effective therapies for ALS.

4.5. Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory demyelinating disease characterized by neurological symptoms including weakness, altered sensation, balance and vision impairment. These symptoms result from immune-mediated CNS events driving the destruction of myelin and oligodendrocytes, which ultimately leads to a progressive axonal loss and synaptic dysfunction [133,134]. Approximately half of MS patients experience cognitive dysfunction, possibly related to the pathological overproduction of reactive oxygen and nitrogen species (RONS) and pro-inflammatory mediators. These factors contribute to mitochondrial and axonal damage, which in turn leads to neurodegeneration in several regions of the CNS [135].

The complexity of the pathophysiological processes in progressive MS suggests that targeting multiple events simultaneously could be a promising therapeutic approach [136]. At present, the therapeutic strategies focus on drugs reducing the frequency and severity of the attacks (methylprednisolone) and on disease-modifying therapies (INF-β1, natalizumab, fingolimod, teriflunomide, dimethylfumarate and alemtuzumab), that slow the progression of the disease. However, despite their efficiency in managing MS symptoms, these therapies still face significant challenges about effectiveness and safety, and slowing disease progression.

Experimental Autoimmune Encephalomyelitis (EAE) is a widely used animal model of MS, used to develop and validate drugs and health interventions for MS [137]. EAE is induced in mice by immunization with the myelin oligodendrocyte glycoprotein (MOG) [138], which triggers the activation and central migration of peripheral myelin-specific T lymphocytes leading to demyelination and axonal degeneration [139]. In EAE mice, activated macrophages and microglial cells release multiple mediators of tissue damage, including proteases,

nitric oxide (NO) and reactive oxygen species (ROS) that contribute to demyelination and axonal injury, as well as the oxidation of genomic and mitochondrial DNA [140]. Interestingly, studies using this model shed light on the biological effects of CBs providing growing evidence for the involvement of the ECS in both the inflammatory and the neurodegenerative processes typical of MS.

Several studies have shown increased levels of anandamide (AEA) and a down-expression of 2-AG in the inflammatory lesions [141], cerebrospinal fluid, lymphocytes [142], and plasma [143] from MS patients. Higher levels of AEA have also been detected in the brains of EAE mice. These findings seem to be due to AEA increased synthesis and reduced degradation [142]. In contrast, other studies showed that both AEA and 2-AG are downregulated in the brains of EAE rats [144] and in the cerebrospinal fluid of MS patients with remitting/relapsing or progressive disease [145]. Furthermore, the expression of FAAH, the enzyme involved in AEA degradation, CB1R and CB2R are upregulated in MS lesions, indicating that the levels of this endocannabinoid might be reduced in MS patients [146].

In CB2R-deficient animals, disease severity correlates specifically with reduced CB2R expression in encephalitogenic T cells, rather than microglia or CNS cells. These animals are more susceptible to EAE induction compared to wild-type mice, and exhibit increased disease severity and mortality [147]. Treatment with Gp1a, a highly selective CB2R agonist, has been shown to reduce disease severity by decreasing neuronal damage and demyelination. This effect is attributed to the prevention of Th1 and Th17 cell differentiation in secondary lymphoid organs [148]. The CB2R agonist also decreases CNS accumulation of encephalitogenic T cells by inhibiting the expression of chemokine receptors and adhesion molecules by leukocytes. In addition, Gp1a ameliorates recovery in EAE with long-term reduction in demyelination and axonal loss, highlighting the relevance of CB2R signaling in disease pathogenesis [149,150].

In 2000, Baker and colleagues first discovered the antispasticity effects of the CB2R-selective agonist JWH-133 in an autoimmune model of MS. Administration of JWH-133 (1.5 mg·kg–1 i.v.) reduced spasticity at both 10 min and 30 min after injection [151]. In a separate study, Gomez and colleagues reported that the treatment of purified oligodendrocyte progenitor cells (OPC) obtained from primary mixed glial cultures, with JWH-133 (0.5 μM), accelerated differentiation and increased the levels of myelin basic protein (MBP), a marker of oligodendrocyte maturity, within 48 h after start of the differentiation process [152,153].

These findings further suggest the significance of CB2R in the progression of demyelinating diseases, such as MS, and underscore the therapeutic value of targeting CB2R signaling in brain repair. To date, Nabiximols (Sativex), a standardized 1:1 (w/w) mix of CBD and Δ9-THC, is prescribed for neuropathic pain and spasticity associated with MS [154,155], demonstrating the pivotal role of CB2R in mediating of the immune system in MS.

4.6. Huntington's Disease

Huntington's Disease (HD) is a rare neurodegenerative disorder characterized by progressive motor dysfunction, cognitive decline, and behavioural impairments. It is caused by a mutation in the HTT gene, which leads to an abnormal expansion of CAG repeats, resulting in the production of mutant huntingtin protein. This toxic protein accumulates in neurons, particularly in the striatum and cortex, leading to neuronal dysfunction and cell death [156,157].

Clinically, HD manifests with involuntary movements (chorea), impaired coordination, mood disturbances (such as depression and irritability), and progressive cognitive impairment. Symptoms usually appear between the ages of 30 and 50, with a gradual worsening over time. The disease follows an autosomal dominant inheritance pattern, meaning that a child of an affected individual has a 50 % chance of inheriting the mutation [158].

Currently, there is no cure for HD, and treatment focuses on symptom management. Research efforts are ongoing to develop disease-modifying therapies, including gene silencing approaches and neuroprotective strategies [159].

In HD, the endocannabinoid system (ECS) undergoes significant dysfunction, contributing to neurodegeneration, synaptic deficits, and neuroinflammation. A hallmark of HD pathology is the early and progressive loss of CB1 receptors in the striatum and cortex, impairing synaptic plasticity and exacerbating motor and cognitive symptoms [160]. Additionally, alterations in endocannabinoid levels, such as reduced 2-arachidonoylglycerol (2-AG), further disrupt neuronal homeostasis [161]. Meanwhile, CB2 receptors become upregulated in reactive microglia, indicating a role in neuroinflammation, which could be targeted for therapeutic benefit [162].

Given these alterations, ECS-based interventions such as CB1 agonists to restore synaptic function, CB2 agonists to counteract inflammation, and inhibitors of endocannabinoid degradation to enhance neuroprotection, are being explored as potential strategies to slow disease progression and alleviate symptoms in HD patients.

Research using cellular models of HD, such as the inducible HD43 cell line derived from rat ST14A cells, has demonstrated a fully functional ECS. These studies revealed alterations in ECS components, including changes in endocannabinoid levels and receptor expression, suggesting that modulating ECS activity could influence disease progression at the cellular level [163]. Moreover, Blázquez and colleagues have demonstrated that CB2 receptor agonists reduce neuroinflammatory markers and protect neuronal cultures from excitotoxicity [164].

Animal models, particularly the R6/2 mouse model of HD, have shown significant alterations in the ECS. Notably, there is a reduction in cannabinoid receptor type 1 (CB1) binding in the striatum, accompanied by changes in endocannabinoid content and enzyme activities. These findings indicate that ECS dysfunction contributes to HD pathology and that restoring ECS balance might offer neuroprotective benefits. *In vivo*, administration of CB2 agonists in HD animal models has been shown to mitigate microglial activation, reduce neuronal loss, and improve motor deficits [165–168].

A pilot clinical trial investigated the effects of Sativex, an oromucosal spray containing a balanced combination of THC and CBD, in HD patients. This double-blind, randomized, placebo-controlled, cross-over study administered up to 12 sprays per day over 12 weeks. While the study aimed to assess the safety and efficacy of ECS modulation in HD patients, further research is necessary to establish definitive therapeutic outcomes.

Clinical studies, although limited, suggest that CB2 receptor activation may offer neuroprotection and symptomatic relief, but further well-designed trials are needed to confirm efficacy and optimize treatment protocols [169–173].

Despite promising preclinical findings, challenges remain, including optimizing the blood-brain barrier permeability of cannabinoid compounds, mitigating side effects, and addressing the heterogeneity of ECS alterations across disease stages. The ECS represents a promising therapeutic target for HD due to its involvement in motor control, neuroprotection, and inflammation modulation, and future research should focus on refining ECS-targeted drug development and conducting robust clinical trials.

4.7. Pain perception and migraine

Both pre-clinical and clinical studies have reported an impairment of ECS in migraine and chronic pain complaints, supporting the ECS as a potential therapeutic target for analgesia in chronic pain disorders [174–176].

Early evidence indicated an increase in FAAH activity in platelets from female patients affected by migraine, suggesting an accelerated degradation of AEA. This, in turn, reduced plasma AEA levels which

correlated with a lowered pain threshold in these individuals [177,178]. Accordingly, cerebrospinal fluid (CSF) concentrations of AEA were found to be significantly lower in chronic migraine patients compared to controls without migraine [179].

These data prompted researchers over the last two decades, to focus on potentiating endocannabinoids through the inhibition of their degradation. In an animal model of nitroglycerin (NTG)-induced migraine, the FAAH inhibitor URB937 significantly alleviated both acute as well as chronic NTG-induced hyperalgesia, reduced c-Fos expression and prevented the typical increase in cytokine transcription [180,181]. URB937 also attenuated the activation of the trigeminal nucleus caudalis (TNC) and the locus coeruleus, two brain areas involved in migraine pain [180]. Moreover, in models of acute inflammation (carrageenan-induced hyperalgesia) and chronic neuropathic pain (streptozotocin-induced allodynia), URB937 attenuated pain-related behaviors producing anti-nociceptive and anti-inflammatory effects in both models [182,183].

Other two FAAH inhibitors, such as URB597 and PF3845, inhibited NTG-induced hypersensitivity and reduced trigeminal neuron activation in a dose-dependent manner in rodents [184,185]. Accordingly, NTG-induced mechanical allodynia as well as activation of TNC were completely abolished in FAAH-deficient mice [184]. Furthermore, both URB597 and PF3845 alleviated mechanical allodynia in a rat model of HIV sensory neuropathy [186], and URB597 demonstrated analgesic effects in an animal model of orofacial pain when administered centrally as well as peripherally [187].

More recently, two analogues of URB597, (ARN14633 and ARN14280), with enhanced solubility and bioavailability, have been synthesized. These inhibitors presented greater anti-hyperalgesic and anti-inflammatory actions compared to URB597 and produced a marked elevation in endocannabinoid levels in the NTG migraine rat model [176]. Another potent and selective FAAH inhibitor, ASP8477, increased brain AEA levels and reduced mechanical allodynia in rat models of neuropathic pain and osteoarthritis [188,189].

In recent pre-clinical studies, JZL195, which inhibits both FAAH and MAGL, was shown to significantly reduce NTG-induced hyperalgesia and cytokine gene expression levels at both central and peripheral levels [181]. Inhibition of MAGL with JZL184 also suppressed morphological and functional signs of collagen-induced arthritis (CIA) in mice [190].

Recently, thanks to its legalization in various countries, the medical use of cannabis has become an alternative and increasingly popular therapy for managing migraine and chronic pain. Patients using medical cannabis have reported reduction in migraine frequency and pain severity compared with baseline [191,192]. Moreover, oral cannabinoid preparations have been shown to reduce the incidence of nausea and vomiting during migraine attacks [193]. In patients with fibromyalgia and neuropathic pain, cannabis treatment reduced pain intensity and related symptoms, such as anxiety and depression [194]. A recent case report described a 72-year-old female patient with diffuse arthritic pain who experienced improved pain control, and a consequent reduction in the use of opioids, following cannabis treatment [195]. These data suggest that medical cannabis may be a useful option for managing migraine and chronic pain disorders, thereby improving patients' quality of life.

5. Preclinical and clinical drug development for CB2R

Since the discovery of the CB2 in 1988, drug discovery approaches targeting the CB2R have flourished. Particular attention has been given to selective agonists targeting the CB2R to overcome the neuropsychotropic side effects associated with CB1R activation. The pharmacological modulation of CB2R holds therapeutic promise for various diseases, such as inflammatory disorders and immunological conditions, pain management and cancer treatment. Despite the numerous efforts made, no CB2R agonists have received regulatory approval for therapeutic use in peripheral or central nervous system disorders. The transition from preclinical studies to approved therapies has faced challenges, including limited efficacy in human trials and potential side effects. Consequently, while several CB2R-targeting drugs have been tested in clinical trials, none have been approved as therapeutic candidates for these conditions.

GW405833, a potent and selective agonist for the CB2R, was initially studied for its anti-inflammatory and anti-hyperalgesic effects in different animal models; however, most recent studies have explored a very wide diversity of other conditions, such as (i) neuroinflammation and oxidative stress, (ii) sepsis, (iii) acute liver failure, (iv) acute pancreatitis, (v) anxiety and depression, as well as (vi) the process of Tau protein deposition in neurodegenerative diseases.

GW405833 has been shown to reduce edema development as well as inhibit the hypersensitivity caused by intraplantar injection of carrageenan [196]. GW405833, up to 30 mg/kg, elicits remarkably efficacious antihyperalgesic effects in different rodent pain models, including neuropathic (Seltzer), incisional and inflammatory (Freund's complete adjuvant) pain. In contrast, analgesia, sedation and catalepsy were not observed in this dose range but appeared at the 100 mg/kg dosage. The antihyperalgesic and analgesic activities of GW405833 are not dependent on the release of endogenous opioids, but the more accepted hypothesis envisages that cannabinoid CB2R modulators affect pain indirectly via modulation of immune cell activity, possibly at the site of injury, resulting in decreased local levels of sensitizing agents, such as NGF, prostanoids, cytokines and histamine, that ultimately affect neuronal excitability [197].

The rat model of neuropathic pain produced by the chronic constriction injury of the sciatic nerve develops a depression-like behaviour, represented by an increase in the time of immobility in the forced swimming test. GW405833 was able to reduce mechanical hypersensitivity as well as depression-like behaviour in rats with neuropathic pain, without affecting the sham-treated animals [198].

In the acute sepsis model, GW405833 significantly prolonged the survival rate and diminished the production of proinflammatory cytokines in macrophages of LPS-treated mice [199]. In keeping with this observation, GW405833 administered at the doses of 3-, 10-, and 30-mg/kg, alleviated the manifestations of EAE in an experimental model of mice with autoimmune encephalomyelitis (EAE), and presented positive effects on locomotor activity and cytokine release. Again, GW405833 significantly reduced inflammation, by decreasing serum levels of IL-12 and TNF-α proinflammatory cytokines, without exerting any significant side effects [200].

The inflammatory response involving infiltration and activation of liver macrophages represents a crucial effector in inducing acute liver failure (ALF). GW405833 displayed positive properties in the animal model of liver injury. In the liver of ALF mice, GW405833 pre-treatment significantly reduced liver macrophage infiltration and M1 proinflammatory polarization; HIF-1α expression was down-regulated, and the release of inflammatory factors such as TNF-α and IL-1β was inhibited and hepatocyte apoptosis diminished [201]. GW405833 treatment remarkably relieved concavalin A-induced liver injury and decreased serum aminotransferase levels [202]. In an *in vitro* model of acute pancreatitis, GW405833 in a concentration-dependent manner, reduced ACh-induced Ca^{2+} oscillations and also blunted the enhanced Ca^{2+} oscillations caused by the pancreatitis inducer L-arginine, thereby abolishing its effects [203]. Recently, GW405833 was able to decrease the fluorescence intensity of tau, a protein whose accumulation can lead to impaired autophagic protein degradation pathways, essential for cellular homeostasis and survival [204]. Despite the various and interesting pharmacological effects of GW405833, its progression to clinical use has been limited, and it has not advanced to become a therapeutic candidate.

AM-1241 is another selective CB2R agonist that has been tested in different pathological conditions, ranging from inflammation, hyperalgesia and allodynia to epilepsy, ischemia-reperfusion cardiac and intestinal damage, fibrosis of different origins and obesity. AM-1241 has

Table 2
Main molecules tested in preclinical studies.

Molecule	Animal model	Effects	References
GW405833	acute inflammation and pain rat model	exerts antihyperalgesic and analgesic effects	[196,214]
	mouse model of chronic pain	stimulates mechanical hypersensitivity	[197]
	acute sepsis mice model	prolongs survival	[199]
	EAE mice model	ameliorates locomotor activity and cytokine release	[200]
	mice acute liver failure model	diminishes hepatocytes apoptosis	[201]
	mice liver injury model	decreases serum aminotransferase levels	[202]
	in vitro mice model of acute pancreatitis	reduces ACh-induced Ca^{2+} oscillations	[203]
	neuroblastoma cellular model of tauopathy	improves autophagy	[204]
AM−1241	mice model of OA	reduces disease progression	[205]
	rat liver injury	reduces liver inflammation and fibrosis	[206]
	rat IR model	reduces myocardial ischemia/reperfusion injury	[207]
	mice model of cardiomyopathy ethanol-induced	protects against necroptosis	[208]
	rat model of intestinal ischemia/reperfusion injury	recovers the functional contractility of ileum	[209]
	rat model of liver fibrosis	decreases the collagen fibre deposition	[210]
	rat model of lung fibrosis	reduces pulmonary fibrosis	[211]
	pilocarpine-induced chronic epilepsy mouse model	alleviates epileptic seizures	[212]
	pentylenetetrazole-induced seizure rat model	increases seizure severity	[213]

been shown to attenuate inflammation in various disease models. In a mice model of osteoarthritis, AM-1241 given once a week at the dose of 3 mg or 9 mg/kg/day, inhibited chondrocyte inflammation and extracellular matrix degradation by modulating the Nrf2/HO-1 and NF-κB signalling pathways, thereby leading to reduced disease progression [205]. Similarly, in a liver rat injury model caused by bile duct ligation, chronic treatment with AM-1241 (3 mg/kg, ip for three consecutive weeks) reduced liver inflammation and fibrosis [206]. AM-1241 was widely investigated as a therapy for myocardial infarction, because of its cardioprotective effects. Indeed, AM-1241 given at the dose of 6 mg/kg ip, 1 hour prior to the damage induction, has been reported to attenuate several markers of myocardial ischemia/reperfusion injury by reducing oxidative stress and inflammation, through the Nrf2/HO-1 pathway [207]. Similarly, in a murine model of ethanol-induced cardiomyopathy, 1-hour pretreatment with AM-1241 (20 mg/kg, ip) protected against the development of necroptosis [208]. Similarly, in a rat model of intestinal ischemia/reperfusion injury, pretreatment with AM-1241 (5 mg/kg) favoured restoration of ileum smooth muscle myocontractility. This effect was accompanied by prevention of intestinal lipid peroxide production, neutrophils infiltration and the release of proinflammatory cytokines (TNF-α and IL-1β) [209]. AM-1241 demonstrated several antifibrotic activities. In a rat model of liver fibrosis, induced by thioacetamide, chronic AM-1241 treatment (3 and 6 mg/kg, daily, for three weeks) improved oxidative stress markers, suppressed the release of the pro-inflammatory cytokines and decreased collagen fibre deposition, ameliorating liver fibrosis [210]. A similar effect was observed in a rat model of lung fibrosis induced by bleomycin; in this case, both pretreatment and chronic treatment with AM-1241 (7 or 28 days, 3 mg/kg, ip) resulted in reduced pulmonary fibrosis. This effect was accompanied by reductions in hydroxyproline and collagen type 1 levels and the inhibition of IL-6 and TNF-α release [211]. Conflicting data regarding the potential anti-seizure effects of AM-1241 have been reported. In a pilocarpine-induced chronic epilepsy mouse model, AM-1241 (1 and 3 mg/kg, administered ip on the 8th day after the induction of status epilepticus and once daily for 21 days) alleviated epileptic seizures and epilepsy-associated depression by inhibiting neuroinflammation [212]. By comparison, another study reported that AM-1241 increased seizure severity in a pentylenetetrazole-induced seizure rat model [213], suggesting that the effects of AM-1241 on seizure activity may depend on the seizure model and experimental conditions. Although it has promising preclinical results, AM-1241 has not progressed to clinical trials or therapeutic applications.

The data described above are summarised in Table 2.

Despite the vast preclinical research, only a small handful, roughly 5–10 selective CB2R agonists, have advanced into clinical trials. Notable examples include compounds such as olorinab and lenabasum.

Olorinab (APD371), originally developed by Arena Pharmaceuticals, now acquired and merged into Pfizer, is an oral highly selective full agonist of the CB2R, peripherally restricted. Preclinical studies showed that olorinab, by targeting primarily the peripheral CB2R, was effective at reducing visceral hypersensitivity in animal models of Inflammatory Bowel diseases (IBD) and Irritable Bowel Syndrome (IBS), while minimizing the risk of psychoactive effects [215]. Olorinab has undergone a phase IIa clinical trial involving 14 patients (18–80 years of age) affected by moderate-to-severe abdominal pain [average abdominal pain score (AAPS) of ≥ 4, on 7 consecutive days during the screening period] due to quiescent to mildly active inflammatory Crohn's Disease. This preliminary study was an open-label, randomized, parallel-group, multicenter trial (NCT03155945). The study comprised a screening period of 4 weeks, an 8-week randomized treatment period, and a 2-week follow-up. Eligible subjects were randomized (stratified by sex) in a 1:1 ratio to olorinab 25 or 100 mg three times daily, for 8 weeks. Results from this study showed a clinically significant reduction in pain scores, with the highest dose yielding the most improvement. Olorinab was well tolerated, with only mild-to-moderate adverse events reported. No CNS-related adverse effects were registered. However, this proof-of-concept study although demonstrating encouraging results, was limited by a small sample size, the open-label study design, and the lack of a placebo control treatment group [216].

The phase IIb CAPTIVATE trial (NCT04043455) evaluated the efficacy and safety of olorinab in treating abdominal pain in patients with IBS. The randomized, double-blind, placebo-controlled, parallel-group trial included 273 subjects (18–70 years of age) with IBS-D (diarrhoea-predominant) and IBS-C (constipation-predominant) subtypes, who were randomized to receive olorinab at doses of 10 mg, 25 mg, 50 mg, or a placebo, administered three times daily over 12 weeks. Treatment response was observed across all groups, and even though the primary endpoint (change in the weekly Average Abdominal Pain Score (AAPS) from baseline to week 12) was not met, in a predefined subgroup analysis of participants with moderate to severe baseline pain (AAPS $\geq$6.5), the 50 mg dose group showed a clinically meaningful and statistically significant reduction in pain compared to placebo.

Olorinab was commonly well tolerated, with adverse event rates comparable to those of the placebo group and no serious adverse events reported. The most frequently reported adverse effects across all treatment groups were nausea (5.5 %), headache (4.8 %), nasopharyngitis (3.7 %), dizziness (2.9 %), dry mouth (2.6 %), and upper respiratory tract infection (2.6 %). Nausea was more frequent in participants who received olorinab (14/202, 6.9 %) than in those who received placebo (1/70, 1.4 %). No clinically meaningful changes in heart rate, ECG readings, or physical examinations were documented, although one participant in the olorinab 10 mg group, one in the 25 mg group and one in the 50 mg group discontinued treatment because of increased blood pressure, orthostatic hypotension and elevated liver transaminases,

Table 3
Main molecules in clinical studies.

Molecule	Phase, typology of clinical trial, clinicaltrials.gov id number	Number of patients /age	Pathologic condition	Duration	Dose (s)	Schedule	Effects	ADR	References
Olorinab (APD371)	phase IIa, randomized, open-label, parallel-group, multicenter; NCT03155945	14 subjects, 18–80 y	quiescent to mild active inflammatory Crohn's Disease	8-week, plus a 2-week follow-up period	25 or 100 mg	three times daily	clinically significant reduction in pain scores	not significant	[216]
	phase IIb, randomized, double-blind, parallel-group, placebo-controlled -CAPTIVATE; NCT04043455	273 subjects, 18–70 y	IBS (IBS-D and IBS-C)	12-week	10, 25 or 50 mg	three times daily	the 50 mg dose group showed a clinically meaningful and statistically significant reduction in pain	nausea (5.5 %), headache (4.8 %), nasopharyngitis (3.7 %), dizziness (2.9 %), dry mouth (2.6 %), and upper respiratory tract infection (2.6 %).	[217]
Lenabasum (JBT−101)	phase III, randomized, double-blind, placebo-controlled, multicenter RESOLVE−1; NCT03398837	365 subjects, > 18 y	diffuse cutaneous systemic sclerosis	52 week	5 or 20 mg	twice daily	trial outcome negative	no significant adverse events	[218]
	phase II; randomized, double-blind, placebo-controlled, single centre; NCT02466243	22 subjects, 18–70 y	dermatomyositis with refractory, moderate-to-severely active skin disease	84 days	20 mg	once daily from day 1–28 twice daily from day 29–84	improved CDASI (Cutaneous Dermatomyositis Disease Area and Severity Index) scores	no significant adverse events	[219]
	phase II, randomized, double-blind, placebo controlled, multicentric; NCT02465450	85 subjects, 27–30 y	cystic fibrosis	16-week	1 or 5 mg 20 mg	once daily from week 1–4 once daily from week 5–12 twice daily from week 5–13	reductions in sputum inflammatory markers, specifically IL−8 and immunoglobulin G, and decreases in neutrophils, eosinophils, and neutrophil elastase	no significant adverse events	[220]
S−777469	phase Ib/IIa, randomized, double-blind, placebo-controlled; NCT00697710	37 subjects, 18–65 y	atopic dermatitis	14 days	50, 200 or 800 mg	twice daily	not results available	not results available	[221]

respectively [217]. Phase II trials showed mixed results, and the prospect of its further development is uncertain.

Lenabasum (JBT-101), also called ajulemic acid, is an oral, selective, CB2R agonist developed by Corbus Pharmaceuticals which has been investigated in clinical trials for conditions associated with inflammation and fibrosis, particularly systemic sclerosis, also known as scleroderma. RESOLVE-1 is a multicentric Phase 3, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of lenabasum in patients (365, >18 years of age) with diffuse cutaneous systemic sclerosis (dcSSc) (NCT03398837). Lenabasum showed promise in earlier-phase studies, but it failed to meet expectations in Phase 3 trials for systemic sclerosis, leading to discontinuation of its development for this indication. However, lenabasum may still have potential in other inflammatory conditions or fibrotic diseases [218].

The efficacy of lenabasum for treatment of fibrotic diseases, such as cystic fibrosis (CF) was also evaluated. A 16-week, phase 2, double-blind, randomized, placebo controlled, multicentric study analyzed the effects of lenabasum during 12 weeks of treatment with a follow up at week 16. Biomarker analyses showed that the treatment was associated with notable reductions in sputum inflammatory markers, specifically IL-8 and immunoglobulin G, and decreases in neutrophils, eosinophils, and neutrophil elastase, consistent with its anti-inflammatory effects [219,220].

S-777469, a CB2R agonist developed by Shionogi & Co., has been studied studied for its anti-inflammatory and analgesic effects in atopic dermatitis. A phase Ib/IIa, multiple-dose, double-blind, randomized, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of s-777469 in subjects with mild to moderate atopic dermatitis (50, 200 or 800 mg or placebo) is ongoing (NCT00697710).

Currently, no pure CB2R agonist has been fully approved for human use, but lenabasum and olorinab have shown promise in clinical trials.

The data described above are summarised in Table 3.

6. Conclusions

The ECS, and especially the CB2R, offers great potential for developing new treatments that target neuroinflammation and neurodegeneration. Modulating CB2R could help restore balance in both neurons and glial cells, reducing degenerative and inflammatory damage without the psychotropic effects of cannabinoids and CB1R activation. Therefore, CB2R modulation is a promising approach for treating complex neurodegenerative diseases.

However, clinical studies are limited, with challenges due to small sample size, inconsistent methods, and a lack of understanding of long-term effects. The safety of CB2R modulation also needs further research.

Future studies should focus on larger clinical trials to test the effectiveness, safety, and long-term impact of CB2R-targeted therapies. Improving preclinical models will also help clarify how these therapies work and guide future treatments.

Funding

This work was supported by Fondo di Ateneo per la Ricerca of the University of Milano-Bicocca, Italy [FAR to AT] and by "Unione europea - Next Generation EU, Missione 4 Componente 1" CUP E63C22002170007.

CRediT authorship contribution statement

Coco Silvia: Writing – review & editing, Writing – original draft, Supervision. **Omeljaniuk Robert:** Writing – review & editing. **Torsello Antonio:** Writing – review & editing, Supervision, Funding acquisition. **Meanti Ramona:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Bresciani Elena:** Writing – original draft. **Rizzi Laura:** Writing – original draft. **Molteni Laura:** Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Conceptualization, R.M.; writing—original draft preparation, R.M., E.B., L.R., L.M. and S.C.; writing—review and editing, R.M., S.C., R.J.O. and A.T.; supervision, R.M., S.C. and A.T.; funding acquisition, A.T. All authors have read and agreed to the published version of the manuscript.

Data availability

No data was used for the research described in the article.

References

[1] W.A. Devane, F.A. Dysarz, M.R. Johnson, L.S. Melvin, A.C. Howlett, Determination and characterization of a cannabinoid receptor in rat brain, Mol. Pharm. 34 (1988) 605–613.
[2] A. Sideris, J. Lauzadis, M. Kaczocha, The Basic Science of Cannabinoids, Anesth. Analg. 138 (2024) 42–53, https://doi.org/10.1213/ANE.0000000000006472.
[3] R.G. Biringer, Endocannabinoid signaling pathways: beyond CB1R and CB2R, J. Cell Commun. Signal 15 (2021) 335–360, https://doi.org/10.1007/s12079-021-00622-6.
[4] H.-C. Lu, K. Mackie, An Introduction to the Endogenous Cannabinoid System, Biol. Psychiatry 79 (2016) 516–525, https://doi.org/10.1016/j.biopsych.2015.07.028.
[5] M. Pistis, M. Melis, From surface to nuclear receptors: the endocannabinoid family extends its assets, Curr. Med Chem. 17 (2010) 1450–1467, https://doi.org/10.2174/092986710790980014.
[6] V.Di Marzo, L.De Petrocellis, Endocannabinoids as regulators of transient receptor potential (TRP) channels: A further opportunity to develop new endocannabinoid-based therapeutic drugs, Curr. Med Chem. 17 (2010) 1430–1449, https://doi.org/10.2174/092986710790980078.
[7] R.A. Ross, Anandamide and vanilloid TRPV1 receptors, Br. J. Pharm. 140 (2003) 790–801, https://doi.org/10.1038/sj.bjp.0705467.
[8] M. Scherma, P. Masia, V. Satta, W. Fratta, P. Fadda, G. Tanda, Brain activity of anandamide: a rewarding bliss? Acta Pharm. Sin. 40 (2019) 309–323, https://doi.org/10.1038/s41401-018-0075-x.
[9] J.M. Sido, P.S. Nagarkatti, M. Nagarkatti, Role of Endocannabinoid Activation of Peripheral CB1 Receptors in the Regulation of Autoimmune Disease, Int Rev. Immunol. 34 (2015) 403–414, https://doi.org/10.3109/08830185.2014.921165.
[10] S.G. Woodhams, D.R. Sagar, J.J. Burston, V. Chapman, The role of the endocannabinoid system in pain, Handb. Exp. Pharm. 227 (2015) 119–143, https://doi.org/10.1007/978-3-662-46450-2_7.
[11] E.-K. Kwon, Y. Choi, S. Sim, Y.-M. Ye, Y.S. Shin, H.-S. Park, G.-Y. Ban, Cannabinoid receptor 2 as a regulator of inflammation induced oleoylethanolamide in eosinophilic asthma, J. Allergy Clin. Immunol. 153 (2024) 998–1009.e9, https://doi.org/10.1016/j.jaci.2023.09.043.
[12] A.A. Coutts, A.A. Izzo, The gastrointestinal pharmacology of cannabinoids: an update, Curr. Opin. Pharm. 4 (2004) 572–579, https://doi.org/10.1016/j.coph.2004.05.007.
[13] U. Grabiec, F. Dehghani, N-Arachidonoyl Dopamine: A Novel Endocannabinoid and Endovanilloid with Widespread Physiological and Pharmacological Activities, Cannabis Cannabinoid Res 2 (2017) 183–196, https://doi.org/10.1089/can.2017.0015.
[14] H. Tutunchi, M. Saghafi-Asl, A. Ostadrahimi, A systematic review of the effects of oleoylethanolamide, a high-affinity endogenous ligand of PPAR-α, on the management and prevention of obesity, Clin. Exp. Pharm. Physiol. 47 (2020) 543–552, https://doi.org/10.1111/1440-1681.13238.
[15] P. Clayton, S. Subah, R. Venkatesh, M. Hill, N. Bogoda, Palmitoylethanolamide: A Potential Alternative to Cannabidiol, J. Diet. Suppl. 20 (2023) 505–530, https://doi.org/10.1080/19390211.2021.2005733.
[16] A.J. Brown, Novel cannabinoid receptors, Br. J. Pharm. 152 (2007) 567–575, https://doi.org/10.1038/sj.bjp.0707481.
[17] The Human Protein Atlas, (n.d.). ⟨https://www.proteinatlas.org/⟩ (accessed September 12, 2024).
[18] M.D. Van Sickle, M. Duncan, P.J. Kingsley, A. Mouihate, P. Urbani, K. Mackie, N. Stella, A. Makriyannis, D. Piomelli, J.S. Davison, L.J. Marnett, V. Di Marzo, Q. J. Pittman, K.D. Patel, K.A. Sharkey, Identification and functional characterization of brainstem cannabinoid CB2 receptors, Science 310 (2005) 329–332, https://doi.org/10.1126/science.1115740.

[19] C. Montero, N.E. Campillo, P. Goya, J.A. Páez, Homology models of the cannabinoid CB1 and CB2 receptors. A docking analysis study, Eur. J. Med Chem. 40 (2005) 75–83, https://doi.org/10.1016/j.ejmech.2004.10.002.
[20] C.A. Brust, M.A. Swanson, L.M. Bohn, Structural and functional insights into the G protein-coupled receptors: CB1 and CB2, Biochem Soc. Trans. 51 (2023) 1533–1543, https://doi.org/10.1042/BST20221316.
[21] K.H. Ahn, M.M. Mahmoud, J.-Y. Shim, D.A. Kendall, Distinct roles of β-arrestin 1 and β-arrestin 2 in ORG27569-induced biased signaling and internalization of the cannabinoid receptor 1 (CB1), J. Biol. Chem. 288 (2013) 9790–9800, https://doi.org/10.1074/jbc.M112.438804.
[22] B.K. Atwood, J. Wager-Miller, C. Haskins, A. Straiker, K. Mackie, Functional selectivity in CB(2) cannabinoid receptor signaling and regulation: implications for the therapeutic potential of CB(2) ligands, Mol. Pharm. 81 (2012) 250–263, https://doi.org/10.1124/mol.111.074013.
[23] C. Zoratti, D. Kipmen-Korgun, K. Osibow, R. Malli, W.F. Graier, Anandamide initiates Ca(2+) signaling via CB2 receptor linked to phospholipase C in calf pulmonary endothelial cells, Br. J. Pharm. 140 (2003) 1351–1362, https://doi.org/10.1038/sj.bjp.0705529.
[24] L. Callén, E. Moreno, P. Barroso-Chinea, D. Moreno-Delgado, A. Cortés, J. Mallol, V. Casadó, J.L. Lanciego, R. Franco, C. Lluis, E.I. Canela, P.J. McCormick, Cannabinoid receptors CB1 and CB2 form functional heteromers in brain, J. Biol. Chem. 287 (2012) 20851–20865, https://doi.org/10.1074/jbc.M111.335273.
[25] C.J. Coke, K.A. Scarlett, M.A. Chetram, K.J. Jones, B.J. Sandifer, A.S. Davis, A. I. Marcus, C.V. Hinton, Simultaneous Activation of Induced Heterodimerization between CXCR4 Chemokine Receptor and Cannabinoid Receptor 2 (CB2) Reveals a Mechanism for Regulation of Tumor Progression, J. Biol. Chem. 291 (2016) 9991–10005, https://doi.org/10.1074/jbc.M115.712661.
[26] P. Pacher, S. Bátkai, G. Kunos, The endocannabinoid system as an emerging target of pharmacotherapy, Pharm. Rev. 58 (2006) 389–462, https://doi.org/10.1124/pr.58.3.2.
[27] J. Wu, Cannabis, cannabinoid receptors, and endocannabinoid system: yesterday, today, and tomorrow, Acta Pharm. Sin. 40 (2019) 297–299, https://doi.org/10.1038/s41401-019-0210-3.
[28] Y. Li, J. Kim, Neuronal expression of CB2 cannabinoid receptor mRNAs in the mouse hippocampus, Neuroscience 311 (2015) 253–267, https://doi.org/10.1016/j.neuroscience.2015.10.041.
[29] W. Grabon, J. Bodennec, S. Rheims, A. Belmeguenai, L. Bezin, Update on the controversial identity of cells expressing cnr2 gene in the nervous system, CNS Neurosci. Ther. 29 (2023) 760–770, https://doi.org/10.1111/cns.13977.
[30] C.E. Martinez Ramirez, G. Ruiz-Pérez, T.M. Stollenwerk, C. Behlke, A. Doherty, C. J. Hillard, Endocannabinoid signaling in the central nervous system, Glia 71 (2023) 5–35, https://doi.org/10.1002/glia.24280.
[31] S.J. Carlisle, F. Marciano-Cabral, A. Staab, C. Ludwick, G.A. Cabral, Differential expression of the CB2 cannabinoid receptor by rodent macrophages and macrophage-like cells in relation to cell activation, Int Immunopharmacol. 2 (2002) 69–82, https://doi.org/10.1016/s1567-5769(01)00147-3.
[32] L. Walter, A. Franklin, A. Witting, C. Wade, Y. Xie, G. Kunos, K. Mackie, N. Stella, Nonpsychotropic cannabinoid receptors regulate microglial cell migration, J. Neurosci. 23 (2003) 1398–1405, https://doi.org/10.1523/JNEUROSCI.23-04-01398.2003.
[33] K. Maresz, E.J. Carrier, E.D. Ponomarev, C.J. Hillard, B.N. Dittel, Modulation of the cannabinoid CB2 receptor in microglial cells in response to inflammatory stimuli, J. Neurochem. 95 (2005) 437–445, https://doi.org/10.1111/j.1471-4159.2005.03380.x.
[34] J. Zhang, C. Hoffert, H.K. Vu, T. Groblewski, S. Ahmad, D. O'Donnell, Induction of CB2 receptor expression in the rat spinal cord of neuropathic but not inflammatory chronic pain models, Eur. J. Neurosci. 17 (2003) 2750–2754, https://doi.org/10.1046/j.1460-9568.2003.02704.x.
[35] N. Stella, Cannabinoid signaling in glial cells, Glia 48 (2004) 267–277, https://doi.org/10.1002/glia.20084.
[36] A.P. Young, E.M. Denovan-Wright, The Dynamic Role of Microglia and the Endocannabinoid System in Neuroinflammation, Front Pharm. 12 (2021) 806417, https://doi.org/10.3389/fphar.2021.806417.
[37] M. Mecha, A. Feliú, F.J. Carrillo-Salinas, A. Rueda-Zubiaurre, S. Ortega-Gutiérrez, R.G. de Sola, C. Guaza, Endocannabinoids drive the acquisition of an alternative phenotype in microglia, Brain Behav. Immun. 49 (2015) 233–245, https://doi.org/10.1016/j.bbi.2015.06.002.
[38] S.S. Duffy, J.P. Hayes, N.T. Fiore, G. Moalem-Taylor, The cannabinoid system and microglia in health and disease, Neuropharmacology 190 (2021) 108555, https://doi.org/10.1016/j.neuropharm.2021.108555.
[39] D.J. Araujo, K. Tjoa, K. Saijo, The Endocannabinoid System as a Window Into Microglial Biology and Its Relationship to Autism, Front Cell Neurosci. 13 (2019) 424, https://doi.org/10.3389/fncel.2019.00424.
[40] Á. Moreno-García, A. Bernal-Chico, T. Colomer, A. Rodríguez-Antigüedad, C. Matute, S. Mato, Gene Expression Analysis of Astrocyte and Microglia Endocannabinoid Signaling during Autoimmune Demyelination, Biomolecules 10 (2020) 1228, https://doi.org/10.3390/biom10091228.
[41] S. Marinelli, M.C. Marrone, M. Di Domenico, S. Marinelli, Endocannabinoid signaling in microglia, Glia 71 (2023) 71–90, https://doi.org/10.1002/glia.24281.
[42] M. Braun, Z.T. Khan, M.B. Khan, M. Kumar, A. Ward, B.R. Achyut, A.S. Arbab, D. C. Hess, M.N. Hoda, B. Baban, K.M. Dhandapani, K. Vaibhav, Selective activation of cannabinoid receptor-2 reduces neuroinflammation after traumatic brain injury via alternative macrophage polarization, Brain Behav. Immun. 68 (2018) 224–237, https://doi.org/10.1016/j.bbi.2017.10.021.
[43] L. Lin, T. Yihao, F. Zhou, N. Yin, T. Qiang, Z. Haowen, C. Qianwei, T. Jun, Z. Yuan, Z. Gang, F. Hua, Y. Yunfeng, C. Zhi, Inflammatory Regulation by Driving Microglial M2 Polarization: Neuroprotective Effects of Cannabinoid Receptor-2 Activation in Intracerebral Hemorrhage, Front Immunol. 8 (2017) 112, https://doi.org/10.3389/fimmu.2017.00112.
[44] M.S. García-Gutiérrez, A.B. Torregrosa, F. Navarrete, D. Navarro, J. Manzanares, A comprehensive review of the multifaceted role of cannabinoid receptor type 2 in neurodegenerative and neuropsychiatric disorders, Pharm. Res 213 (2025) 107657, https://doi.org/10.1016/j.phrs.2025.107657.
[45] W. Grabon, S. Rheims, J. Smith, J. Bodennec, A. Belmeguenai, L. Bezin, CB2 receptor in the CNS: From immune and neuronal modulation to behavior, Neurosci. Biobehav Rev. 150 (2023) 105226, https://doi.org/10.1016/j.neubiorev.2023.105226.
[46] S. Zoppi, J.L. Madrigal, J.R. Caso, M.S. García-Gutiérrez, J. Manzanares, J. C. Leza, B. García-Bueno, Regulatory role of the cannabinoid CB2 receptor in stress-induced neuroinflammation in mice, Br. J. Pharm. 171 (2014) 2814–2826, https://doi.org/10.1111/bph.12607.
[47] H. Yu, X. Liu, B. Chen, C.R. Vickstrom, V. Friedman, T.J. Kelly, X. Bai, L. Zhao, C. J. Hillard, Q.-S. Liu, The Neuroprotective Effects of the CB2 Agonist GW842166x in the 6-OHDA Mouse Model of Parkinson's Disease, Cells 10 (2021) 3548, https://doi.org/10.3390/cells10123548.
[48] H.-Y. Zhang, H. Shen, M. Gao, Z. Ma, B.J. Hempel, G.-H. Bi, E.L. Gardner, J. Wu, Z.-X. Xi, Cannabinoid CB2 receptors are expressed in glutamate neurons in the red nucleus and functionally modulate motor behavior in mice, Neuropharmacology 189 (2021) 108538, https://doi.org/10.1016/j.neuropharm.2021.108538.
[49] R.D. Andó, J. Bíró, C. Csölle, C. Ledent, B. Sperlágh, The inhibitory action of exo- and endocannabinoids on [^{3}H]GABA release are mediated by both $CB_1$and CB_2receptors in the mouse hippocampus, Neurochem. Int 60 (2012) 145–152, https://doi.org/10.1016/j.neuint.2011.11.012.
[50] G. López-Ramírez, R. Sánchez-Zavaleta, A. Ávalos-Fuentes, J. José Sierra, F. Paz-Bermúdez, G. Leyva-Gómez, J. Segovia Vila, H. Cortés, B. Florán, D2 autoreceptor switches CB2 receptor effects on [3H]-dopamine release in the striatum, Synapse 74 (2020) e22139, https://doi.org/10.1002/syn.22139.
[51] R. Sánchez-Zavaleta, H. Cortés, J.A. Avalos-Fuentes, U. García, J. Segovia Vila, D. Erlij, B. Florán, Presynaptic cannabinoid CB2 receptors modulate [3H]-Glutamate release at subthalamo-nigral terminals of the rat, Synapse 72 (2018) e22061, https://doi.org/10.1002/syn.22061.
[52] L. Zheng, X. Wu, X. Dong, X. Ding, C. Song, Effects of Chronic Alcohol Exposure on the Modulation of Ischemia-Induced Glutamate Release via Cannabinoid Receptors in the Dorsal Hippocampus, Alcohol Clin. Exp. Res 39 (2015) 1908–1916, https://doi.org/10.1111/acer.12845.
[53] F.S. den Boon, P. Chameau, Q. Schaafsma-Zhao, W. van Aken, M. Bari, S. Oddi, C. G. Kruse, M. Maccarrone, W.J. Wadman, T.R. Werkman, Excitability of prefrontal cortical pyramidal neurons is modulated by activation of intracellular type-2 cannabinoid receptors, Proc. Natl. Acad. Sci. USA 109 (2012) 3534–3539, https://doi.org/10.1073/pnas.1118167109.
[54] A. Stumpf, D. Parthier, R.P. Sammons, A.V. Stempel, J. Breustedt, B.R. Rost, D. Schmitz, Cannabinoid type 2 receptors mediate a cell type-specific self-inhibition in cortical neurons, Neuropharmacology 139 (2018) 217–225, https://doi.org/10.1016/j.neuropharm.2018.07.020.
[55] A.V. Stempel, A. Stumpf, H.-Y. Zhang, T. Özdoğan, U. Pannasch, A.-K. Theis, D.-M. Otte, A. Wojtalla, I. Rácz, A. Ponomarenko, Z.-X. Xi, A. Zimmer, D. Schmitz, Cannabinoid Type 2 Receptors Mediate a Cell Type-Specific Plasticity in the Hippocampus, Neuron 90 (2016) 795–809, https://doi.org/10.1016/j.neuron.2016.03.034.
[56] W.S. Sheng, S. Hu, X. Min, G.A. Cabral, J.R. Lokensgard, P.K. Peterson, Synthetic cannabinoid WIN55,212-2 inhibits generation of inflammatory mediators by IL-1beta-stimulated human astrocytes, Glia 49 (2005) 211–219, https://doi.org/10.1002/glia.20108.
[57] I.-Y. Choi, C. Ju, A.M.A. Anthony Jalin, D.I. Lee, P.L. Prather, W.-K. Kim, Activation of cannabinoid CB2 receptor-mediated AMPK/CREB pathway reduces cerebral ischemic injury, Am. J. Pathol. 182 (2013) 928–939, https://doi.org/10.1016/j.ajpath.2012.11.024.
[58] P. González-Naranjo, N. Pérez-Macias, N.E. Campillo, C. Pérez, V.J. Arán, R. Girón, E. Sánchez-Robles, M.I. Martín, M. Gómez-Cañas, M. García-Arencibia, J. Fernández-Ruiz, J.A. Páez, Cannabinoid agonists showing BuChE inhibition as potential therapeutic agents for Alzheimer's disease, Eur. J. Med Chem. 73 (2014) 56–72, https://doi.org/10.1016/j.ejmech.2013.11.026.
[59] J. Wu, M. Hocevar, J.F. Foss, B. Bie, M. Naguib, Activation of CB2 receptor system restores cognitive capacity and hippocampal Sox2 expression in a transgenic mouse model of Alzheimer's disease, Eur. J. Pharm. 811 (2017) 12–20, https://doi.org/10.1016/j.ejphar.2017.05.044.
[60] C.J. Jordan, Z.-X. Xi, Progress in brain cannabinoid CB2 receptor research: From genes to behavior, Neurosci. Biobehav Rev. 98 (2019) 208–220, https://doi.org/10.1016/j.neubiorev.2018.12.026.
[61] Q. Lu, A. Straiker, Q. Lu, G. Maguire, Expression of CB2 cannabinoid receptor mRNA in adult rat retina, Vis. Neurosci. 17 (2000) 91–95, https://doi.org/10.1017/s0952523800171093.
[62] B.K. Atwood, K. Mackie, CB2: a cannabinoid receptor with an identity crisis, Br. J. Pharm. 160 (2010) 467–479, https://doi.org/10.1111/j.1476-5381.2010.00729.x.
[63] N.E. Buckley, The peripheral cannabinoid receptor knockout mice: an update, Br. J. Pharm. 153 (2008) 309–318, https://doi.org/10.1038/sj.bjp.0707527.
[64] N.E. Buckley, K.L. McCoy, E. Mezey, T. Bonner, A. Zimmer, C.C. Felder, M. Glass, A. Zimmer, Immunomodulation by cannabinoids is absent in mice deficient for

the cannabinoid CB(2) receptor, Eur. J. Pharm. 396 (2000) 141–149, https://doi.org/10.1016/s0014-2999(00)00211-9.
[65] G. Navarro, K. Varani, I. Reyes-Resina, V. Sánchez de Medina, R. Rivas-Santisteban, C. Sánchez-Carnerero Callado, F. Vincenzi, S. Casano, C. Ferreiro-Vera, E.I. Canela, P.A. Borea, X. Nadal, R. Franco, Cannabigerol Action at Cannabinoid CB1 and CB2 Receptors and at CB1-CB2 Heteroreceptor Complexes, Front Pharm. 9 (2018) 632, https://doi.org/10.3389/fphar.2018.00632.
[66] S. Zou, U. Kumar, Somatostatin and cannabinoid receptors crosstalk in protection of huntingtin knock-in striatal neuronal cells in response to quinolinic acid, Neurochem. Int. 129 (2019) 104518, https://doi.org/10.1016/j.neuint.2019.104518.
[67] R.S. Rodrigues, F.F. Ribeiro, F. Ferreira, S.H. Vaz, A.M. Sebastião, S. Xapelli, Interaction between Cannabinoid Type 1 and Type 2 Receptors in the Modulation of Subventricular Zone and Dentate Gyrus Neurogenesis, Front Pharm. 8 (2017) 516, https://doi.org/10.3389/fphar.2017.00516.
[68] R. Wi, Y.C. Chung, B.K. Jin, Functional Crosstalk between CB and TRPV1 Receptors Protects Nigrostriatal Dopaminergic Neurons in the MPTP Model of Parkinson's Disease, J. Immunol. Res 2020 (2020) 5093493, https://doi.org/10.1155/2020/5093493.
[69] Y. Lu, H.D. Anderson, Cannabinoid signaling in health and disease, Can. J. Physiol. Pharm. 95 (2017) 311–327, https://doi.org/10.1139/cjpp-2016-0346.
[70] S. Zou, U. Kumar, Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System, Int J. Mol. Sci. 19 (2018) 833, https://doi.org/10.3390/ijms19030833.
[71] D. Haspula, M.A. Clark, Cannabinoid Receptors: An Update on Cell Signaling, Pathophysiological Roles and Therapeutic Opportunities in Neurological, Cardiovascular, and Inflammatory Diseases, Int J. Mol. Sci. 21 (2020) 7693, https://doi.org/10.3390/ijms21207693.
[72] B. Bie, J. Wu, J.F. Foss, M. Naguib, An overview of the cannabinoid type 2 receptor system and its therapeutic potential, Curr. Opin. Anaesthesiol. 31 (2018) 407–414, https://doi.org/10.1097/ACO.0000000000000616.
[73] V. Reddy, D. Grogan, M. Ahluwalia, É .L. Salles, P. Ahluwalia, H. Khodadadi, K. Alverson, A. Nguyen, S.P. Raju, P. Gaur, M. Braun, F.L. Vale, V. Costigliola, K. Dhandapani, B. Baban, K. Vaibhav, Targeting the endocannabinoid system: a predictive, preventive, and personalized medicine-directed approach to the management of brain pathologies, EPMA J. 11 (2020) 217–250, https://doi.org/10.1007/s13167-020-00203-4.
[74] J.-F. Yang, A.H. Williams, N.R. Penthala, P.L. Prather, P.A. Crooks, C.-G. Zhan, Binding Modes and Selectivity of Cannabinoid 1 (CB1) and Cannabinoid 2 (CB2) Receptor Ligands, ACS Chem. Neurosci. 11 (2020) 3455–3463, https://doi.org/10.1021/acschemneuro.0c00551.
[75] A. Antinori, G. Arendt, J.T. Becker, B.J. Brew, D.A. Byrd, M. Cherner, D. B. Clifford, P. Cinque, L.G. Epstein, K. Goodkin, M. Gisslen, I. Grant, R.K. Heaton, J. Joseph, K. Marder, C.M. Marra, J.C. McArthur, M. Nunn, R.W. Price, L. Pulliam, K.R. Robertson, N. Sacktor, V. Valcour, V.E. Wojna, Updated research nosology for HIV-associated neurocognitive disorders, Neurology 69 (2007) 1789–1799, https://doi.org/10.1212/01.WNL.0000287431.88658.8b.
[76] R. Ellis, D. Langford, E. Masliah, HIV and antiretroviral therapy in the brain: neuronal injury and repair, Nat. Rev. Neurosci. 8 (2007) 33–44, https://doi.org/10.1038/nrn2040.
[77] D.B. Clifford, B.M. Ances, HIV-associated neurocognitive disorder, Lancet Infect. Dis. 13 (2013) 976–986, https://doi.org/10.1016/S1473-3099(13)70269-X.
[78] N. Sacktor, Changing clinical phenotypes of HIV-associated neurocognitive disorders, J. Neurovirol 24 (2018) 141–145, https://doi.org/10.1007/s13365-017-0556-6.
[79] K. Alford, S. Daley, S. Banerjee, J.H. Vera, Quality of life in people living with HIV-associated neurocognitive disorder: A scoping review study, PLoS One 16 (2021) e0251944, https://doi.org/10.1371/journal.pone.0251944.
[80] J. Martinez-Picado, S.G. Deeks, Persistent HIV-1 replication during antiretroviral therapy, Curr. Opin. HIV AIDS 11 (2016) 417–423, https://doi.org/10.1097/COH.0000000000000287.
[81] C. Wallet, M. De Rovere, J. Van Assche, F. Daouad, S. De Wit, V. Gautier, P.W. G. Mallon, A. Marcello, C. Van Lint, O. Rohr, C. Schwartz, Microglial Cells: The Main HIV-1 Reservoir in the Brain, Front Cell Infect. Microbiol 9 (2019) 362, https://doi.org/10.3389/fcimb.2019.00362.
[82] O. Osborne, N. Peyravian, M. Nair, S. Daunert, M. Toborek, The Paradox of HIV Blood-Brain Barrier Penetrance and Antiretroviral Drug Delivery Deficiencies, Trends Neurosci. 43 (2020) 695–708, https://doi.org/10.1016/j.tins.2020.06.007.
[83] D. Fraga, E.S. Raborn, G.A. Ferreira, G.A. Cabral, Cannabinoids inhibit migration of microglial-like cells to the HIV protein Tat, J. Neuroimmune Pharm. 6 (2011) 566–577, https://doi.org/10.1007/s11481-011-9291-6.
[84] J.A. Komorowska-Müller, A.-C. Schmöle, CB2 Receptor in Microglia: The Guardian of Self-Control, Int J. Mol. Sci. 22 (2020) 19, https://doi.org/10.3390/ijms22010019.
[85] M.A. Cosenza-Nashat, A. Bauman, M.-L. Zhao, S. Morgello, H.-S. Suh, S.C. Lee, Cannabinoid receptor expression in HIV encephalitis and HIV-associated neuropathologic comorbidities, Neuropathol. Appl. Neurobiol. 37 (2011) 464–483, https://doi.org/10.1111/j.1365-2990.2011.01177.x.
[86] C. Benito, W.-K. Kim, I. Chavarría, C.J. Hillard, K. Mackie, R.M. Tolón, K. Williams, J. Romero, A glial endogenous cannabinoid system is upregulated in the brains of macaques with simian immunodeficiency virus-induced encephalitis, J. Neurosci. 25 (2005) 2530–2536, https://doi.org/10.1523/JNEUROSCI.3923-04.2005.
[87] C. Benito, R.M. Tolón, M.R. Pazos, E. Núñez, A.I. Castillo, J. Romero, Cannabinoid CB2 receptors in human brain inflammation, Br. J. Pharm. 153 (2008) 277–285, https://doi.org/10.1038/sj.bjp.0707505.
[88] H.J. Kim, A.H. Shin, S.A. Thayer, Activation of cannabinoid type 2 receptors inhibits HIV-1 envelope glycoprotein gp120-induced synapse loss, Mol. Pharm. 80 (2011) 357–366, https://doi.org/10.1124/mol.111.071647.
[89] J. Liu, J. Xie, D. Dutta, H. Xiong, HIV-1 envelope protein gp120 modulation of glutamate effects on cortical neuronal synapses: implications for HIV-1-associated neuropathogenesis, Int J. Physiol. Pathophysiol. Pharm. 15 (2023) 75–87.
[90] A.K. Min, A.M. Keane, M.P. Weinstein, T.H. Swartz, The impact of cannabinoids on inflammasome signaling in HIV-1 infection, NeuroImmune Pharm. Ther. 2 (2023) 79–88, https://doi.org/10.1515/nipt-2023-0002.
[91] N.K. Jha, C. Sharma, H.M. Hashiesh, S. Arunachalam, M.N. Meeran, H. Javed, C. R. Patil, S.N. Goyal, S. Ojha, β-Caryophyllene, A Natural Dietary CB2 Receptor Selective Cannabinoid can be a Candidate to Target the Trinity of Infection, Immunity, and Inflammation in COVID-19, Front Pharm. 12 (2021) 590201, https://doi.org/10.3389/fphar.2021.590201.
[92] E. Aly, W. Masocha, Targeting the endocannabinoid system for management of HIV-associated neuropathic pain: A systematic review, IBRO Neurosci. Rep. 10 (2021) 109–118, https://doi.org/10.1016/j.ibneur.2021.01.004.
[93] R.-S. Mboumba Bouassa, E. Comeau, Y. Alexandrova, A. Pagliuzza, A. Yero, S. Samarani, J. Needham, J. Singer, T. Lee, F. Bobeuf, C. Vertzagias, G. Sebastiani, S. Margolese, E. Mandarino, M.B. Klein, B. Lebouché, J.-P. Routy, N. Chomont, C. T. Costiniuk, M.-A. Jenabian, Effects of Oral Cannabinoids on Systemic Inflammation and Viral Reservoir Markers in People with HIV on Antiretroviral Therapy: Results of the CTN PT028 Pilot Clinical Trial, Cells 12 (2023) 1811, https://doi.org/10.3390/cells12141811.
[94] A.D. International, World Alzheimer Report 2023: Reducing Dementia Risk: Never too early, never too late, (2023). ⟨https://www.alzint.org/resource/world-alzheimer-report-2023/⟩ (accessed September 13, 2024).
[95] Z. Cai, M.D. Hussain, L.-J. Yan, Microglia, neuroinflammation, and beta-amyloid protein in Alzheimer's disease, Int J. Neurosci. 124 (2014) 307–321, https://doi.org/10.3109/00207454.2013.833510.
[96] M.T. Heneka, M.J. Carson, J.El Khoury, G.E. Landreth, F. Brosseron, D. L. Feinstein, A.H. Jacobs, T. Wyss-Coray, J. Vitorica, R.M. Ransohoff, K. Herrup, S.A. Frautschy, B. Finsen, G.C. Brown, A. Verkhratsky, K. Yamanaka, J. Koistinaho, E. Latz, A. Halle, G.C. Petzold, T. Town, D. Morgan, M. L. Shinohara, V.H. Perry, C. Holmes, N.G. Bazan, D.J. Brooks, S. Hunot, B. Joseph, N. Deigendesch, O. Garaschuk, E. Boddeke, C.A. Dinarello, J.C. Breitner, G. M. Cole, D.T. Golenbock, M.P. Kummer, Neuroinflammation in Alzheimer's disease, Lancet Neurol. 14 (2015) 388–405, https://doi.org/10.1016/S1474-4422(15)70016-5.
[97] V.Di Marzo, M. Bifulco, L.De Petrocellis, The endocannabinoid system and its therapeutic exploitation, Nat. Rev. Drug Discov. 3 (2004) 771–784, https://doi.org/10.1038/nrd1495.
[98] M. Coles, G.Z. Steiner-Lim, T. Karl, Therapeutic properties of multi-cannabinoid treatment strategies for Alzheimer's disease, Front Neurosci. 16 (2022) 962922, https://doi.org/10.3389/fnins.2022.962922.
[99] B.G. Ramírez, C. Blázquez, T.Gómez del Pulgar, M. Guzmán, M.L. de Ceballos, Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation, J. Neurosci. 25 (2005) 1904–1913, https://doi.org/10.1523/JNEUROSCI.4540-04.2005.
[100] M.A. Kamaruzzaman, M.H. Romli, R. Abas, S. Vidyadaran, M.T. Hidayat Baharuldin, M.L. Nasaruddin, V. Thirupathirao, S. Sura, K. Warsito, N.H. Mohd Nor, M.A. Azwaruddin, M.A. Alshawsh, M.A. Mohd Moklas, Regulatory role of the endocannabinoid system on glial cells toward cognitive function in Alzheimer's disease: A systematic review and meta-analysis of animal studies, Front Pharm. 14 (2023) 1053680, https://doi.org/10.3389/fphar.2023.1053680.
[101] L. Ruiz-Valdepeñas, C. Benito, R.M. Tolón, J.A. Martínez Orgado, J. Romero, The endocannabinoid system and amyloid-related diseases, Exp. Neurol. 224 (2010) 66–73, https://doi.org/10.1016/j.expneurol.2010.03.024.
[102] J. Kim, P. Choi, Y.-T. Park, T. Kim, J. Ham, J.-C. Kim, The Cannabinoids, CBDA and THCA, Rescue Memory Deficits and Reduce Amyloid-Beta and Tau Pathology in an Alzheimer's Disease-like Mouse Model, Int J. Mol. Sci. 24 (2023) 6827, https://doi.org/10.3390/ijms24076827.
[103] A.C. Ruver-Martins, M.A. Bicca, F.S. de Araujo, B.H.L. de Noronha Sales Maia, F. A. Pamplona, E.G. da Silva, F.P. Nascimento, Cannabinoid extract in microdoses ameliorates mnemonic and nonmnemonic Alzheimer's disease symptoms: a case report, J. Med Case Rep. 16 (2022) 277, https://doi.org/10.1186/s13256-022-03457-w.
[104] G. Talarico, A. Trebbastoni, G. Bruno, C. de Lena, Modulation of the Cannabinoid System: A New Perspective for the Treatment of the Alzheimer's Disease, Curr. Neuropharmacol. 17 (2019) 176–183, https://doi.org/10.2174/1570159X16666180702144644.
[105] J. Ehrhart, D. Obregon, T. Mori, H. Hou, N. Sun, Y. Bai, T. Klein, F. Fernandez, J. Tan, R.D. Shytle, Stimulation of cannabinoid receptor 2 (CB2) suppresses microglial activation, J. Neuroinflamm. 2 (2005) 29, https://doi.org/10.1186/1742-2094-2-29.
[106] E. Aso, I. Ferrer, CB2 Cannabinoid Receptor As Potential Target against Alzheimer's Disease, Front Neurosci. 10 (2016) 243, https://doi.org/10.3389/fnins.2016.00243.
[107] A. López, N. Aparicio, M.R. Pazos, M.T. Grande, M.A. Barreda-Manso, I. Benito-Cuesta, C. Vázquez, M. Amores, G. Ruiz-Pérez, E. García-García, M. Beatka, R. M. Tolón, B.N. Dittel, C.J. Hillard, J. Romero, Cannabinoid CB2 receptors in the mouse brain: relevance for Alzheimer's disease, J. Neuroinflamm. 15 (2018) 158, https://doi.org/10.1186/s12974-018-1174-9.

[108] M. Solas, P.T. Francis, R. Franco, M.J. Ramirez, CB2 receptor and amyloid pathology in frontal cortex of Alzheimer's disease patients, Neurobiol. Aging 34 (2013) 805–808, https://doi.org/10.1016/j.neurobiolaging.2012.06.005.
[109] A. Bahji, N. Breward, W. Duff, N. Absher, S.B. Patten, J. Alcorn, D.D. Mousseau, Cannabinoids in the management of behavioral, psychological, and motor symptoms of neurocognitive disorders: a mixed studies systematic review, J. Cannabis Res 4 (2022) 11, https://doi.org/10.1186/s42238-022-00119-y.
[110] H. Kanwal, M. Sangineto, M. Ciarnelli, P. Castaldo, R. Villani, A.D. Romano, G. Serviddio, T. Cassano, Potential Therapeutic Targets to Modulate the Endocannabinoid System in Alzheimer's Disease, Int J. Mol. Sci. 25 (2024) 4050, https://doi.org/10.3390/ijms25074050.
[111] B.S. Connolly, A.E. Lang, Pharmacological treatment of Parkinson disease: a review, JAMA 311 (2014) 1670–1683, https://doi.org/10.1001/jama.2014.3654.
[112] M. García-Arencibia, C. García, J. Fernández-Ruiz, Cannabinoids and Parkinson's disease, CNS Neurol. Disord. Drug Targets 8 (2009) 432–439, https://doi.org/10.2174/187152709789824642.
[113] K. Varshney, A. Patel, S. Ansari, P. Shet, S.S. Panag, Cannabinoids in Treating Parkinson's Disease Symptoms: A Systematic Review of Clinical Studies, Cannabis Cannabinoid Res 8 (2023) 716–730, https://doi.org/10.1089/can.2023.0023.
[114] M. Figura, D. Koziorowski, J. Sławek, Cannabis in Parkinson's Disease - the patient's perspective versus clinical trials: a systematic literature review, Neurol. Neurochir. Pol. 56 (2022) 21–27, https://doi.org/10.5603/PJNNS.a2022.0004.
[115] C. Buhmann, T. Mainka, G. Ebersbach, F. Gandor, Evidence for the use of cannabinoids in Parkinson's disease, J. Neural Transm. (Vienna) 126 (2019) 913–924, https://doi.org/10.1007/s00702-019-02018-8.
[116] M.S. Basile, E. Mazzon, The Role of Cannabinoid Type 2 Receptors in Parkinson's Disease, Biomedicines 10 (2022) 2986, https://doi.org/10.3390/biomedicines10112986.
[117] R. Mejzini, L.L. Flynn, I.L. Pitout, S. Fletcher, S.D. Wilton, P.A. Akkari, ALS Genetics, Mechanisms, and Therapeutics: Where Are We Now? Front Neurosci. 13 (2019) https://doi.org/10.3389/fnins.2019.01310.
[118] R. Meanti, E. Bresciani, L. Rizzi, S. Coco, V. Zambelli, A. Dimitroulas, L. Molteni, R.J. Omeljaniuk, V. Locatelli, A. Torsello, Potential Applications for Growth Hormone Secretagogues Treatment of Amyotrophic Lateral Sclerosis, Curr. Neuropharmacol. (2022), https://doi.org/10.2174/1570159X20666220915103613.
[119] C. Rodríguez-Cueto, L. García-Toscano, I. Santos-García, M. Gómez-Almería, C. Gonzalo-Consuegra, F. Espejo-Porras, J. Fernández-Ruiz, E. de Lago, Targeting the CB2 receptor and other endocannabinoid elements to delay disease progression in amyotrophic lateral sclerosis, Br. J. Pharm. 178 (2021) 1373–1387, https://doi.org/10.1111/bph.15386.
[120] M. Moreno-Martet, F. Espejo-Porras, J. Fernández-Ruiz, E. de Lago, Changes in endocannabinoid receptors and enzymes in the spinal cord of SOD1(G93A) transgenic mice and evaluation of a Sativex(®) -like combination of phytocannabinoids: interest for future therapies in amyotrophic lateral sclerosis, CNS Neurosci. Ther. 20 (2014) 809–815, https://doi.org/10.1111/cns.12262.
[121] J.L. Shoemaker, K.A. Seely, R.L. Reed, J.P. Crow, P.L. Prather, The CB2 cannabinoid agonist AM-1241 prolongs survival in a transgenic mouse model of amyotrophic lateral sclerosis when initiated at symptom onset, J. Neurochem. 101 (2007) 87–98, https://doi.org/10.1111/j.1471-4159.2006.04346.x.
[122] L.G. Bilsland, J.R.T. Dick, G. Pryce, S. Petrosino, V. Di Marzo, D. Baker, L. Greensmith, Increasing cannabinoid levels by pharmacological and genetic manipulation delay disease progression in SOD1 mice, FASEB J. 20 (2006) 1003–1005, https://doi.org/10.1096/fj.05-4743fje.
[123] A. Witting, P. Weydt, S. Hong, M. Kliot, T. Moller, N. Stella, Endocannabinoids accumulate in spinal cord of SOD1 G93A transgenic mice, J. Neurochem. 89 (2004) 1555–1557, https://doi.org/10.1111/j.1471-4159.2004.02544.x.
[124] F. Espejo-Porras, F. Piscitelli, R. Verde, J.A. Ramos, V. Di Marzo, E. de Lago, J. Fernández-Ruiz, Changes in the endocannabinoid signaling system in CNS structures of TDP-43 transgenic mice: relevance for a neuroprotective therapy in TDP-43-related disorders, J. Neuroimmune Pharm. 10 (2015) 233–244, https://doi.org/10.1007/s11481-015-9602-4.
[125] F. Espejo-Porras, L. García-Toscano, C. Rodríguez-Cueto, I. Santos-García, E. de Lago, J. Fernandez-Ruiz, Targeting glial cannabinoid CB2 receptors to delay the progression of the pathological phenotype in TDP-43 (A315T) transgenic mice, a model of amyotrophic lateral sclerosis, Br. J. Pharm. 176 (2019) 1585–1600, https://doi.org/10.1111/bph.14216.
[126] M. Fernández-Trapero, F. Espejo-Porras, C. Rodríguez-Cueto, J.R. Coates, C. Pérez-Díaz, E. de Lago, J. Fernández-Ruiz, Upregulation of CB2 receptors in reactive astrocytes in canine degenerative myelopathy, a disease model of amyotrophic lateral sclerosis, Dis. Model Mech. 10 (2017) 551–558, https://doi.org/10.1242/dmm.028373.
[127] Y. Yiangou, P. Facer, P. Durrenberger, I.P. Chessell, A. Naylor, C. Bountra, R. R. Banati, P. Anand, COX-2, CB2 and P2X7-immunoreactivities are increased in activated microglial cells/macrophages of multiple sclerosis and amyotrophic lateral sclerosis spinal cord, BMC Neurol. 6 (2006) 12, https://doi.org/10.1186/1471-2377-6-12.
[128] C. Raman, S.D. McAllister, G. Rizvi, S.G. Patel, D.H. Moore, M.E. Abood, Amyotrophic lateral sclerosis: delayed disease progression in mice by treatment with a cannabinoid, Amyotroph. Lateral Scler. Other Mot. Neuron Disord. 5 (2004) 33–39, https://doi.org/10.1080/14660820310016813.
[129] N. Pasquarelli, M. Engelskirchen, J. Hanselmann, S. Endres, C. Porazik, H. Bayer, E. Buck, M. Karsak, P. Weydt, B. Ferger, A. Witting, Evaluation of monoacylglycerol lipase as a therapeutic target in a transgenic mouse model of ALS, Neuropharmacology 124 (2017) 157–169, https://doi.org/10.1016/j.neuropharm.2017.03.037.
[130] M. Weber, B. Goldman, S. Truniger, Tetrahydrocannabinol (THC) for cramps in amyotrophic lateral sclerosis: a randomised, double-blind crossover trial, J. Neurol. Neurosurg. Psychiatry 81 (2010) 1135–1140, https://doi.org/10.1136/jnnp.2009.200642.
[131] M. Joerger, J. Wilkins, S. Fagagnini, R. Baldinger, R. Brenneisen, U. Schneider, B. Goldman, M. Weber, Single-dose pharmacokinetics and tolerability of oral delta-9- tetrahydrocannabinol in patients with amyotrophic lateral sclerosis, Drug Metab. Lett. 6 (2012) 102–108.
[132] N. Riva, G. Mora, G. Sorarù, C. Lunetta, O.E. Ferraro, Y. Falzone, L. Leocani, R. Fazio, M. Comola, G. Comi, F. Formaglio, P. Rossi, M. Clerici, Y.M. Falzone, L. Pozzi, D. Martinelli, F. Cerri, I.D. Lopez, F. Martinelli-Boneschi, A. Quattrini, E. Pieri, K. Marinou, G. Querin, V. Sansone, E. Maestri, A. Calvo, A. Chio, Safety and efficacy of nabiximols on spasticity symptoms in patients with motor neuron disease (CANALS): a multicentre, double-blind, randomised, placebo-controlled, phase 2 trial, Lancet Neurol. 18 (2019) 155–164, https://doi.org/10.1016/S1474-4422(18)30406-X.
[133] R. Dutta, B.D. Trapp, Mechanisms of neuronal dysfunction and degeneration in multiple sclerosis, Prog. Neurobiol. 93 (2011) 1–12, https://doi.org/10.1016/j.pneurobio.2010.09.005.
[134] G. Mandolesi, A. Gentile, A. Musella, D. Fresegna, F. De Vito, S. Bullitta, H. Sepman, G.A. Marfia, D. Centonze, Synaptopathy connects inflammation and neurodegeneration in multiple sclerosis, Nat. Rev. Neurol. 11 (2015) 711–724, https://doi.org/10.1038/nrneurol.2015.222.
[135] M. Filippi, A. Bar-Or, F. Piehl, P. Preziosa, A. Solari, S. Vukusic, M.A. Rocca, Multiple sclerosis, Nat. Rev. Dis. Prim. 4 (2018) 43, https://doi.org/10.1038/s41572-018-0041-4.
[136] S. Faissner, R. Gold, Progressive multiple sclerosis: latest therapeutic developments and future directions, Ther. Adv. Neurol. Disord. 12 (2019) 1756286419878323, https://doi.org/10.1177/1756286419878323.
[137] C.S. Constantinescu, N. Farooqi, K. O'Brien, B. Gran, Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS), Br. J. Pharm. 164 (2011) 1079–1106, https://doi.org/10.1111/j.1476-5381.2011.01302.x.
[138] E. Mix, H. Meyer-Rienecker, H.-P. Hartung, U.K. Zettl, Animal models of multiple sclerosis–potentials and limitations, Prog. Neurobiol. 92 (2010) 386–404, https://doi.org/10.1016/j.pneurobio.2010.06.005.
[139] I. Bjelobaba, V. Begovic-Kupresanin, S. Pekovic, I. Lavrnja, Animal models of multiple sclerosis: Focus on experimental autoimmune encephalomyelitis, J. Neurosci. Res 96 (2018) 1021–1042, https://doi.org/10.1002/jnr.24224.
[140] B. Packialakshmi, X. Zhou, Experimental autoimmune encephalomyelitis (EAE) up-regulates the mitochondrial activity and manganese superoxide dismutase (MnSOD) in the mouse renal cortex, PLoS One 13 (2018) e0196277, https://doi.org/10.1371/journal.pone.0196277.
[141] E. Eljaschewitsch, A. Witting, C. Mawrin, T. Lee, P.M. Schmidt, S. Wolf, H. Hoertnagl, C.S. Raine, R. Schneider-Stock, R. Nitsch, O. Ullrich, The endocannabinoid anandamide protects neurons during CNS inflammation by induction of MKP-1 in microglial cells, Neuron 49 (2006) 67–79, https://doi.org/10.1016/j.neuron.2005.11.027.
[142] D. Centonze, M. Bari, S. Rossi, C. Prosperetti, R. Furlan, F. Fezza, V. De Chiara, L. Battistini, G. Bernardi, S. Bernardini, G. Martino, M. Maccarrone, The endocannabinoid system is dysregulated in multiple sclerosis and in experimental autoimmune encephalomyelitis, Brain 130 (2007) 2543–2553, https://doi.org/10.1093/brain/awm160.
[143] L. Jean-Gilles, S. Feng, C.R. Tench, V. Chapman, D.A. Kendall, D.A. Barrett, C. S. Constantinescu, Plasma endocannabinoid levels in multiple sclerosis, J. Neurol. Sci. 287 (2009) 212–215, https://doi.org/10.1016/j.jns.2009.07.021.
[144] A. Cabranes, K. Venderova, E. de Lago, F. Fezza, A. Sánchez, L. Mestre, M. Valenti, A. García-Merino, J.A. Ramos, V. Di Marzo, J. Fernández-Ruiz, Decreased endocannabinoid levels in the brain and beneficial effects of agents activating cannabinoid and/or vanilloid receptors in a rat model of multiple sclerosis, Neurobiol. Dis. 20 (2005) 207–217, https://doi.org/10.1016/j.nbd.2005.03.002.
[145] M. Di Filippo, L.A. Pini, G.P. Pelliccioli, P. Calabresi, P. Sarchielli, Abnormalities in the cerebrospinal fluid levels of endocannabinoids in multiple sclerosis, J. Neurol. Neurosurg. Psychiatry 79 (2008) 1224–1229, https://doi.org/10.1136/jnnp.2007.139071.
[146] C. Benito, J.P. Romero, R.M. Tolón, D. Clemente, F. Docagne, C.J. Hillard, C. Guaza, J. Romero, Cannabinoid CB1 and CB2 receptors and fatty acid amide hydrolase are specific markers of plaque cell subtypes in human multiple sclerosis, J. Neurosci. 27 (2007) 2396–2402, https://doi.org/10.1523/JNEUROSCI.4814-06.2007.
[147] K. Maresz, G. Pryce, E.D. Ponomarev, G. Marsicano, J.L. Croxford, L.P. Shriver, C. Ledent, X. Cheng, E.J. Carrier, M.K. Mann, G. Giovannoni, R.G. Pertwee, T. Yamamura, N.E. Buckley, C.J. Hillard, B. Lutz, D. Baker, B.N. Dittel, Direct suppression of CNS autoimmune inflammation via the cannabinoid receptor CB1 on neurons and CB2 on autoreactive T cells, Nat. Med 13 (2007) 492–497, https://doi.org/10.1038/nm1561.
[148] W. Kong, H. Li, R.F. Tuma, D. Ganea, Selective CB2 receptor activation ameliorates EAE by reducing Th17 differentiation and immune cell accumulation in the CNS, Cell Immunol. 287 (2014) 1–17, https://doi.org/10.1016/j.cellimm.2013.11.002.
[149] R. Ferrisi, C. Ceni, S. Bertini, M. Macchia, C. Manera, F. Gado, Medicinal Chemistry approach, pharmacology and neuroprotective benefits of CB2R modulators in neurodegenerative diseases, Pharmacol. Res. 170 (2021) 105607, https://doi.org/10.1016/j.phrs.2021.105607.
[150] J.A. Estrada, I. Contreras, Endocannabinoid Receptors in the CNS: Potential Drug Targets for the Prevention and Treatment of Neurologic and Psychiatric

Disorders, Curr. Neuropharmacol. 18 (2020) 769–787, https://doi.org/10.2174/1570159X18666200217140255.
[151] D. Baker, G. Pryce, J.L. Croxford, P. Brown, R.G. Pertwee, J.W. Huffman, L. Layward, Cannabinoids control spasticity and tremor in a multiple sclerosis model, Nature 404 (2000) 84–87, https://doi.org/10.1038/35003583.
[152] O. Gomez, A. Sanchez-Rodriguez, M. Le, C. Sanchez-Caro, F. Molina-Holgado, E. Molina-Holgado, Cannabinoid receptor agonists modulate oligodendrocyte differentiation by activating PI3K/Akt and the mammalian target of rapamycin (mTOR) pathways, Br. J. Pharm. 163 (2011) 1520–1532, https://doi.org/10.1111/j.1476-5381.2011.01414.x.
[153] H.M. Hashiesh, N.K. Jha, C. Sharma, P.K. Gupta, S.K. Jha, C.R. Patil, S.N. Goyal, S.K. Ojha, Pharmacological potential of JWH133, a cannabinoid type 2 receptor agonist in neurodegenerative, neurodevelopmental and neuropsychiatric diseases, Eur. J. Pharm. 909 (2021) 174398, https://doi.org/10.1016/j.ejphar.2021.174398.
[154] D.J. Rog, T.J. Nurmikko, C.A. Young, Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial, Clin. Ther. 29 (2007) 2068–2079, https://doi.org/10.1016/j.clinthera.2007.09.013.
[155] W. Notcutt, R. Langford, P. Davies, S. Ratcliffe, R. Potts, A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex® (nabiximols), Mult. Scler. 18 (2012) 219–228, https://doi.org/10.1177/1352458511419700.
[156] K.A. Jellinger, The pathobiology of depression in Huntington's disease: an unresolved puzzle, J. Neural Transm. (Vienna) 131 (2024) 1511–1522, https://doi.org/10.1007/s00702-024-02750-w.
[157] F.O. Walker, Huntington's disease, Lancet 369 (2007) 218–228, https://doi.org/10.1016/S0140-6736(07)60111-1.
[158] R. Ghosh, S.J. Tabrizi, Clinical Features of Huntington's Disease, Adv. Exp. Med Biol. 1049 (2018) 1–28, https://doi.org/10.1007/978-3-319-71779-1_1.
[159] J. Saade, T.A. Mestre, Huntington's Disease: Latest Frontiers in Therapeutics, Curr. Neurol. Neurosci. Rep. 24 (2024) 255–264, https://doi.org/10.1007/s11910-024-01345-y.
[160] K.V. Laere, C. Casteels, I. Dhollander, K. Goffin, I. Grachev, G. Bormans, W. Vandenberghe, Widespread Decrease of Type 1 Cannabinoid Receptor Availability in Huntington Disease In Vivo, J. Nucl. Med. 51 (2010) 1413–1417, https://doi.org/10.2967/jnumed.110.077156.
[161] T. Bisogno, A. Martire, S. Petrosino, P. Popoli, V. Marzo, Symptom-related changes of endocannabinoid and palmitoylethanolamide levels in brain areas of R6/2 mice, a transgenic model of Huntington's disease, Neurochem. Int. 52 (2008) 307–313, https://doi.org/10.1016/j.neuint.2007.06.031.
[162] C. Casteels, R. Ahmad, M. Vandenbulcke, W. Vandenberghe, K. Laere, Cannabinoids and Huntington's disease, (2015) 61–97. https://doi.org/10.1016/B978-0-12-417041-4.00004-7.
[163] M. Bari, N. Battista, M. Valenza, N. Mastrangelo, M. Malaponti, G. Catanzaro, D. Centonze, A. Finazzi-Agrò, E. Cattaneo, M. Maccarrone, In vitro and in vivo models of Huntington's disease show alterations in the endocannabinoid system, FEBS J. 280 (2013) 3376–3388, https://doi.org/10.1111/febs.12329.
[164] C. Blázquez, A. Chiarlone, O. Sagredo, T. Aguado, M.R. Pazos, E. Resel, J. Palazuelos, B. Julien, M. Salazar, C. Börner, C. Benito, C. Carrasco, M. Diez-Zaera, P. Paoletti, M. Diaz-hernandez, C. Ruíz, M. Sendtner, J.J. Lucas, J.G. de Yébenes, G. Marsicano, K. Monory, B. Lutz, J. Romero, J. Alberch, S. Ginés, J. Kraus, J. Fernández-Ruiz, I. Galve-Roperh, M. Guzmán, Loss of striatal type 1 cannabinoid receptors is a key pathogenic factor in Huntington's disease, Brain: A J. Neurol. 134 (Pt 1) (2011) 119–136, https://doi.org/10.1093/brain/awq278.
[165] I. Lastres-Becker, R. Miguel, J. Fernández-Ruiz, The endocannabinoid system and Huntington's disease, Curr. Drug Targets CNS Neurol. Disord. 2 (5) (2003) 335–347, https://doi.org/10.2174/1568007033482751.
[166] S. Valdeolivas, C. Navarrete, I. Cantarero, M.L. Bellido, E. Muñoz, O. Sagredo, Neuroprotective properties of cannabigerol in Huntington's disease: studies in R6/2 mice and 3-nitropropionate-lesioned mice, Neurotherapeutics 12 (2015) 185–199, https://doi.org/10.1007/s13311-014-0304-z.
[167] J. Palazuelos, T. Aguado, M.R. Pazos, B. Julien, C. Carrasco, E. Resel, O. Sagredo, C. Benito, J. Romero, I. Azcoitia, J. Fernández-Ruiz, M. Guzmán, I. Galve-Roperh, Microglial CB2 cannabinoid receptors are neuroprotective in Huntington's disease excitotoxicity, Brain 132 (2009) 3152–3164, https://doi.org/10.1093/brain/awp239.
[168] O. Sagredo, S. González, I. Aroyo, M.R. Pazos, C. Benito, I. Lastres-Becker, J. P. Romero, R.M. Tolón, R. Mechoulam, E. Brouillet, J. Romero, J. Fernández-Ruiz, Cannabinoid CB2 receptor agonists protect the striatum against malonate toxicity: relevance for Huntington's disease, Glia 57 (2009) 1154–1167, https://doi.org/10.1002/glia.20838.
[169] J.L. López-Sendón Moreno, J. García Caldentey, P. Trigo Cubillo, C. Ruiz Romero, G. García Ribas, M.A.A. Alonso Arias, M.J. García de Yébenes, R.M. Tolón, I. Galve-Roperh, O. Sagredo, S. Valdeolivas, E. Resel, S. Ortega-Gutierrez, M. L. García-Bermejo, J. Fernández Ruiz, M. Guzmán, J. García de Yébenes Prous, A double-blind, randomized, cross-over, placebo-controlled, pilot trial with Sativex in Huntington's disease, J. Neurol. 263 (2016) 1390–1400, https://doi.org/10.1007/s00415-016-8145-9.
[170] C. Saft, S.M. von Hein, T. Lücke, C. Thiels, M. Peball, A. Djamshidian, B. Heim, K. Seppi, Cannabinoids for Treatment of Dystonia in Huntington's Disease, J. Huntingt. Dis. 7 (2018) 167–173, https://doi.org/10.3233/JHD-170283.
[171] O. Sagredo, M.R. Pazos, S. Valdeolivas, J. Fernandez-Ruiz, Cannabinoids: novel medicines for the treatment of Huntington's disease, Recent Pat. CNS Drug Discov. 7 (2012) 41–48, https://doi.org/10.2174/157488912798842278.
[172] D. Kumar, T.F. Usmani, M. Tariq, Therapeutic use of cannabinoids for the treatment of neurodegenerative disorders: a potential breakthrough, J. Pak. Med Assoc. 73 (2023) 1164–1165, https://doi.org/10.47391/JPMA.7805.
[173] C. Pérez-Olives, R. Rivas-Santisteban, J. Lillo, G. Navarro, R. Franco, Recent Advances in the Potential of Cannabinoids for Neuroprotection in Alzheimer's, Parkinson's, and Huntington's Diseases, Adv. Exp. Med Biol. 1264 (2021) 81–92, https://doi.org/10.1007/978-3-030-57369-0_6.
[174] B.F. Cravatt, A.H. Lichtman, Fatty acid amide hydrolase: an emerging therapeutic target in the endocannabinoid system, Curr. Opin. Chem. Biol. 7 (2003) 469–475, https://doi.org/10.1016/s1367-5931(03)00079-6.
[175] A. Della Pietra, J. Savinainen, R. Giniatullin, Inhibiting Endocannabinoid Hydrolysis as Emerging Analgesic Strategy Targeting a Spectrum of Ion Channels Implicated in Migraine Pain, Int J. Mol. Sci. 23 (2022) 4407, https://doi.org/10.3390/ijms23084407.
[176] R. Greco, C. Demartini, A.M. Zanaboni, M. Francavilla, A. Reggiani, N. Realini, R. Scarpelli, D. Piomelli, C. Tassorelli, Potentiation of endocannabinoids and other lipid amides prevents hyperalgesia and inflammation in a pre-clinical model of migraine, J. Headache Pain. 23 (2022) 79, https://doi.org/10.1186/s10194-022-01449-1.
[177] L.M. Cupini, M. Bari, N. Battista, G. Argirò, A. Finazzi-Agrò, P. Calabresi, M. Maccarrone, Biochemical changes in endocannabinoid system are expressed in platelets of female but not male migraineurs, Cephalalgia 26 (2006) 277–281, https://doi.org/10.1111/j.1468-2982.2005.01031.x.
[178] L.M. Cupini, C. Costa, P. Sarchielli, M. Bari, N. Battista, P. Eusebi, P. Calabresi, M. Maccarrone, Degradation of endocannabinoids in chronic migraine and medication overuse headache, Neurobiol. Dis. 30 (2008) 186–189, https://doi.org/10.1016/j.nbd.2008.01.003.
[179] P. Sarchielli, L.A. Pini, F. Coppola, C. Rossi, A. Baldi, M.L. Mancini, P. Calabresi, Endocannabinoids in chronic migraine: CSF findings suggest a system failure, Neuropsychopharmacology 32 (2007) 1384–1390, https://doi.org/10.1038/sj.npp.1301246.
[180] R. Greco, T. Bandiera, A.S. Mangione, C. Demartini, F. Siani, G. Nappi, G. Sandrini, A. Guijarro, A. Armirotti, D. Piomelli, C. Tassorelli, Effects of peripheral FAAH blockade on NTG-induced hyperalgesia–evaluation of URB937 in an animal model of migraine, Cephalalgia 35 (2015) 1065–1076, https://doi.org/10.1177/0333102414566862.
[181] R. Greco, C. Demartini, A. Zanaboni, I. Casini, R. De Icco, A. Reggiani, A. Misto, D. Piomelli, C. Tassorelli, Characterization of the peripheral FAAH inhibitor, URB937, in animal models of acute and chronic migraine, Neurobiol. Dis. 147 (2021) 105157, https://doi.org/10.1016/j.nbd.2020.105157.
[182] O. Sasso, K. Wagner, C. Morisseau, B. Inceoglu, B.D. Hammock, D. Piomelli, Peripheral FAAH and soluble epoxide hydrolase inhibitors are synergistically antinociceptive, Pharm. Res 97 (2015) 7–15, https://doi.org/10.1016/j.phrs.2015.04.001.
[183] A. Mabou Tagne, Y. Fotio, P.S. Uppal, D. Piomelli, Synergistic antinociceptive effects of concomitant NAAA and peripheral FAAH inhibition, Exp. Neurol. 357 (2022) 114194, https://doi.org/10.1016/j.expneurol.2022.114194.
[184] C. Nozaki, A. Markert, A. Zimmer, Inhibition of FAAH reduces nitroglycerin-induced migraine-like pain and trigeminal neuronal hyperactivity in mice, Eur. Neuropsychopharmacol. 25 (2015) 1388–1396, https://doi.org/10.1016/j.euroneuro.2015.04.001.
[185] R. Greco, C. Demartini, A.M. Zanaboni, E. Tumelero, A. Reggiani, A. Misto, D. Piomelli, C. Tassorelli, FAAH inhibition as a preventive treatment for migraine: A pre-clinical study, Neurobiol. Dis. 134 (2020) 104624, https://doi.org/10.1016/j.nbd.2019.104624.
[186] F. Nasirinezhad, S. Jergova, J.P. Pearson, J. Sagen, Attenuation of persistent pain-related behavior by fatty acid amide hydrolase (FAAH) inhibitors in a rat model of HIV sensory neuropathy, Neuropharmacology 95 (2015) 100–109, https://doi.org/10.1016/j.neuropharm.2014.11.024.
[187] M. Zubrzycki, M. Zubrzycka, G. Wysiadecki, J. Szemraj, H. Jerczynska, M. Stasiolek, Effect of Fatty Acid Amide Hydrolase Inhibitor URB597 on Orofacial Pain Perception in Rats, Int J. Mol. Sci. 23 (2022) 4665, https://doi.org/10.3390/ijms23094665.
[188] T. Watabiki, N. Tsuji, T. Kiso, T. Ozawa, F. Narazaki, S. Kakimoto, In vitro and in vivo pharmacological characterization of ASP8477: A novel highly selective fatty acid amide hydrolase inhibitor, Eur. J. Pharm. 815 (2017) 42–48, https://doi.org/10.1016/j.ejphar.2017.10.007.
[189] T. Kiso, T. Watabiki, T. Sekizawa, ASP8477, a fatty acid amide hydrolase inhibitor, exerts analgesic effects in rat models of neuropathic and dysfunctional pain, Eur. J. Pharm. 881 (2020) 173194, https://doi.org/10.1016/j.ejphar.2020.173194.
[190] S.R. Nass, F.F. Steele, T.B. Ware, A.H. Libby, K.-L. Hsu, S.G. Kinsey, Monoacylglycerol Lipase Inhibition Using JZL184 Attenuates Paw Inflammation and Functional Deficits in a Mouse Model of Inflammatory Arthritis, Cannabis Cannabinoid Res 6 (2021) 233–241, https://doi.org/10.1089/can.2020.0177.
[191] F. Lo Castro, C. Baraldi, L. Pellesi, S. Guerzoni, Clinical Evidence of Cannabinoids in Migraine: A Narrative Review, J. Clin. Med 11 (2022) 1479, https://doi.org/10.3390/jcm11061479.
[192] B.O. Okusanya, B.E. Lott, J. Ehiri, J. McClelland, C. Rosales, Medical Cannabis for the Treatment of Migraine in Adults: A Review of the Evidence, Front Neurol. 13 (2022) 871187, https://doi.org/10.3389/fneur.2022.871187.
[193] C. Baraldi, F. Lo Castro, A. Negro, A. Ferrari, M.M. Cainazzo, L. Pani, S. Guerzoni, Oral Cannabinoid Preparations for the Treatment of Chronic Migraine: A Retrospective Study, Pain. Med 23 (2022) 396–402, https://doi.org/10.1093/pm/pnab245.

[194] P. Poli, F. Crestani, C. Salvadori, I. Valenti, C. Sannino, Medical Cannabis in Patients with Chronic Pain: Effect on Pain Relief, Pain Disability, and Psychological aspects. A Prospective Non randomized Single Arm Clinical Trial, Clin. Ter. 169 (2018) e102–e107, https://doi.org/10.7417/T.2018.2062.
[195] G.E. Maurer, N.S. Imperato, C.M. Juybari, H. Kincaid, A. Koons, The Utility of Cannabis-Based Medicine in Chronic Pain Management: A Case Report, Cureus 14 (2022) e31555, https://doi.org/10.7759/cureus.31555.
[196] A. Parlar, S.O. Arslan, M.F. Doğan, S.A. Çam, A. Yalçin, E. Elibol, M.K. Özer, F. Üçkardeş, H. Kara, The exogenous administration of CB2 specific agonist, GW405833, inhibits inflammation by reducing cytokine production and oxidative stress, Exp. Ther. Med 16 (2018) 4900–4908, https://doi.org/10.3892/etm.2018.6753.
[197] G.T. Whiteside, S.L. Gottshall, J.M. Boulet, S.M. Chaffer, J.E. Harrison, M. S. Pearson, P.I. Turchin, L. Mark, A.E. Garrison, K.J. Valenzano, A role for cannabinoid receptors, but not endogenous opioids, in the antinociceptive activity of the CB2-selective agonist, GW405833, Eur. J. Pharm. 528 (2005) 65–72, https://doi.org/10.1016/j.ejphar.2005.10.043.
[198] B. Hu, H. Doods, R.-D. Treede, A. Ceci, Depression-like behaviour in rats with mononeuropathy is reduced by the CB2-selective agonist GW405833, Pain 143 (2009) 206–212, https://doi.org/10.1016/j.pain.2009.02.018.
[199] H. Gui, Y. Sun, Z.-M. Luo, D.-F. Su, S.-M. Dai, X. Liu, Cannabinoid receptor 2 protects against acute experimental sepsis in mice, Mediat. Inflamm. 2013 (2013) 741303, https://doi.org/10.1155/2013/741303.
[200] K. Parastouei, M.H. Aarabi, G.A. Hamidi, Z. Nasehi, S. Kabiri-Arani, F. Jozi, M.E. Shahaboddin, A CB2 Receptor Agonist Reduces the Production of Inflammatory Mediators and Improves Locomotor Activity in Experimental Autoimmune Encephalomyelitis, Rep. Biochem Mol. Biol. 11 (2022) 1–9, https://doi.org/10.52547/rbmb.11.1.1.
[201] S.-L. Cai, X.-G. Fan, J. Wu, Y. Wang, X.-W. Hu, S.-Y. Pei, Y.-X. Zheng, J. Chen, Y. Huang, N. Li, Z.-B. Huang, CB2R agonist GW405833 alleviates acute liver failure in mice via inhibiting HIF-1α-mediated reprogramming of glycometabolism and macrophage proliferation, Acta Pharm. Sin. 44 (2023) 1391–1403, https://doi.org/10.1038/s41401-022-01037-8.
[202] Z.-B. Huang, Y.-X. Zheng, N. Li, S.-L. Cai, Y. Huang, J. Wang, X.-W. Hu, Y. Wang, J. Wu, X.-G. Fan, Protective effects of specific cannabinoid receptor 2 agonist GW405833 on concanavalin A-induced acute liver injury in mice, Acta Pharm. Sin. 40 (2019) 1404–1411, https://doi.org/10.1038/s41401-019-0213-0.
[203] Z. Huang, H. Wang, J. Wang, M. Zhao, N. Sun, F. Sun, J. Shen, H. Zhang, K. Xia, D. Chen, M. Gao, R.P. Hammer, Q. Liu, Z. Xi, X. Fan, J. Wu, Cannabinoid receptor subtype 2 (CB2R) agonist, GW405833 reduces agonist-induced Ca(2+) oscillations in mouse pancreatic acinar cells, Sci. Rep. 6 (2016) 29757, https://doi.org/10.1038/srep29757.
[204] T.A.M. Vrechi, G.C. Guarache, R.B. Oliveira, E. da C. Guedes, A.G. Erustes, A.H.F. F. Leão, V.C. Abílio, A.W. Zuardi, J.E.C. Hallak, J.A. Crippa, C. Bincoletto, R. P. Ureshino, S.S. Smaili, G.J.S. Pereira, Cannabidiol-Induced Autophagy Ameliorates Tau Protein Clearance, Neurotox. Res 43 (2025) 8, https://doi.org/10.1007/s12640-025-00729-3.
[205] Z. Zou, S. Pan, C. Sun, J. Wei, Y. Xu, K. Xiao, J. Zhao, R. Gu, AM1241 inhibits chondrocyte inflammation and ECM degradation through the Nrf2/HO-1 and NF-κB pathways and alleviates osteoarthritis in mice, Mol. Med 31 (2025) 9, https://doi.org/10.1186/s10020-024-01012-5.
[206] H.M. Mahmoud, M. Osman, O. Elshabrawy, H.M.I. Abdallah, A. Khairallah, AM-1241 CB2 Receptor Agonist Attenuates Inflammation, Apoptosis and Stimulate Progenitor Cells in Bile Duct Ligated Rats, Open Access Maced. J. Med Sci. 7 (2019) 925–936, https://doi.org/10.3889/oamjms.2019.194.
[207] M. Zhang, Q. Tian, J. Liu, Cannabinoid Receptor-2 agonist AM1241 Attenuates Myocardial Ischemia-Reperfusion-Induced Oxidative Stress in Rats via Nrf2/HO-1 Pathway, Med Princ. Pr. 33 (2024) 597–606, https://doi.org/10.1159/000540751.
[208] X. Liu, D. Zhang, X. Dong, R. Zhu, Y. Ye, L. Li, Y. Jiang, Pharmacological activation of CB2 receptor protects against ethanol-induced myocardial injury related to RIP1/RIP3/MLKL-mediated necroptosis, Mol. Cell Biochem 474 (2020) 1–14, https://doi.org/10.1007/s11010-020-03828-1.
[209] S. Bayram, A. Parlar, S.O. Arslan, The curative effect of cannabinoid 2 receptor agonist on functional failure and disruptive inflammation caused by intestinal ischemia and reperfusion, Fundam. Clin. Pharm. 34 (2020) 80–90, https://doi.org/10.1111/fcp.12502.
[210] A.M. Ali, O.S. El-Tawil, A.K. Al-Mokaddem, S.S. Abd El-Rahman, Promoted inhibition of TLR4/miR-155/ NFkB p65 signaling by cannabinoid receptor 2 agonist (AM1241), aborts inflammation and progress of hepatic fibrosis induced by thioacetamide, Chem. Biol. Inter. 336 (2021) 109398, https://doi.org/10.1016/j.cbi.2021.109398.
[211] A. Parlar, S.O. Arslan, O. Yumrutas, E. Elibol, A. Yalcin, F. Uckardes, H. Aydin, M. F. Dogan, E. Kayhan Kustepe, M.K. Ozer, Effects of cannabinoid receptor 2 synthetic agonist, AM1241, on bleomycin induced pulmonary fibrosis, Biotech. Histochem 96 (2021) 48–59, https://doi.org/10.1080/10520295.2020.1758343.
[212] Y. Cai, F. Tong, K. Li, Q. Wang, J. Ding, X. Wang, Cannabinoid receptor 2 agonist AM1241 alleviates epileptic seizures and epilepsy-associated depression via inhibiting neuroinflammation in a pilocarpine-induced chronic epilepsy mouse model, Mol. Cell Neurosci. 130 (2024) 103958, https://doi.org/10.1016/j.mcn.2024.103958.
[213] C.R. de Carvalho, A.A. Hoeller, P.L.C. Franco, A.P.S. Martini, F.M.S. Soares, K. Lin, R.D. Prediger, B.J. Whalley, R. Walz, The cannabinoid CB2 receptor-specific agonist AM1241 increases pentylenetetrazole-induced seizure severity in Wistar rats, Epilepsy Res 127 (2016) 160–167, https://doi.org/10.1016/j.eplepsyres.2016.08.011.
[214] N. Clayton, F.H. Marshall, C. Bountra, C.T. O'Shaughnessy, CB1 and CB2 cannabinoid receptors are implicated in inflammatory pain, Pain 96 (2002) 253–260, https://doi.org/10.1016/S0304-3959(01)00454-7.
[215] J. Castro, S. Garcia-Caraballo, J. Maddern, G. Schober, A. Lumsden, A. Harrington, S. Schmiel, B. Lindstrom, J. Adams, S.M. Brierley, Olorinab (APD371), a peripherally acting, highly selective, full agonist of the cannabinoid receptor 2, reduces colitis-induced acute and chronic visceral hypersensitivity in rodents, Pain 163 (2022) e72–e86, https://doi.org/10.1097/j.pain.0000000000002314.
[216] B.R. Yacyshyn, S. Hanauer, P. Klassen, B.A. English, K. Stauber, C.F. Barish, K. Gilder, S. Turner, P.D.R. Higgins, Safety, Pharmacokinetics, and Efficacy of Olorinab, a Peripherally Acting, Highly Selective, Full Agonist of the Cannabinoid Receptor 2, in a Phase 2a Study of Patients With Chronic Abdominal Pain Associated With Crohn's Disease, Crohns Colitis 360 3 (2021) otaa089, https://doi.org/10.1093/crocol/otaa089.
[217] L. Chang, B.D. Cash, A. Lembo, D.C. Kunkel, B.A. English, B. Lindstrom, G. Gu, S. Skare, K. Gilder, S. Turner, F. Cataldi, D. Lipkis, J. Tack, Efficacy and safety of olorinab, a full agonist of the cannabinoid receptor 2, for the treatment of abdominal pain in patients with irritable bowel syndrome: Results from a phase 2b randomized placebo-controlled trial (CAPTIVATE), Neurogastroenterol. Motil. 35 (2023) e14539, https://doi.org/10.1111/nmo.14539.
[218] R. Spiera, M. Kuwana, D. Khanna, L. Hummers, T.M. Frech, W. Stevens, M. Matucci-Cerinic, S. Kafaja, O. Distler, J.-B. Jun, Y. Levy, P. Leszczyński, J. Gordon, V. Steen, E.B. Lee, T. Jankowski, I. Litinsky, L. Chung, V. Hsu, M. Mayes, N. Sandorfi, R.W. Simms, S. Finzel, J. de Vries-Bouwstra, S. Constantine, N. Dgetluck, Q. Dinh, B.J. Bloom, D.E. Furst, B. White, C. P. Denton, the R.-1 S. Group, Efficacy and Safety of Lenabasum, a Cannabinoid Type 2 Receptor Agonist, in a Phase 3 Randomized Trial in Diffuse Cutaneous Systemic Sclerosis, Arthritis Rheumatol. 75 (2023) 1608–1618, https://doi.org/10.1002/art.42510.
[219] V.P. Werth, E. Hejazi, S.M. Pena, J. Haber, M. Zeidi, N. Reddy, J. Okawa, R. Feng, M.M. Bashir, K. Gebre, A.S. Jadoo, J.S.S. Concha, N. Dgetluck, S. Constantine, B. White, Safety and Efficacy of Lenabasum, a Cannabinoid Receptor Type 2 Agonist, in Patients with Dermatomyositis with Refractory Skin Disease: A Randomized Clinical Trial, J. Invest Dermatol. 142 (2022) 2651–2659.e1, https://doi.org/10.1016/j.jid.2022.03.029.
[220] J.F. Chmiel, P. Flume, D.G. Downey, A.J. Dozor, C. Colombo, H. Mazurek, E. Sapiejka, M. Rachel, S. Constantine, B. Conley, N. Dgetluck, Q. Dinh, B. White, J.S. Elborn, Lenabasum JBT101-CF-001 Study Group, Safety and efficacy of lenabasum in a phase 2 randomized, placebo-controlled trial in adults with cystic fibrosis, J. Cyst. Fibros. 20 (2021) 78–85, https://doi.org/10.1016/j.jcf.2020.09.008.
[221] Shionogi, A Phase Ib/IIa, Multiple-Dose, Double-Blind, Randomized, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of S-777469 in Subjects With Mild to Moderate Atopic Dermatitis, clinicaltrials.gov, 2018. ⟨https://clinicaltrials.gov/study/NCT00697710⟩ (accessed March 23, 2025).