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Analogues and Derivatives of Cannabidiol: Pharmacological Insights and Recent Efforts in the Search for Novel Drug Candidates for Inflammation and Pain - a Brief Review Over the Past 3 Decades

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Cannabidiol is a metabolite present in *Cannabis* with several pharmacological properties, including neuroprotection, anti-convulsive, antimicrobial, antinociceptive, and anti-inflammatory. Although these activities are promising for drug development and clinical uses, the neuroprotective action is the most investigated, while the anti-inflammatory and antinociceptive mechanisms are not fully known. Therefore, this brief review aims to report the knowledge advances over the last 3 decades regarding the anti-inflammatory and anti-nociceptive/analgesic properties of cannabidiol and its derivatives or analogues designed as novel drug candidates. Recent studies of the mechanisms of action underlying the anti-inflammatory effects of cannabidiol have revealed its interaction with different inflammatory mediators, including cannabinoid receptor 1 and cyclooxygenase 2, among others. On the other hand, there is a lack of information related to the analgesic activity of cannabidiol, with some reports pointing out the involvement only of transient receptor potential vanilloid receptors. In addition, several cannabidiol derivatives and structural analogues with anti-inflammatory and antinociceptive activities have been described, but their mechanisms of action have not yet been fully elucidated. Therefore, it is clear that greater efforts are still needed to unravel the mechanisms involved in such activities of great interest in drug discovery.

Keywords: cannabidiol, anti-inflammatory activity, analgesic activity, cannabinoids

1. Introduction

The use of *Cannabis* can be traced to around 2900 B.C. in China, where it was used to treat inflammation and pain.[1] Cannabinoids are one class of the many other compounds present in *Cannabis* species. They can be divided into endogenous, synthetic, and phytocannabinoids, such as Δ^9-tetrahydrocannabinol (Δ^9-THC, **1**) and cannabidiol (CBD, **2**, Figure 1).[2] Adams *et al.*[3] isolated the CBD (**2**) for the first time in 1940, while its structure was elucidated only in 1963.[4] CBD (**2**) is a lipidic structure, with a molecular architecture based on an alkyl-resorcinol (AR) fragment connected to a monoterpene subunit,[5] varying in the stereochemistry and diverse functionalization, and (–)-CBD ((–)-**2**) is the naturally occurring stereoisomer in *Cannabis*, whereas (+)-CBD (+-(**2**)) is obtained only by organic synthesis.[6]

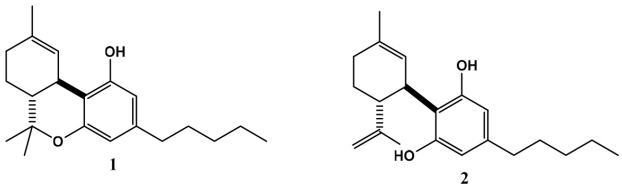

Figure 1. Chemical structure of THC (**1**) and (–)-CBD (**2**).

Cannabinoids can act in the immune system, central nervous system (CNS), endocrine and digestive systems,[7] showing anxiolytic and anesthetic activities.[5] Pharmacokinetics and medicinal effects of this class depend on the formulation and route of administration, as well as the bioavailability.[8] Regarding the anti-inflammatory activity of CBD (**2**), it has been described in *in vivo* and *in vitro* studies, as a result of an inhibition of nitric oxide synthase (NOS), as well as nitric oxide (NO), tumor

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necrosis factor-alpha (TNF-α), and interleukin 1-β (IL-1β).[9] More detailed biomarkers related to CBD (**2**) will be covered in this review.

The cannabinoid 1 (CB1) receptor is the most relevant cannabinoid target in the CNS, exerting a central role by blocking the Ca^{2+} influx in the pre-synaptic nerve and interfering in the release of some neurotransmitters, such as glutamate. CB1 is more widespread throughout the body with a particular expression in nociceptive areas of the central nervous system and spinal cord,[9] having CBD (**2**) as its noncompetitive allosteric modulator.[10,11] The cannabinoid 2 (CB2) receptor is more prominent in lymphatic and immune tissues and plays an important role in the modulation of pain and inflammatory processes. CBD (**2**) so interacts with the protein G55 receptor (GPR55), transient receptor potential vanilloid (TRPV), and peroxisome proliferator-activated receptor gamma (PPARγ).[12] In Table 1 we summarize some information about the different activities of CBD (**2**) which are discussed in this review, as well as the possible mechanism of action associated to different pathologies.

In the view of clinical uses, there are currently two cannabinoid-based medicines approved for the treatment of chronic pain in the USA, Canada, and several European countries, namely Sativex, based on mixed natural extracts of Δ^9-THC (**1**) and CBD (**2**), and Epidiolex, containing only CBD (**2**).[10] It has also been proposed that CBD (**2**), as well as other cannabinoids, may have drug-drug and dose-response interactions, but this is not fully understood, with a notable lack of information on this aspect related to cannabinoids.[8]

Therefore, this review aims to report the contribution of biological sciences and medicinal chemistry efforts in the comprehension of the pharmacological basis of the

Table 1. Activities of CBD (**2**), possible mechanisms of action, and associated pathologies

Activity	Possible mechanism of action	Pathology	Target; potency
Anti-inflammatory	inhibition of nitric oxide synthase (iNOS) and nitric oxide (NO), TNF-alpha inhibition and IL-1β inhibition;[9] inverse agonism of GPR12, GPR6, and GPR3;[13,14] activation of CB2 and A2A receptors, reducing inflammatory mediators (IL-6, COX-2, TNF-α, and iNOS). Reduction of pro-inflammatory cytokines (IL-4, IL-5, and IL-13, of the matrix metalloproteinases (MMPs) 3 and 13, and p38 mitogen-activated protein kinase (p38 MAPK); competitive inhibition of ENT;[15] agonism of PPARγ, inhibition of NF-κB, interaction with Nrf2[15-19]	Alzheimer's disease (AD), Parkinson's disease (PD), cancer and infertility	PPARγ; EC_{50} > 25 μM[20]
Anti-nociception/analgesic	agonism on the capsaicin receptor TRPV1; modulation of several pro-inflammatory mediators, such as IL-2, IL-4, and interferon-γ (IFN-γ);[15,21,22] prevention of opening of the voltage-gated sodium channel (Nav)[23-25]	chronic neuroinflammation, neuropathic pain, and fibromyalgia	Nav1.1/7; potency: 1.9 to 3.8 μM[23]
Neuroprotection and chronic diseases	THC and CBD reduced NMDA, AMPA, and kainate through a different mechanism from the glutamate receptor;[26] downregulation of GSK-3β, inhibiting the WNT/β-catenin pathway; or the upregulate of WNT/β-catenin pathway by the downregulation of caspase3[6]	PD and AD	GPR55; EC_{50}: 445 nM[27]
Neurological and neuropsychiatric disorders	5-HT1A agonism, as well as adenosine G protein-coupled (GPR55, 18, and 19), TRPV2, TRPV3 and TRPV4 receptors;[28] interaction with the Cys-loop superfamily of ligand-gated ion channels through $GABA_A$ receptor, 5-HT3Rs, and glycine receptor (GlyRs)[29]	depression and other behavioral-related pathologies	CB1; K_i: 1.459 ± 0.159 μM[30] CB2; K_i: 0.372 ± 0.058 μM[30] FAAH; IC_{50} 53.2 ± 11.3 μM[30]

TNF: tumor necrosis factor; IL: interleukin; GPR12, GPR6, GPR3, GPR55; adenosine protein G12, 6, 3, 55 receptor; CB2, CB1: cannabinoid 2 and 1; A2A: adenosine receptor A2A; COX-2: cyclooxygenase-2; ENT: balanced nucleoside transporter; PPARγ: peroxisome proliferator-activated receptor gamma; NF-κB: nuclear factor kappa B; Nrf2: nuclear erythroid-related factor 2; EC_{50}: half-maximal effective concentration; TRPV: transient vanilloid receptor potential; THC: tetrahydrocannabinol; CBD: cannabidiol; NMDA: *N*-methyl-D-aspartate; AMPA: amino-3-hydroxy-5-methyl-4 isoxazolepropionate; GSK-3β: glycogen synthase kinase 3β; WNT: signaling pathways are a group of intercellular signal transduction pathways, Wnt is a linguistic blend of the names Wingless and Int-1; 5-HT1A: 5-hydroxytryptamine type 1A receptor; $GABA_A$: type A aminobutyric acid receptor; 5-HT3R: 5-hydroxytryptamine type 3 receptor; K_i: inhibitory constant; FAAH: fatty acid amide hydrolase; IC_{50}: half-maximal inhibitory concentration.

anti-inflammatory and antinociceptive activity of CBD (**2**) during the last three decades, as well as numerous synthetic CBD-based analogues and derivatives designed as novel potential innovative anti-inflammatory and analgesic drug candidate prototypes. For such a goal, PubMed, Scopus, and SciFinder were used as electronic databases for searching literature data related to the pharmacology of CBD (**2**) as an anti-inflammatory and antinociceptive agent, covering the last 3 decades period (1993-2023). Literature data were accessed by using the terms "CBD", "Cannabidiol", "Cannabidiol derivatives" and "Cannabidiol analogues" in combination with "anti-inflammatory", "antinociceptive" and "analgesic" as keywords. Inclusion criteria were applied for studies that addressed the synthesis and/or evaluation of CBD analogues. Exclusion criteria were applied for (*i*) studies that addressed other compounds present in *Cannabis*; (*ii*) studies that excluded synthetic analogues; (*iii*) gray literature (e.g., thesis and dissertations, books, unpublished works). The results were grouped and discussed into the first (1993-2003), second (2004-2013), and third (2014-2023) decades separately along the text.

1.1. 1993-2003: the first decade of pharmacological studies on the potential of CBD as an analgesic and anti-inflammatory drug candidate

From 1993 to 2003, ten papers were selected, with only three approaching the pharmacology and metabolism of CBD (**2**), but none of them related to CBD's anti-inflammatory and antinociceptive mechanism.

In 1995, Yamamoto *et al.*[31] reported that CBD (**2**) was capable of inactivating enzymes of the cytochrome P450 (CYP450) family, especially CYP2C11, 2A, and 3A subfamilies in animals, and CYP2C29 in human hepatic microsomes, providing information about CBD's metabolism. In 1999, Emil Pop[11] investigated some natural and synthetic cannabinoid ligands to understand the potential medicinal use of these compounds by modulation of CB1 and CB2 receptors, focusing on the neuroprotective activity, such as protection against toxic levels of glutamate (CBD (**2**), 10 mM).[32] In his review,[11] this author states that cannabinoids have antinociceptive activity, possible due to interaction with CBs. Despite those findings, the mechanism of action had only been proposed, requiring further studies.

However, prejudice and unreliable reports contributed to the avoidance of clinical use of cannabinoids, even though there were clinical protocols that avoided the application of THC. Until the 2000s, there were reports of CBD's analgesic and anti-inflammatory activities,[33] including data from patients with improved conditions related to depression and anxiety, as well as reports of neuroprotection.[34] However, the slow elimination of cannabinoids was cited[33] as a relevant obstacle to the safety of their use, which may vary according to the route of administration. This occurs because cannabinoids quickly enter the bloodstream due to their lipophilicity, being quickly absorbed and converted into their metabolites.[33]

Regarding neuroprotection, one study identified that THC (**1**) and CBD (**2**) reduced toxicity mediated by *N*-methyl-D-aspartate (NMDA), amino-3-hydroxy-5-methyl-4 isoxazoleproprionate (AMPA), and kainate through a different mechanism from the glutamate receptor. In the glutamatergic-based mechanism there is the involvement of cannabinoid receptors in the reduction of reactive oxygen species (ROS), while THC (**1**) and CBD (**2**) seem to reduce toxicity independently of these receptors.[26] A possible anti-inflammatory activity was also suggested despite the complexity and multifactorial aspects of this condition since some studies identified that CBD (**2**) could effectively suppress TNF production. Regarding cannabinoid receptors, both anticonvulsant and anti-inflammatory activities seemed to be stereospecific, once (+)-CBD and its analogues favorably bind to CB1 and CB2 receptors, as opposed to (–)-CBD (**2**) that could not bind to either of them. It is known that CBD (**2**) does not act through the modulation of CB receptors, suggesting that there could be other receptors responsible for its anti-inflammatory properties.[35]

In 2003, a review paper published by Grotenhermen[36] summarized and discussed the state-of-art of CBD (**2**) pharmacokinetics, making it possible to identify some physicochemical similarities to THC (**1**), and that their different effects could be a result of higher brain concentrations of unchanged CBD (**2**) in comparison to THC (**1**).[35,36] However, the author focused only on the ability of THC (**1**) to modulate CB1 and CB2, evidencing that its effects in activation of the CB1 are similar to marijuana, and that activation of the CB2 induces analgesic, antineoplastic, and anti-inflammatory responses, suggesting also the existence of other subtypes of cannabinoid receptors. In this sense, other types of receptors, such as transient receptor potential (TRP), which include vanilloid receptors (TRPV1, TRPV2, TRPV3, TRPV4, among others),[37,38] seems to play individual or synergic roles in the pharmacological effects of CBD (**2**) as antiepileptic, anti-inflammatory, neuroprotective, antitumor, anxiolytic, and antimicrobial agent.[36]

As a result of extensive biological studies about cannabinoid receptors, anandamide and 2-arachidonylglycerol were recognized as two of the main endogenous ligands for CB1 and CB2, the so-called

endocannabinoids. Those endocannabinoid ligands are released through a stimulus-dependent mechanism, and show different affinities for such receptors,[11,39] serving as inspiration for the design of several synthetic cannabinoids with increased affinity and selectivity.[36]

1.2. 2004-2013: the second decade of pharmacological studies on the potential of CBD as an analgesic and anti-inflammatory drug candidate

In the second decade, covering the period of 2004 to 2013, it was found 95 papers reported studies of CBD (**2**) and other phytocannabinoids as bioactive compounds, but only three were addressed to the pharmacology of CBD (**2**). Among these, Pertwee and co-workers[40-42] reviewed the aspects of some phytocannabinoids, highlighting the low affinity of CBD (**2**) for CB1 and CB2 receptors, interacting only in the [^{3}H]CP55940 region. Further studies make clear that this interaction was sufficient to antagonize these two receptors (K_B = 79 nM for CB1 and 138 nM for CB2, where K_B is intrinsic binding constant) in a non-competitive manner, acting as an inverse agonist when in insufficient concentrations to bind to the orthosteric sites. In addition, the authors[40] showed that CBD was capable of acting as an inverse agonist of CB2, showing anti-inflammatory activity, and reinforced that different mechanisms of action should be enlightened as responsible for such activity.

De Petrocellis and Di Marzo[43] investigated the action of cannabinoids in non-CB1 and CB2 receptors, such as G-protein-coupled receptors (GPCR) and transient receptor potential channels (TRPC), which mediates some responses related to the known 'tetrad effects' of THC (**1**), as well as in antinociception and molecular modulation of anti-inflammatory cytokines. CBD (**2**) showed high ability for interaction with GPR55 (half-maximal effective concentration (EC_{50}) = 350 nM; $[Ca^{2+}]_i$ mobilization 10 μM), TRPV1 (EC_{50} = 3.5 ± 0.3 μM), TRPV2 (EC_{50} = 3.7 μM), TRPM8 (EC_{50} = 80 ± 10 nM), and TRPA1 (EC_{50} = 96 ± 12 nM),[43] corroborating some previous findings reported by Pertwee and co-workers[40,41,44] about the potential ability of CBD (**2**) to bind in receptors other than CB1 and CB2.

In 2008, Luzi *et al*.[45] published a study related to *Cannabis* and its effects on psychosis. Based on an *in vivo* study of behavioral changes in rats, it was proposed that CBD (**2**) (15-480 mg kg^{-1}) could exert antipsychotic activity, with greater activity and lower toxicity than other clinical antipsychotics such as haloperidol (0.062-1.0 mg kg^{-1}), even though the mechanism of this activity was unclear.[45,46] One year later, Lader[47] published a revision of the pharmacological aspects of marijuana addiction and several physiological effects of CBD (**2**), including tachycardia, increased blood pressure, relaxation, and euphoria, highlighting the lack of detailed and comprehensive information on the pharmacology of CBD (**2**).

1.3. 2014-2023: the third decade of pharmacological studies on the potential of CBD as an analgesic and anti-inflammatory drug candidate

In the last decade (2014-2023), we observed an exponential increase in publications related to the pharmacology, toxicology, and medicinal uses of CBD (**2**), besides other several studies on biotechnological and biological studies for improved production of *Cannabis* derivatives and CBD-enriched plant variants, reaching more than 587 publications in different scientific journals. However, despite a strong interest in CBD (**2**) as a potential multifunctional active metabolite, only five publications addressed its anti-inflammatory and antinociceptive effects, suggesting a lack of information about these properties related to CBD (**2**) and other cannabinoids, as well as few molecular targets and possible mechanisms of action. In one of these studies, Sklenárová *et al*.[48] reviewed clinical and preclinical findings of CBD (**2**) in inflammation, but it was not possible to conclude about its effects on pain relief, given the different methods used by the different research groups.

In 2020, Dume and Lammers[49] reviewed some pharmacological and toxicological aspects of *Cannabis*, as well as its main cannabinoid constituents, THC (**1**) and CBD (**2**), as potential agents against neuropathic and rheumatic pain conditions. In this study, the authors highlighted the non-psychomimetic effects of CBD (**2**) and its ability to bind to CB1 and CB2 receptors. It also emphasized the beneficial clinical effects of preparations based on mixtures of THC/CBD or single CBD (**2**) medications in pain relief in more than 50% of adult patients.[49,50] In addition, pharmacokinetic studies revealed that CBD (**2**) is significantly affected by first-pass metabolism, with only 6% bioavailability, being capable of being rapidly distributed in tissues, and with a high capacity of binding to plasmatic proteins.[51] The use of *Cannabis* or cannabinoid/CBD-containing products was also evaluated in a group of 159 patients with different painful and inflammatory chronic conditions, including fibromyalgia, osteoarthritis, chronic spinal pain, and rheumatoid arthritis, with symptoms refractory to conventional treatment. However, as observed in other similar studies,[52,53] the quality of the available data was not sufficient for a recommendation for routine clinical use. Boyaji *et al*.[53] also highlighted the lack of clinical or pharmacological information related to

a single administration of CBD (**2**) in pain management, since the majority of the reported studies had been conducted with preparations of *Cannabis* extracts or a mixture of THC/CBD in a 1:1 ratio. The authors drew attention that in 2020, Nabiximols was the only approved and commercially standardized extract containing CBD (**2**) to treat pain and other central disturbs, with available data in the literature.[53-55] Regarding neuropathic pain, clinical use of Nabiximols (Sativex®) demonstrated statistically significant analgesic effects, with medium to moderate side effects, but no conclusive insights about its mechanism of action were observed.[53]

The literature data has shown the first data for a clearer understanding of the complex and multifaceted molecular environment related to pharmacology and possible mechanisms of action underlying analgesic and anti-inflammatory properties of CBD (**2**). In 2020, Sunda and Arowolo[15] reviewed the anti-inflammatory activity of CBD (**2**) as a result of its action on CB2 and adenosine A2A receptors, mediating the reduction of inflammatory mediators such as interleukin-6 (IL-6), cyclooxygenase-2 (COX-2), TNF-α, and nitric oxide synthase (iNOS). Moreover, it was experimentally shown that CBD (**2**) was capable of reducing inflammation in the airways and fibrosis, reducing some pro-inflammatory cytokines, such as IL-4, IL-5, and IL-13. On the other hand, activation of the CB2 receptor could lead to the inhibition of the production of inflammatory mediators, such as IL-6, matrix metalloproteinases (MMPs) 3 and 13, and p38 mitogen-activated protein kinase (p38 MAPK). CBD (**2**) also affects inflammatory response by acting as a competitive inhibitor of extracellular adenosine receptors in the balanced nucleoside transporter (ENT), which generates an anti-inflammatory response in different tissues. However, the mechanism of action related to adenosine remains unclear.[15] It was also identified that CBD (**2**) can act as an agonist of PPARγ, being an inhibitor of the transcription of nuclear factor kappa B (NF-κB) and interacting with nuclear erythroid-related factor 2 (Nrf2), resulting in a positive modulation of the oxidative stress (OS) related to inflammation.[15-17,19] It has been demonstrated that CBD (**2**) can interact with TRPV channels, especially acting as an agonist of the capsaicin receptor TRPV1 and reducing chronic neuroinflammatory and neuropathic pain, besides acting through Ca^{2+} ion influx and modulating the secretion of several pro-inflammatory mediators, such as IL-2, IL-4, and interferon-γ (IFN-γ).[15,21,22]

CBD (**2**) can also act through indirect mechanisms involving endocannabinoid receptors, such as negative allosteric modulation of CB1 and CB2, and inhibition of fatty acid amide hydrolase (FAAH), which can interfere in the immune system, but with an unclear type of an inhibitory or activator response. To date, nearly 65 CBD-related targets have been identified, responding to the multiple CBD (**2**) effects, including neuroprotective, anticonvulsant, antipsychotic, and immunomodulator. In addition to the above-mentioned endocannabinoid and TRPV1 receptors, and FAAH (half-maximal inhibitory concentration (IC_{50}) = 53.2 ± 11.3 μM), A2A, MMPs, PPARγ (EC_{50} > 25 μM), and NF-κB, serotonin receptors ($5\text{-}HT_{1A}$) were also recently reported[28] as targets for an agonist effect of CBD (**2**), leading to antidepressant and other behavioral effects, as well as adenosine G protein-coupled receptors (GPR55, 18, and 19), TRPV2, TRPV3 and TRPV4. CBD (**2**) has also been studied for its potential neuroprotective and anti-neuroinflammatory properties with potential therapeutic application against neurodegenerative diseases, such as Parkinson's disease (PD), and Alzheimer's disease (AD). In such chronic diseases, CBD (**2**) could act in the downregulation of glycogen synthase kinase 3β (GSK-3β), inhibiting the WNT/β-catenin pathway, which is related to OS and inflammation.[10,56] Other studies[6] have suggested that CBD (**2**) can upregulate the WNT/β-catenin pathway by the downregulation of caspase 3, reducing the production of neurofibrillary tangles and inhibiting neuronal death.

Ghovanloo and co-workers[23-25] have recently shown that CBD (**2**) prevents the opening of the voltage-gated sodium channel (Nav), affecting sensory neurons acting in pain treatment, being, therefore, a non-selective inhibitor of Nav, with a potency range of 1.9 to 3.8 μM, besides acting as an inverse agonist/antagonist of CB1, and a modulator of biomembranes.

In neurological and neuropsychiatric disorders, CBD (**2**) interacts with the Cys-loop superfamily of ligand-gated ion channels through type A aminobutyric acid receptor ($GABA_A$), 5-HT3Rs, and glycine receptor (GlyRs). Alldred *et al.*[57] developed a molecular model to evaluate the affinity of $GABA_A$ subunits suggesting that CBD (**2**) has a higher affinity for the α2β3γ2 isoform, which could be responsible for the fast heterosynapses effect.[57] In GlyRs, CBD (**2**) interacts with the S296 residue, while in the 5-HT3Rs there is a lack of more detailed information related to its allosteric inhibitory interaction.[58]

Even though the neuroprotective activity of CBD (**2**) is the most reported issue in the literature, in 2023, Tambe *et al.*[13] stated that the molecular mechanisms underlying neuroprotection attributed to CBD (**2**) were still not completely understood. It seems that a multitude of cross-talked biochemical and cellular signaling cascades are capable of being modulated by CBD (**2**) interaction and one proposed mechanism is that CBD (**2**) acts as an

inverse agonist of GPR12, GPR6, and GPR3,[13] that are important G-protein coupled receptors related to several chronic and inflammatory conditions, such as AD, PD, cancer, and infertility.[14]

Overall, the available literature data from the last thirty years of research on CBD (**2**) pharmacology and therapeutical uses, especially that focused on the clinics of painful and inflammatory conditions, give us a clear perception of the complexity underlying a more complete and accurate knowledge related to the molecular basis of CBD's mechanisms of action. Therefore, in more recent years, intensive efforts have been addressed to a better understanding of such properties, possible molecular targets, cross-talking interactions, and concomitant modulation of interconnected biochemical cascades, not only focused on the action of CBD (**2**) but also on its synthetic analogues and derivatives that could represent innovative drug candidate prototypes against chronic dysfunctions, especially those related to inflammation and pain.

2. Synthetic Derivatives and Analogues of CBD Designed as Potential Analgesic and Anti-Inflammatory Drug Candidates

Abnormal cannabidiol (Abn-CBD, **3**, Figure 2) is a non-psychotropic synthetic regioisomer of CBD (**2**) with low affinity for CB1 and CB2 receptors, acting as a GPR55 agonist, that has been reported[37,38] for its cardiovascular, anti-tumoral, and anti-diabetes effects. Von Widdern *et al*.[59] conducted *in vitro* anti-inflammatory studies on astrocytic-microglial cocultures and astrocytic isolated cultures from neonatal C57BL/6 mice (a CB2 knockout mice) at 1 and 10 μM concentrations of **3**. As a result, in both models was observed a significant reduction in the lipopolysaccharide (LPS)-induced production of NO in astrocytic-microglial cocultures, as well as for TNF-α production on astrocytic-microglial cocultures and wild type of astrocytic isolated cultures, especially at 10 μM. However, it was not observed significant effect on IL-6 production in models. Thus, Abn-CBD was considered a promising glial cell modulator, altering the secretion of pro-inflammatory cytokines independent of CB1/CB2 receptors.[59] In another study,[60] it was shown that administration of compound **3** (5 mg kg^{-1}, i.p. (intraperitoneal), 3 days) attenuates the degree of colitis by decreasing myeloperoxidase (MPO) activity. MPO is an enzyme with a central role in the cell signaling process and the production of reactive oxygen species (ROS), especially during inflammation.

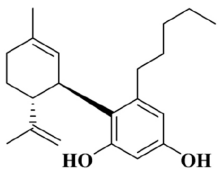

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Figure 2. Abn-CBD (**3**).

In previous studies, Abn-CBD (**3**) had been already investigated by Ruz-Maldonado *et al*.[61] for its potential influence on inflammatory models by using transgenic mice C57BL/6J ($GPR55^{+/+}$; $GPR55^{-/-}$) and human β-cell islets. Experimental results demonstrated that Abn-CBD (**3**) increases insulin secretion from human and mouse islets at all tested concentrations (0.1, 1, and 10 μM) and that in the higher dose, it was capable of protecting islet cells against cytokine-induced apoptosis (IL-1β, TNF-α, IFN-γ), especially in $GPR55^{+/+}$ mice and human cells. In addition, at 1 μM of compound **3**, it was observed a significant stimulation in the proliferation of β-cells on islets. Further studies[59] suggested that a possible mechanism of action underlying these results could be related to the increase in phosphorylation of protein kinase B (AKT) through GPR55.

In another approach, Romero-Zerbo *et al*.[62] investigated the *in vivo* effects of Abn-CBD (**3**) in the DIO-mouse (diet-induced obesity) model of prediabetics. This assay was based on the treatment of transgenic C57BL/6J male mice with 0.05 mg kg^{-1} (i.p.) of **3** for 2 weeks, but no changes were observed in body weight and plasma lipid profile between animal groups with a high-fat diet (HFD) and standard diet (SD). However, a comparative analysis of animals from the HFD-vehicle group treated with Abn-CBD (**3**) evidenced a marked increase in the proliferation of β cells, decreasing apoptosis beyond restoring the level of IL-6, chemokine ligand 1 (CXCL-1) and IL-5, and lowered phosphorylation rate of NF-κB. In *in vivo* experimental models of diabetes, especially for type 1 diabetes (T1D), compound **3** has been identified as a potent modulator of the inflammatory response in two complementary animal models, the non-obese diabetic mouse model (NOD), which is considered the gold standard model of T1D, and the streptozotocin model (STZ), based on the injection of STZ in C57BL/6J mice inducing damage to β-cells and loss of insulin. The treatment of 0.1 or 1.0 μM (i.p.) of Abn-CBD (**3**) led to a reduced progression of insulitis, with lowering blood glucose, and reduced cell apoptosis, but without significant changes in the levels of TNF-α and IL-6 in the NOD model. Moreover, pre-treated animals with a higher dose of **3** (1 mg kg^{-1}) showed reduced cell apoptosis compared to vehicle, with lower activation of NF-κB and pro-inflammatory cytokines (IL-6, TNF-α), suggesting a potent modulatory response of Abn-CBD (**3**) in T1D.[63]

In 2001, Kunos and Billy[64] synthesized the compound O-1602 (**4**, Figure 3), another bioactive CBD (**2**) regioisomer, with significant vasodilation activity. Additional studies[61] revealed that O-1602 (**4**) does not bind to cannabinoid receptors, but has a high affinity for GPR55, and a prominent effect in nociception regulation. *In vivo* experiments showed that in the acute inflammation model, compound O-1602 (**4**) was capable of altering nociception in rats at a dose of 100 μg (intra-arterial injection), reducing significantly the mechanical sensitivity mediated by C-fibers. Further mechanistic investigations evidenced that O-1602 (**4**) acts through peripheral GPR55 receptors.[65]

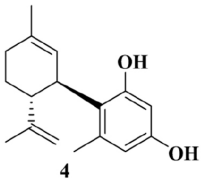

Figure 3. Structure of O-1602 (**4**).

Li *et al*.[66] investigated the anti-inflammatory properties of O-1602 (**4**) in an acute pancreatitis (AP) model using C57BL mice treated with 10 mg kg^{-1} (i.p.). Histopathological analysis and quantification of inflammatory mediators showed that compound O-1602 (**4**) significantly reversed the cerulein-induced AP, decreasing TNF-α levels, but not IL-6, and protecting pancreatic tissues, as an apparent effect on GPR55.

In a more recent study, Wróbel *et al*.[67] investigated the potential benefits of O-1602 (**4**) in hemorrhagic cystitis. Female Wistar rats were injected with a single dose of cyclophosphamide (CYP, 200 mg kg^{-1}, i.p.) to induce hemorrhagic cystitis, and treated with O-1602 (0.25 mg kg^{-1}, i.v. (intravenous)) for 7 days. As a result, treated animals showed a restored level of some biomarkers related to inflammation, such as IL-1β, IL-6, TNF-α, oxidative stress, CGRP (calcitonin gene related peptide), and NIT (3-nitrotyrosine) that play a role in the urinary tract-related inflammatory process. Taken together, the experimental data indicate that O-1602 (**4**) is effective in the modification of the histological and cytometric properties of the bladder, through anti-inflammatory and antioxidant pathways. In another study, the effects of O-1602 (**4**) were studied by Wei *et al*.[68] in the acute TNBS-induced (2,4,6-trinitro-benzene sulfonic acid) colitis model. Animals were treated with O-1602 (**4**, 10 mg kg^{-1}, i.p.), and CBD (**2**, 1 mg kg^{-1}) 30 min before intraretal administration of TNBS (125 mg kg^{-1}), and cytokine levels in plasma and other inflammatory parameters were evaluated. As a result, the increased levels of IL-6 and TNF-α induced by TNBS were partially reverted by the co-administration of O-1602/CBD, reducing IL-6 levels, but not TNF-α, in an independent pathway of GPR55 receptor.

The DMH-CBD or HU-219 (**5**, Figure 4) is a CBD (**2**) analogue with a modified hydrocarbon chain and was first synthesized in 1985 by Consroe and co-workers,[69] showing anti-inflammatory effects in two independent studies. First, in 2016, Juknat *et al*.[16] investigated its anti-inflammatory activity in microglial (BV-2) cells. Pre-treatment of LPS-stimulated BV-2 cultures with 1, 5, and 10 μM of **5** were analyzed by qPCR (quantitave polymerase chain reaction), showing 88 and 82% decreased levels of messenger ribonucleic acid (mRNA) of interleukins IL-1β and IL-6 at 10 μM, respectively, in a dose-dependent manner, as well as an increase in expression of mRNA genes related to oxidative stress. More recently (2018), a second study was carried out by dos Santos Filho *et al*.[70] to evaluate the *in vitro* anti-inflammatory response of LPS-stimulated macrophages, focusing on the quantification of TNF-α levels through the NF-κB pathway, after a pre-treatment with compound **5** at 10, 30, 100, and 300 μM dosages. Experimental data evidenced a marked reduction in the TNF-α production/release through the NF-κB signaling pathway in a dose-dependent manner with an IC_{50} of 38 μM, without acute cytotoxicity. Further studies[70] revealed that these effects are mediated through A2a receptors and inhibition of phosphorylation MAK-p38, reinforcing the anti-inflammatory properties of DMH-CBD (**5**) and its relevance for drug development.

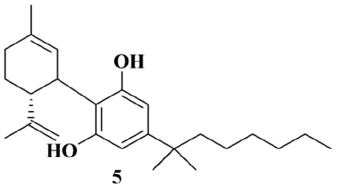

Figure 4. Chemical structure of DMH-CBD (**5**).

Seeking novel CBD (**2**) derivatives with improved central effects on behavioral disturbs led Breuer *et al*.[71] to synthesize three new fluorinated CBD (**2**) derivatives. Among them, 4'-F-CBD or HUF-101 (or PECS-101, **6**, Figure 5), showed to be considerably more potent than CBD (**2**) in behavioral assays in mice, with a predictive promising anxiolytic, antidepressant, antipsychotic, and anti-compulsive activities. Silva *et al*.[72] investigated HUF-101 (**6**) for its antinociceptive effects in three different nociceptive acute animal models at doses of 3, 10, and 30 mg kg^{-1}. In both hot place and acetic acid-induced hyperalgesia assays, HUF-101 (**6**) showed significant antinociceptive activity at the highest dose of 30 mg kg^{-1}, whereas all doses led to reduced hyperalgesia in the

carrageenan test. Additional experiments[72] suggested that such antinociceptive effects are mediated by activation of CB1 and CB2. In another study,[73] the same group evaluated compound **6** on the paclitaxel (PTX)-induced neuropathic pain model. PTX is widely used for the treatment of various tumors, but it is responsible for peripheral neuropathic pain as a side effect due to the activation of the immune system, leading to the release of pro-inflammatory cytokines and sensitization of nociceptive neurons. An *in vivo* trial in male C57BL/6 mice showed that HUF-101 (**6**) prevented PTX-induced neuropathic pain (mechanical and cold allodynia) at doses of 1 and 3 mg kg^{-1}. Prevention of mechanical and cold allodynia occurs through activation of the PPRAγ receptor, especially those found in macrophages. Furthermore, at the lowest dose, this compound was able to attenuate the expression of the pro-inflammatory markers TNF-α, and IL-6, without induction of the tetrad of cannabinoid effects, with good safety, good tolerance, and no interference in the chemotherapeutic effect of PTX.[73]

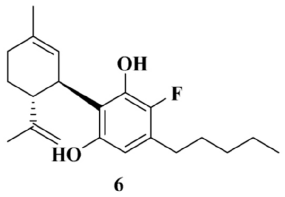

Figure 5. Structure of HUF-101 or PECS-101 (**6**).

Zi *et al.*[74] proposed a series of new CBD derivatives, leading to compounds **7a**-**7e** (Figure 6). A preliminary screening against RAW264.7 cells in the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay showed compounds **7a**, **7b**, and **7e** as strongly cytotoxic (IC_{50} < 10 μM), in contrast to **7c** (IC_{50} = 13.94 μM), and **7d** (IC_{50} = 20.48 μM) that did not elicit toxic effects at low concentrations. The pharmacological evaluation highlighted compound **7d** for its significant anti-inflammatory activity by increasing cell viability when compared to the LPS-induced macrophage group in a dose-dependent manner. Western blot analysis showed a significant decrease in the expression of TNF-α in different low concentrations (1-8 μM) of **7d**, in a dose-dependent manner. Furthermore, docking studies at the active site of TNF-α have shown that the binding free energy (ΔG°) is favorable for **7d** (ΔG° = –4.26 kcal mol^{-1}), similarly to CBD (**2**, ΔG° = –5.09 kcal mol^{-1}), and that molecular recognition may occur through H bond (between Gly122 and OH of the sugar moiety) and hydrophobic interactions (between Tyl119 and Tyl59 residues). In addition to the promising anti-inflammatory activity, this compound showed higher water solubility (505.8 μg mL^{-1}) than CBD (**2**).[74]

New *O*-methylated CBD derivatives (**8**, **9a**-**9d**, Figure 7) were described by Lavi *et al.*[75] for their anti-inflammatory activity. All derivatives were evaluated in comparison to CBD (**2**) used as a positive control, in different *in vivo* inflammatory models, showing ability for reducing swelling, pain sensation, and TNF-α levels. Compounds **9b** and **9c** were more effective in the swelling paw assay at 25 mg kg^{-1}, while derivative **9a** showed the best antinociceptive effect at 50 mg kg^{-1}. In comparison to CBD (**2**), compounds **9a**-**9c** exhibited a marked reduction in the TNF-α levels at a dose of 25 mg kg^{-1}. Compounds **8** and **9d** (5 and 10 mg kg^{-1}) were also evaluated for their activities in the reduction of TNF-α, IL-1β, and IL-6 levels, induced by LPS injection. At the lower dose, compound **8** reduced TNF-α and IL-1β blood levels, while derivative **9d** only showed effect over TNF-α levels at 10 mg kg^{-1}. Overall, when compared to CBD (**2**), compound **8** exhibited a better antinociceptive profile, being more potent in inhibiting the expression of IL-1β in human macrophages (IC_{50} = 5 μM),[75] corroborating that structural modifications made in the structure of CBD (**2**) played important auxophoric function to preserve or enhance antinociceptive and anti-inflammatory activity.

In 2016, Kynney and co-workers[76] synthesized the cyclic amide KLS-13019 (**10**, Figure 8) as a CBD analogue to be explored for its potential neuroprotective activity. Preliminary studies on physicochemical properties and pharmacokinetic parameters showed adequate safety and cell permeability, showing improved properties compared to CBD (**2**), such as oral bioavailability and greater cell viability. In addition, it was demonstrated in an *in vitro* model of chemotherapy-induced peripheral neuropathy (CIPN), that KLS-13019 (**10**) was more potent than CBD in reducing PTX-induced neurotoxicity.[77] Recently,

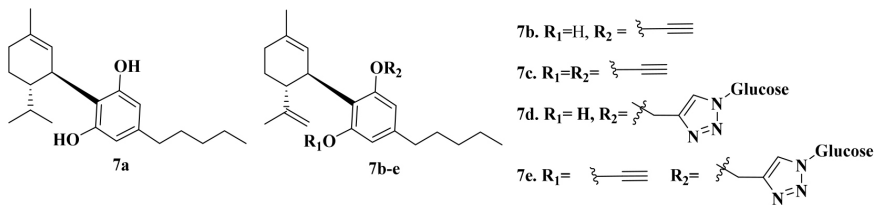

Figure 6. Chemical structures of the CBD derivatives **7a**-**7e**.

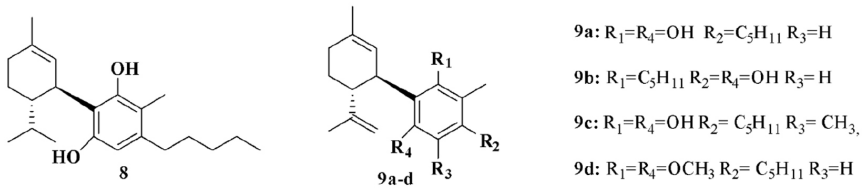

Figure 7. Derivatives *O*-methylated CBD (**8** and **9a**-**9d**).

its anti-inflammatory and analgesic properties have been investigated *in vivo* by Foss *et al*.,[78] who verified the ability of compound **10** to attenuate PTX-induced mechanical sensitivity, and thermal sensitivity in the hot plate model, by using C57BL/6 male mice pre-treated with 2.5 mg kg^{-1} of KLS-13019 (i.p.). Oral administration of KLS-13019 (**10**) also prevented sensitivity at a dose of 2.5 and 25 mg kg^{-1}, and it was observed a significant reversion of CIPN at 2.5 mg kg^{-1} (i.p. and p.o., (*per* oral)) and 5 mg kg^{-1} (i.p.). Antinociception was evaluated in mice using the hot plate assay and demonstrated that KLS-13019 (**10**) is effective in a dose-dependent manner (10, 30, and 100 mg kg^{-1}).

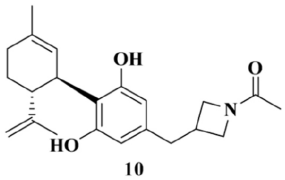

Figure 8. Chemical structure of CBD-analogue KLS-13019 (**10**).

In another approach, Brenneman *et al*.[77] evaluated the anti-inflammatory activity of KLS-13019 (**10**) in cultures of dorsal root ganglia (DRG) neurons that are relevant to CIPN and in hippocampal cultures. It was shown that treatment with PTX (3 μM) or a GPR55 agonist (lysophosphatidylinositol, LPIA, 1 nM) increased the GRP55 immunoreactive (IR) area for cell body, which was reversed with co-treatment with KLS-13019 for 16 h, in a picomolar range and dose-dependent manner (IC_{50} = 117 pM), as well as improved cell viability (EC_{50} = 200 pM). Treatment with PTX increased the IL-1β IR area by 74%, and the inflammasome-3 marker (NLRP3), a member of the NOD-like receptor family that promotes acute and chronic inflammatory responses,[79] by 29% after 30 min of treatment, whereas co-treatment with KLS-13019 resulted in a decrease in IL-1β and NLRP3 levels with IC_{50} values of 156 and 140 pM, respectively. In the hippocampus, treatment with LPIA (1 nM) increased the IR area, and co-treatment with KLS-13019 (**10**) led to a decreased GPR55 in a dose-dependent manner (IC_{50} = 107 pM), as well as for IL-1β (IC_{50} = 208 pM) and NRLP3 (IC_{50} = 129 pM). Additionally, it was demonstrated that KLS-13019 did not bind to opioid receptors, acting as a GPR55 antagonist, being considered a promising new drug candidate prototype for the treatment of pain related to CIPN.[54,55]

Based on the structure of resiniferatoxin (RTX, **11**, Figure 9), a potent TRPV1 agonist, and CBD (**2**), Jin *et al*.[80] synthesized a series of seven benzylamides, designed as potential ligands of capsaicin receptor TRPV1. TRPV1 is an unselective calcium channel, widely distributed in the central and peripheral neurons, which activation leads to a painful and burning sensation.[41,42] *In silico* studies of the structures of RTX (**11**, PDB id: 5IRX) complexed with TRPV1 and CBD (**2**) led to identification of 3 molecular regions of ligands capable of interacting with representative binding sites, furnishing insights for structural modifications. Pharmacological evaluation led to the identification of compound **12** as a lead in the series, showing an agonistic activity of antagonist of human TRPV1 (*h*TRPV1) (EC_{50} = 37.9 μM), almost equipotent to CBD (**2**, EC_{50} = 38.53 μM), and with a 2.7-fold higher binding affinity for TRPV1 (K_d = 40.34 μM, where K_d is the dissociation constant) than CBD (K_d = 110.4 μM). In addition, a moderate antinociceptive activity was observed for compound **12** (50 mg kg^{-1}) in the hot plate assay. One of the side effects of TRPV1 agonists is hypothermia and compound **12** was able to lower the temperature by 3 °C within 15 min after an administration of 50 mg kg^{-1}. Finally, molecular docking studies corroborated the effect of **12** on TRPV1, making important binding interactions in its active site, particularly with an Arg557 residue.[41,42]

VCE-004.8 (**13**, Figure 10) is a semi-synthetic quinone-like CBD derivative and dual PPARγ/CB2 agonist. This compound was investigated by del Río *et al*.[81] on scleroderma (SC), a rare disease associated with inflammation and vascular injury followed by fibroblast activation, affecting the skin and organs multiple internal. *In vitro* studies showed that VCE-004.8 (**13**) binds to PPARγ (IC_{50} = 1.7 μM), a receptor playing a pivotal role in the inflammatory process and connective tissue homeostasis, with no significant cytotoxicity on NIH-3T3 cells. In a murine model, using BALB/c female mice submitted to subcutaneous injection of bleomycin (20 μg) for 6 weeks, followed by treatment with VCE-004.8 (**13**, 10 or 20 mg kg^{-1}) for 3 weeks, it was observed a reduction

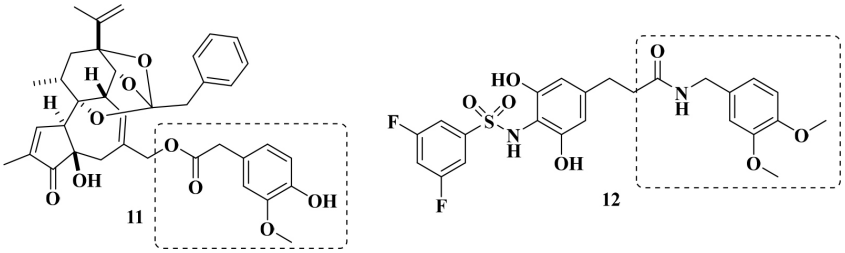

Figure 9. Chemical structure of RTX (**11**) and CBD-based analogue **12**.

in fibrosis and skin thickness, with recovering lipoatrophy at a dose of 20 mg kg^{-1}. Notably, the use of PPARγ and CB2 antagonists nullified the effect of VCE-004.8 (**13**), and an analysis of the expression 84 inflammation-related genes by qRT-PCR (quantitave real-time polymerase chain reaction), revealed that collagen type III alpha 1 (Col3A1), type I alpha 2 (Col1A2), IL-1β, and IL-13 were inhibited by treatment. By contrast, administration of 20 mg kg^{-1} of VCE-004.8 (**13**) did not affect the increased levels of TGFβ1 (transforming growth factor beta) which is a highly expressed gene in scleroderma.[81]

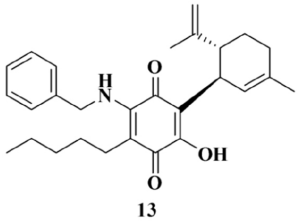

Figure 10. Chemical structure of the quinone-like CBD derivative VCE-004.8 (**13**).

In another research, Navarrete *et al*.[82] proposed the investigation of VCE-004.8 (**13**) for the treatment of multiple sclerosis (MS), a chronic autoimmune disease, whose pathophysiological hallmarks include loss of myelin sheath in neurons, neuroinflammation, and axonal damage. *In vitro* studies on RAW264.7 and BV-2 cell lines demonstrated that VCE-004.8 (**13**) activates the hypoxia-inducible factor (HIF) pathway through the erythropoietin (EPO) gene in a concentration-dependent manner. This transcription factor regulates several genes related to angiogenesis and immunity, and its activation is thought to play a central role in MS-related neuroinflammation. Treatment of macrophages (RAW264.7) with IL-17 promoted polarization to a pro-inflammatory phenotype (M1), and the treatment with VCE-004.8 (**13**) caused a decrease in the levels of the inflammatory cytokines TNF-α, IL-6, besides a strong inhibition of COX-2 expression induced by LPS in primary microglia cells. *In vivo* studies using the animal MS models EAE (experimental autoimmune/allergic encephalomyelitis) and TMEV (Theiler's murine encephalitis virus-induced demyelinating disease) corroborated the *in vitro* results, showing that the treatment of female C57BL/6 and SJL/J mice with VCE-004.8 (**13**, 10 mg kg^{-1}) led to inhibition of several chemokines and inflammatory cytokines, including Ccl12, Ccl3, Ccl5 (C–C motif chemokine ligand 12, 3 and 5), Cxcl10, Cxcl11, Cxcl9, Infg, IL-1β, IL-6, TNF-α, and IL-17.[82]

Face to these promising results, Navarrete *et al*.[83] evaluated EHP-101 (**13**), an oral lipid formulation of VCE-004.8 (**13**) in the EAE murine model. Experimental data pointed out the attenuation of the MS-induced symptoms and neuroinflammation in a dose-dependent manner, as well as preventing demyelination in the CNS. The gene expression of several cytokines was determined by RT-PCR in spinal cord, proving that IL-6, IL-1β, Timp1 (tissue inhibitor matrix metalloproteinase 1), Vcam (vascular cell adhesion molecule 1), Ccl2, and Ccl4 were downregulated due to the treatment with EHP-101 (**13**, 20 mg kg^{-1}).[83] Currently, EHP-101 (**13**) is in phase II clinical trial for treatment of MS (NCT04909502) under the responsibility of Emerald Health Pharmaceuticals.[84] Another study[85] with EHP-101 (**13**) formulation has shown its effects on the reduction of inflammation and fibrosis caused by angiotensin-2 (ANG-2) in heart tissues, skin, lungs, and kidneys. Moreover, it was demonstrated that VCE-004.8 (**13**) inhibits mRNA expression of IL-1β, IL-6, Col1A2, and Ccl2 induced by ANG-2, by reducing the infiltration of T cells and macrophages in the analyzed tissues.

In a more recent work, Navarrete *et al*.[86] published in 2022 the results of their investigation of the effects of VCE-004.8 (**13**) on traumatic brain injury (TBI). In this study, the authors have identified the PP2A/$BB_{55\alpha}$ pathway through which VCE-004.8 (**13**) exerts its mechanism of action by inhibiting phosphorylation of PHD2 (prolyl hydroxylase-2) Ser125 in more than 50%. In addition to being associated with HIF-α stabilization, this pathway is also involved in tauopathies, and in turn, may represent a strategic molecular target to be addressed for therapeutics. Administration of VCE-004.8 (**13**) prevented blood-brain barrier (BBB) disruption in *in vitro* and *in vivo* (20 mg kg^{-1}) models and was shown to counteract neuroinflammation, leading to a decrease in the levels of the inflammatory cytokines IL-1β,

IL-6, and Ccl2, after 24 h, 72 h, and 7 days of treatment, and increase anti-inflammatory cytokine IL-10.[86]

In 2023, Lavayen *et al*.[87] reported their studies on the *in vivo* effect of VCE-004.8 (**13**) on the ischemic stroke model MCAO (middle cerebral artery occlusion) model.[88] Male C57BL/6J mice were subjected to a stroke and after receiving treatment with VCE-004.8 (**13**, 10, or 20 mg kg^{-1}, i.p.) either at the onset of reperfusion, or 4 or 6 h after the reperfusion. The onset treatment for 4 h after reperfusion led to a reduction of infarct volume, and the analysis of gene expression related to neuroinflammation evidenced that the treatment with 20 mg kg^{-1} of VCE-004.8 (**13**) reduced IL-6 levels (6 h after stroke), IL-1β, CXCL1, and Ccl2 (24 h after treatment). Altogether, experimental data confirmed the neuroprotective effectiveness of VCE-0004.8 (**13**) in the acute phase of ischemic stroke and preventing BBB breakdown.[87]

VCE-004.3 (**14**, Figure 11) is another semi-synthetic CBD-like aminoquinone derivative that has been explored by del Rio *et al*.[89] for the treatment of systemic sclerosis (SC). It was demonstrated that VCE-004.3 (**14**) is a selective PPRAγ agonist (IC_{50} = 3.5 μM), acting also as an antagonist of CB1 (pKi = 5.61 μM, where pKi: negative logarithm of the Ki value (Ki = affinitiy constant)) and agonist of CB2 (pKi = 6.69 μM) receptors. This compound was also submitted to *in vivo* anti-inflammatory and anti-fibrotic evaluation on the bleomycin model, showing to cause downregulation of pro-inflammatory cytokines, IL-1β, IL-6, IL-4, TGFβ, and Ccl2 in mice treated with 20 mg kg^{-1} (i.p.). In addition, treatment with VCE-004.3 (**14**) reduced $F4/80^{+}$ macrophage and CD^{3+} lymphocyte infiltration, and the *in vivo* effects were proven to be mediated by PPARγ and CB2 receptors.

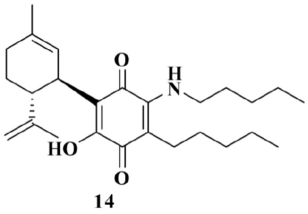

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Figure 11. Chemical structure of CBD aminoquinone derivative VCE-004.3 (**14**).

Casares *et al*.[90] synthesized and studied two novel *O*-methyl-CBD quinone derivatives (**15** and **16**, Figure 12) on the BACH1/NRF2 pathway. The Nrf2 pathway activation regulates the antioxidant response in the body through translocation to the cellular nucleus and binding with the ARE (antioxidant response element),[91-93] while BACH1 inhibition has anti-inflammatory and antioxidant properties.[94-96] This pathway regulates the expression of the HMOX1 (heme oxygenase-1) gene, which has antioxidant and anti-inflammatory properties.[97] Thus, the regulation of this pathway is important for the body's homeostasis, being an alternative for the treatment of chronic inflammatory diseases, such as neurodegeneration. *In vitro* studies with immortalized human keratinocytes (HaCaT cells) have shown that compounds **15** and **16** (at 10 μM) were capable of stabilizing Nrf2 and reducing transcription regulator protein BACH1 levels through increased expression of HMOX1. However, compound **16** showed expressive cytotoxicity and thermal instability. Additional data evidenced that the effects of compound **15** over Nrf2 and BACH1 are independent, that is, the activation of the Nrf2 pathway through Keap-1 does not depend on BACH1. To investigate these effects on a neurodegenerative condition, a cellular model for Huntington's disease was used (THP lines cell and SH-SY-5Y neuroblastoma cell line), showing that compound **15** (10 μM) was able to decrease BACH1 levels, induce HMOX1 and activate Nrf2, in addition to a direct antioxidant activity.[90]

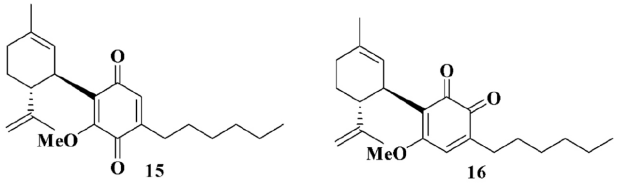

Figure 12. Chemical structures of *O*-methyl-cannabidiol quinone derivatives **15** and **16**.

Dennis *et al*.[98] synthesized several structurally diverse *Cannabis*-occurring minor phytocannabinoids, using readily available CBD (**2**) as starting material, aiming to evaluate their anti-inflammatory activity. Among all tested compounds, cannabimovone (CBM, **17**), 3'-epicannabimovone (EPI-CBM, **18**), cannabifuran (CBF, **19**), cannabielsoin (CBE, **20**), and dehydrocannabielsoin (DCBE, **21**, Figure 13) stood out for their *in vitro* effects on BV2 cells stimulated by LPS, without significant cytotoxicity. Evaluation of inflammatory biomarkers showed a marked reduction of 83.7% in the production of NO by cells treated with 1.0 μM of CBM (**17**), followed by compounds EPI-CBM (**18**, 60.5%), CBE (**20**, 7.8%), DCBE (**21**, 83.9%) that showed the best results only at 2.5 μM concentration. On the other hand, CBM (**17**) and EPI-CBM (**18**) showed the highest reductions of 80.8 and 90.2%, respectively, at 1.0 μM, whereas CBE (**20**) and DCBE (**21**) reached prevention of IL-6 in 61.9 and 51.3%, respectively, at a 2.5 μM concentration. In contrast, gene expression levels of pro and anti-inflammatory cytokines such as IL-10, Arg-1, IL-6, TNF-α, and IL-1β were measured at a dose of 5 μM, demonstrating that the

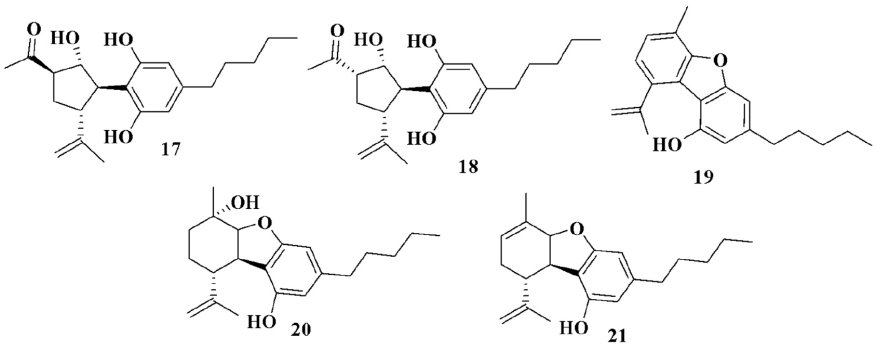

Figure 13. Chemical structures of minor cannabinoids CBM (**17**), EPI-CBM (**18**), CBF (**19**), CBE (**20**), DCBE (**21**).

EPI-CBM (**18**) raised the levels of IL-6 (4.4-fold) and TNF-α (2.9-fold), while CBM (**17**) increased 55.7-fold Arg-1 expression and downregulation NO levels, and compound **19** showed a pro-inflammatory activity.[98]

Aiming at new drug candidates to combat morphine addiction and based on structure-activity relationship (SAR) studies, Jin *et al.*[99] synthesized the CBD-like triazole analogue CIAC-001 (**22**, Figure 14). Chemical dependence on morphine and other opioids causes neuroinflammation and leads to exacerbated release of pro-inflammatory cytokines, justifying the development of new anti-neuroinflammatory agents as an alternative treatment for opioid addiction. *In vitro* pharmacological evaluation of the anti-inflammatory profile of CIAC-001 (**22**) was performed in BV-2 cells, showing a promising inhibition of the production of LPS-induced NO (IC_{50} = 2.5 μM), with an acceptable cytotoxicity (IC_{50} = 57.8 μM). Further studies[99] revealed that this compound is capable of inhibiting the pro-inflammatory cytokines IL-6, IL-1, and TNF-α in a dose-dependent manner in LPS-stimulated cells. Subsequently, *in vivo* studies[99] using a morphine addiction model in mice were performed, showing that the treatment with different doses of CIAC-001 (**22**, 0.2 μg kg^{-1}, 20 μg kg^{-1}, and 0.2 mg kg^{-1}, i.p.) led to the prevention of morphine dependence in a dose-dependent manner. Additionally, chronic morphine treatment (10 mg kg^{-1}, i.p.) for 7 days

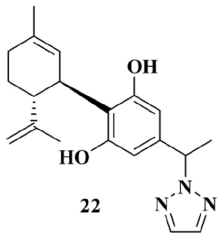

Figure 14. Chemical structures of the compound CIAC-001 (**22**).

increased IL-1β levels in brain areas, which was reverted by the treatment with CIAC-001 (**22**). Mechanistic studies[99] evidenced that CIAC-001 (**22**) does not bind to endocannabinoid receptors, but it interacts with PKM2 (pyruvate kinase M2) targets, whose inhibition conduces to a decrease in pro-inflammatory factors, through the PKM2-Hif-1α-IL-1β pathway. This compound also exhibited good BBB permeability and safety, without THC-like psychoactive adverse effects,[99] and may represent a genuine innovation for drug development addressed to neuroinflammatory illnesses and opioid addiction.

Finally, in order to summarize the most common structural modifications proposed by several research groups worldwide in the search for new improved CBD synthetic analogues and derivatives, Figure 15 provides succinctly the identification of pharmacophoric and auxophoric moieties related to their contribution to

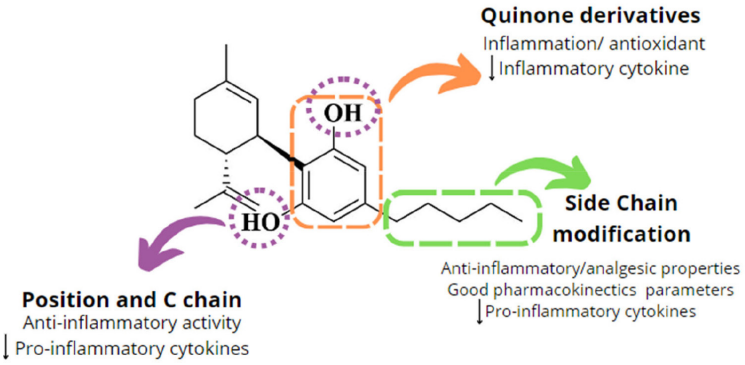

Figure 15. Summary of structural modifications observed in CBD-derivatives and their contribution to the anti-inflammatory and analgesic activities.

anti-inflammatory, analgesic and other related biological properties.

3. Concluding Remarks

Despite the secular use of *Cannabis* in human civilization, whether for religious purposes, leisure, or medicinal use, only in recent years there has been a greater interest in its therapeutic value in different neuropathologies, psychiatric disturbs, autism, neuropathic pain, and chronic inflammation, among others. In a controversial context, with regulatory discussions and legislative changes around the world aimed at their release for clinical use, a great race has been observed by the scientific community for a better understanding of the medicinal value of *Cannabis* and its most abundant active constituents, THC (**1**) and CBD (**2**). The increasing number of publications, especially in the last 10 years, clearly demonstrates the effort of the world scientific community in the search for a better understanding of the pharmacological bases of the broad spectrum of medicinal properties shown by *Cannabis* and, mainly by CBD (**2**), one of its most abundant constituents, without psychotropic effects. In this context, combined with all the commitment of medicine and various areas of biological sciences in the recognition of molecular targets, mechanisms of action, and toxicology of CBD (**2**), medicinal chemists have contributed to the design and synthesis of several novel compounds with molecular architecture based on CBD (**2**), with promising pharmacological attributes for drug development. The search for literature data in the last 30 years revealed a lack of rigorous scientific information regarding the pharmacology of CBD (**2**). Until now, most of the research has focused on the characterization and comprehension of the neuroprotective activity of CBD (**2**), and only in the last decade, the pharmacology of CBD (**2**) began to be unveiled, including other therapeutical uses, such as anti-inflammatory and analgesic. The most recent studies have evidenced the anti-inflammatory effects of CBD (**2**) as a result of its ability to bind to G protein-coupled receptors (e.g., GPR55), Nav channels, cannabinoid receptor type 2 (CB2), adenosine type 2 receptor (A2), and the family of transient receptor potential cation channels (TRPV), especially the capsaicin receptor TRPV1. Regarding the antinociceptive properties of CBD (**2**), it is clearer that there is much more to be elucidated since only TRPV1 has been identified as a suitable target. Despite the urgent demand for new drugs to combat painful and inflammatory-based chronic conditions, a few CBD-structurally related compounds have been synthesized and evaluated, leading to the discovery of new bioactive ligands, such as O-1602 (**4**) and HU-219 (**5**), with promising anti-inflammatory properties, and O-1602 (**4**) and HUF-101 (**6**) showing antinociceptive activity, but whose mechanisms of action remain unclear. However, considering that only in recent years CBD (**2**) and its derivatives have received massive interest and investment, and that currently cannabinoid research is being done worldwide, it is plausible to expect major advances in the coming years, with findings that ensure the safe use of CBD (**2**) and other cannabinoids and their analogues, contributing to a better quality of life and greater clinical effectiveness in the treatment of chronic painful and inflammatory diseases.

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