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Molecular Targets of the Phytocannabinoids-A Complex Picture

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1 Introduction

For centuries, hashish and marihuana, both derived from the Indian hemp *Cannabis sativa L.,* have been used for their medicinal, as well as, their psychotropic effects. Phytocannabinoids are oxygen containing C_{21} aromatic hydrocarbons found in *Cannabis sativa L.* To date, over 120 phytocannabinoids have been isolated from *Cannabis*, including two compounds, (−)-trans-Δ^9-tetrahydrocannabinol (Δ^9-THC) and (−)-trans-Δ^8-THC (Δ^8-THC) that have been shown to bind to cannabinoid receptors and elicit the characteristic psychotropic effect associated with *Cannabis* [1]. These compounds also have beneficial effects, such as appetite stimulation [2], analgesia [3], anti-glaucoma [4] and anti-emetic effects [5]. Non-psychotropic phytocannabinoids are currently emerging as key constituents of *Cannabis* as well. For example, the non-psychotropic phytocannabinoid, CBD, is of great interest because of its anti-inflammatory, analgesic, anti-anxiety and anti-tumor properties [6]. For many years, it was assumed that the beneficial effects of the cannabinoids were mediated by the cannabinoid receptors, CB_1 and CB_2. However, today we know that the picture is much more complex, with the same phytocannabinoid acting at multiple targets. This chapter focuses on the molecular pharmacology of the phytocannabinoids, including Δ^9-THC and CBD, from the prospective of the targets at which these important compounds act.

2 Pharmacology of selected phytocannabinoids

To date over 120 cannabinoids, the so-called phytocannabinoids (pCB), have been isolated from the cannabis plant. Contrary to other naturally occurring drugs, such as opioids, nicotine, cocaine or caffeine, cannabinoids do not contain nitrogen, and hence are not alkaloids. Most phytocannabinoids share common structural features that include a dibenzopyran ring and a hydrophobic alkyl chain. The most abundant cannabinoids in the plant are Δ^9-tetrahydrocannabinol (Δ^9-THC), Δ^8-tetrahydrocannabinol (Δ^8-THC), cannabinol (CBN), cannabidiol (CBD), cannabigerol (CBG), and cannabichromene (CBC), Δ^9-tetrahydrocannabivarin (THCV), cannabivarin (CBV),cannabidivarin (CBDV) (Figure 1). Despite their lower presence in the plant, other phytocannabinoids such as cannabinodiol

(CBND), cannabielsion (CBE), cannabicyclol (CBL) and cannabitriol (CBT) have also been the subjects of study in the last decades (Figure 2) [7].

Phytocannabinoids show different affinities for CB_1 and CB_2 receptors. In addition, over the last years, molecular targets outside the endocannabinoid system have been identified for certain plant cannabinoids. These compounds have been shown to interact with other G-protein coupled receptors such as the putative cannabinoid receptors GPR55 or GPR18, and other well-known GPCRs such as the opioid or the serotonin receptors. In addition, several papers have reported the ability of certain phytocannabinoids to modulate nuclear receptors, ligand-gated ion channels or transient receptor potential (TRP) channels, among others.

2.1 Abundant constituents of *cannabis sativa L*

Table 1 provides a pharmacology summary for each of the abundant constituents of *Cannabis*.

2.1.1 Δ^9- Tetrahydrocannabinol (Δ^9-THC)—Δ^9-THC is the principal component of the cannabis plant. As demonstrated by numerous *in vitro* and *in vivo* assays, Δ^9-THC is a moderate partial agonist of CB_1 and CB_2 receptors [8–10]. As a partial agonist, it presents a mixed agonist-antagonist profile depending on the cell type, expression of receptors and presence of endocannabinoids or other full agonists [11]. This compound is largely responsible for the pharmacological properties, as well as, the psychoactive effects associated with marijuana use. Δ^9-THC is also a multitarget ligand, the non-CB_1, non-CB_2 activity of this compound is responsible for some of the physiological effects reported for this phytocannabinoid *in vitro* and *in vivo*.

Conflicting reports about the ability of this phytocannabinoid to modulate the putative cannabinoid receptor GPR55 have been published. Δ^9-THC exhibits activation of GPR55 in [^{35}S]GTPγS binding, RhoA assays and intracellular calcium mobilization in transiently transfected *h*GPR55-HEK293 cells [12–14]. However, this phytocannabinoid was unable to stimulate ERK1/2 phosphorylation or β-arrestin recruitment [15–17]. It remains to be determined whether this is a consequence of experimental variability, differences in functional readouts or GPR55 intrinsic properties. In addition, studies from Anavi-Goffer and coworkers [18] have shown that Δ^9-THC is able to inhibit the response generated by lysophosphatidylinositol (LPI), the proposed GPR55 endogenous ligand. For the putative cannabinoid receptor, GPR18, studies in different cell models demonstrate that Δ^9-THC acts as a potent agonist of this receptor [19, 20].

Δ^9-THC has also been proposed to be a serotonin $5HT_{3A}$ receptor antagonist [21, 22] and an allosteric modulator of the opioid receptors [23]. Certain non-GPCRs have also been suggested as targets of Δ^9-THC. This compound is a peroxisome proliferator-activated receptor gamma (PPARγ) agonist. Through this agonistic effects it exerts some of its The vascular relaxation and antitumor effects of Δ^9-THC have been linked to its agonism at PPARγ [24, 25]. Low concentrations of Δ^9-THC have been shown to significantly potentiate the amplitudes of glycine-activated currents [26, 27]. The activity of Δ^9-THC at the glycine receptors seems to contribute to the cannabis-induced analgesia in behavioral mice models [26].

Δ^9-THC did not show a response at the vanilloid type 1 receptor (TRPV1, also known as the capsaicin receptor), whereas several reports describe its agonistic effects at the TRPV2, TRPV3, and TRPV4 channels [28–30]. As further detailed in this chapter, Δ^9-THC is also an agonist of the ankyrin channel TRPA1 and an antagonist of the melastatin receptor TRPM8 [28, 31].

2.1.2 Δ^8- Tetrahydrocannabinol (Δ^8-THC)—Δ^8-THC is an isobaric isomer of Δ^9-THC that differs in the position of the double bond (Figure 1). Δ^8-THC also displays psychoactivity and is chemically more stable than Δ^9-THC [32, 33]. Δ^8-THC shows moderate partial agonistic effects on CB_1 and CB_2 receptors [34, 35]. Likewise, it exhibits similar *in vitro* and *in vivo* properties in different studies [32, 36, 37]. There is not much literature reported on the activity of Δ^8-THC at other targets such as GPR55, GPR18, TRP channels or PPAR nuclear receptors. However, this compound will presumably present a similar pharmacological profile to Δ^9-THC.

2.1.3 Cannabinol (CBN)—Cannabinol is an oxidized metabolite of THC [38]. Its acid form is widely present in the plant and CBN is formed upon heating of its acid. CBN is a weak psychoactive compound that binds the cannabinoid receptors showing higher affinity towards CB_2. CBN has been consistently reported to be a weak CB_1 agonist, however, different results have been found regarding its CB_2 modulation. cAMP assays performed by Mechoulam and coworkers [39] revealed its agonist capacity, whereas in GTPγS experiments, this compound behaved as a CB_2 inverse agonist [40]. These divergences may be due to the experimental outcome or the dose utilized in each case.

Cannabinol has also shown CB_1, CB_2 independent activity. This compound is a potent agonist of TRPA1 and antagonist of TPRM8 channels [29]. Besides the TRP channels, its activity at other receptors outside the endocannabinoid system has not been determined.

2.1.4 Cannabidiol (CBD)—Due to its promising therapeutic effects, cannabidiol is one of the most studied cannabinoids today. This non-psychoactive compound has demonstrated anti-inflammatory, analgesic, anti-anxiety and anti-tumor properties, among others [6].

Diverse research groups have reported its lack of affinity for the cannabinoid CB_1 and CB_2 receptors [41]. However, *in vitro* studies revealed that CBD displays weak CB_1 and CB_2 antagonistic effects [42, 43]. Recent results from Laprairie and colleagues [44], show that CBD behaves as an negative allosteric modulator of Δ^9-THC- and 2-AG [45]. These results may explain some of the *in vivo* effects of CBD. In addition, CBD is able to inhibit cellular uptake of the endogenous CB_1 ligand, anandamide, directly affecting endocannabinoid tone. At the GPR55 receptor, this non-psychoactive phytocannabinoid acts as an antagonist preventing [^{35}S]GTPγS binding and Rho activation [14, 46, 47]. However, CBD was inactive in Ca^{2+} mobilization assays [12] and β-arrestin recruitment [15]. As demonstarted by McHugh and coworkers [19, 20], CBD is an antagonist of the putative cannabinoid receptor GPR18.

CBD is further involved in the modulation of different receptors outside the endocannabinoid system (ECS). The serotonin receptors have been implicated in the

therapeutic effects of CBD. Different studies revealed that this phytocannabinoid acts as a full $5HT_{1A}$ agonist, a $5HT_{2A}$ weak partial agonist and a non-competitive antagonist of $5HT_{3A}$ [48–50]. The ability of CBD to activate the A_{1A} adenosine receptors has also been proposed [51]. Its activity at these receptors could mediate the anti-inflammatory and immunosuppressive effects of CBD. The activity of CBD at the nuclear receptors PPARγ [52–54], the ligand-gated ion channels glycine [55, 56] and $GABA_A$ receptors [57], or at the transient receptor potential channels [29, 30] is summarized in Table 1.

Despite all of this pharmacological data, the mechanistic bases of the CBD effects remain unclear. Therefore, great efforts are currently being made to fully elucidate the molecular pharmacology of CBD.

2.1.5 Cannabigerol (CBG)—CBG is a non-psychoactive phytocannabinoid found in high concentration in the plant; its carboxylic acid form (CBDA, cannabigerolic acid) is the precursor of other important phytocannabinoids. CBG has low affinity for the cannabinoid CB_1 and CB_2 receptors [58–60], but it affects the endocannabinoid system because of its ability to inhibit anandamide (AEA) uptake [29]. CBG has also been shown to weakly inhibit the LPI response in GPR55 assays [18]. The non-cannabinoid activity reported for CBG involves its ability to potently activate the α2 adrenergic receptor and moderately block the serotonin $5HT_{1A}$ receptor [61].

As with many other phytocannabinoids, CBG interacts with different TRP channels acting as a weak TRPV1 and TRPV2 agonist, a potent TRPM8 antagonist, and a potent TRPA1 agonist [29, 31].

2.1.6 Cannabichromene (CBC)—Cannabichromene (CBC) is one of the most abundant phytocannabinoids in the plant; it was discovered in 1966 by Gaoni and Mechoulam [59]. This phytocannabinoid does not display significant affinity for the cannabinoid CB_1 and CB_2 receptors [58]. Nonetheless, it directly influences the endocannabinoid system by inhibiting anandamide (AEA) uptake [29]. The more relevant pharmacological activity of CBC explored so far, is at TRP channels. Among the phytocannabinoids tested by De Petrocellis and coworkers [29], CBC is the most potent agonist of the TRPA1 channels. Although at a lower potency, CBC is also able to activate TRPV3 and TRPV4, and block TPRM8 receptors in the same cellular and functional outcome [29, 30].

2.1.7 Δ^9- Tetrahydrocannabivarin (Δ^9-THCV)—THCV is a propyl analogue of tetrahydrocannabinol. Even though it only varies from Δ^9-THC by the length of its lipophilic alkyl chain, it possesses a different pharmacological profile at certain molecular targets.

Discrepancies have been found regarding its activity at CB_1 receptors. Although the *in vitro* evaluation of this compound consistently displays antagonistic/inverse agonistic effects [62–64], at higher doses, the *in vivo* effects indicate agonism in an antinociception model [65]. THCV is a CB_2 partial agonist as demonstrated in different *in vitro* and *in vivo* assays [66]. Recent studies suggest that this phytocannabinoid is a partial agonist of GPR55 being also able to inhibit the activity of the full agonist LPI [18]. Beyond the endocannabinoid system,

THCV has been reported to activate $5HT_{1A}$ receptors [67], as well as different TRP channels subtypes [29] (Table 1).

2.1.8 Cannabivarin (CBV)—Cannabivarin (CBV) is a non-psychoactive phytocannabinoid found in the plant in low concentrations. It is a propyl derivative of cannabinol and can be obtained as an oxidation product of tetrahydrocannabivarin [68–70]. Its pharmacology has not been explored so far.

2.1.9 Cannabidivarin (CBDV)—Cannabidivarin (CBDV) is a propyl analogue of CBD that lacks psychoactive properties. This compound displays very weak affinity for CB_1 and CB_2 receptors [58, 71]. Its ability to inhibit the activity of the putative endogenous ligand LPI has been reported in *h*GPR55-HEK293 cells [18].

Molecular targets outside the ECS have also been found for CBDV. The TRP channels are tightly involved in the therapeutic potential of this phytocannabinoid. CBDV potently activates human TRPA1 channel, being a weak agonist of the TRPV1, TRPV2 and TRPV3 cation channels [29, 30].

2.2 Less abundant constituents of *cannabis sativa L*

Other compounds from the cannabis plant have been identified and structurally characterized. Total synthesis approaches have been intended for some of them, but the pharmacology of these phytocannabinoids has not been properly studied. Indeed, to the best of our knowledge, their activity at the well-known cannabinoid CB_1 and CB_2 receptors, or other molecular targets has not been reported so far.

2.2.1 Cannabinodiol (CBND)—Cannabinodiol (CBND) is a fully aromatized CBD analogue which was first characterized in 1977 [72]. This phytocannabinoid can be obtained as a product of CBD photochemical conversion. Although its concentration in the plant is quite low, CBND is one of the psychoactive compounds found in the plant's flowers [73]. There is no available experimental data at present related to its pharmacological action on specific targets.

2.2.2 Cannabielsoin (CBE)—Cannabielsoin (CBE) is a phytocannabinoid metabolite which can be produced by photo-oxidation from CBD and CBDA [74, 75], or by biotransformation using tissue cultures under normal growth conditions [76, 77]. The ability of this compound to modulate the cannabinoid CB_1 and CB_2 receptors has not been described thus far.

2.2.3 Cannabicyclol (CBL)—Cannabicyclol (CBL) is a photochemical product that originates from the phytocannabinoid cannabichromene under heating conditions [78, 79]. This is important to take into account when considering that cannabis is frequently smoked for both medicinal and recreational purposes. No pharmacological evaluation of this phytocannabinoid has been reported.

2.2.4 Cannabitriol (CBT)—Cannabitriol (CBT) was first isolated by Obata and Ishikawa in 1966 [80], but the structures of its *cis* and *trans* isomers were not fully determined until

years later [73, 81]. CBT has been synthesized by antibody-catalyzed oxidation of Δ^9-THC [82]. No pharmacological evaluation of this phytocannabinoid has been reported.

3 Molecular targets of phytocannabinoids

3.1 G-Protein Coupled Receptors

Many of the phytocannabinoids interact with the cannabinoid CB_1 and CB_2 receptors. The cannabinoid CB_1 [84] and CB_2 [85] receptors belong to the Class A (rhodopsin (Rho) family) of G-protein coupled receptors (GPCRs). Figure 3A illustrates that the general topology of a Class A GPCR includes: (1) an extracellular (EC) N terminus; (2) seven transmembrane alpha helices (TMHs) arranged to form a closed bundle; (3) loops connecting TMHs that extend intra- and extracellularly; and, (4) an intracellular (IC) C terminus that begins with a short helical segment (Helix 8) oriented parallel to the membrane surface. Ligands for Class A GPCRs are generally thought to enter the receptor via the extracellular space. Figure 3B illustrates an extracellular view of the 2.8 Å resolution mu opioid receptor structure (PDB entry 4DKL). Here you see the opening that allows the ligand, beta-funaltrexamine to descend into the receptor binding pocket.

The docking of a GPCR agonist ligand triggers a conformational change in the receptor on its intracellular (IC) side most commonly by altering the proline kink angle in the TMH6 CWXP motif, allowing TMH6 to straighten. This change in angle breaks the IC salt bridge between R3.50 and D/E6.30 that maintains the GPCR inactive state. The overall conformational change creates an IC opening that allows the G-protein alpha-5 helix (which is located intracellularly) to insert into the receptor opening and form a receptor/G-protein complex. This, then, is the beginning of signal transduction.

In many ways the CB_1 and CB_2 receptors are atypical within the Class A GPCRs [86]. The endogenous ligands for these receptors, sn-2-arachidonoylglycerol (2-AG) (CB_1 and CB_2) [87, 88] and anandamide (CB_1) [89] are lipid-derived agonists that are made on demand from the lipid bilayer and degraded by membrane associated enzymes [90–92], negating the need for vesicle storage. The CB_1 receptor and its endogenous ligand, 2-AG have been shown to mediate depolarization-induced suppression of inhibition (DSI) and depolarization-induced suppression of excitation (DSE), at GABAergic and glutamatergic synapses [93]. To accomplish this regulation of neurotransmission, CB_1 has a presynaptic location, an atypical location for neuronal GPCRs. Although neither cannabinoid receptor has yet been crystallized, two Class A GPCRs that recognize lipid-derived ligands have been crystallized. This includes the $S1P_1$ receptor, which has over 60% homology with hCB_1 in the transmembrane helix (TMH) regions and whose endogenous ligand is also lipid-derived, sphingosine-1-phosphate [94]. The second GPCR is GPR40 which binds long chain free fatty acids [95]. Two very striking features are evident in these crystal structures: (1) the extracellular domain of the receptor is completely covered by either the N-terminus [85] or the EC-2 loop [95], precluding ligand access from the EC milieu; (2) portals between TMHs through which ligands can be shuttled have been identified for each of these receptors and the location of the TMH portal varies between receptors and is dependent on the sequence of each receptor [86]. For the S1P1 receptor, the N-terminus occludes the binding site. Instead

a portal between TMH1 and TMH7 allows ligand access from the lipid bilayer. This is illustrated in Figure 4 (PDB 3V2Y; antagonist, ML056 bound; 2.8 Å resolution).

How do phytocannabinoids reach the CB_1/CB_2 binding domain?—Molecular dynamics (MD) simulations reported by the Reggio lab have suggested that for CB_1 and CB_2, there is a ligand portal between TMH6 and TMH7 [96]. Figure 5 illustrates the CB_1/CB_2 ligand, 2-AG entering the CB_2 receptor via the lipid bilayer. This result is supported experimentally by covalent labeling studies from the Makriyannis lab which pinpoint C6.47 (a lipid facing TMH6 residue) in CB_1 and CB_2 as the residue covalently labeled by the classical cannabinoid, AM841 which is isothiocyanate derivatized. This labeling of a **lipid facing residue** occurs despite the fact that other Cys residues face into the ligand binding pocket and are extracellular to C6.47 [97, 98].

Thus, for the cannabinoids, it is likely that high ligand lipophilicity is required for ligand access to the entry portal into CB_1 or CB_2. Table 2 provides calculated QlogP values for the phytocannabinoids. Here it is clear that the phytocannabinoids do possess high lipophilicites.

Table 1 lists additional Class A GPCRs that have been implicated in various phytocannabinoid actions. These include the putative cannabinoid receptors GPR55 and GPR18; the serotonin-1A, -2A, -3A receptors ($5HT_{1A}$ $5HT_{2A}$ $5HT_{3A}$), the μ - and δ-opioid (MOR and DOR) receptors,; the adenosine A_{1A}, receptor; and, the α_2-adrenergic receptor (α_2-AR).

3.2 Beyond GPCRs: PPARs, GlyR and TRP channels

3.2.1 Peroxisome Proliferator-Activated Receptors (PPARs)—

In the last decade, increasing research has shown that cannabinoids can modulate peroxisome proliferator-activated receptors (PPARs) [99–102]. Some of the physiological responses triggered by phytocannabinoids are partially mediated by these nuclear hormone receptors which control the transcription of target genes. Activation of PPARα and PPARγ isoforms is associated with some of the neuroprotective, antinociceptive, antiproliferative, anti-inflammatory and metabolic properties of cannabinoids. Therefore, the activity of phytocannabinoids at these receptors is tighly related with its therapeutic potential for the treatment of pathologies such as cancer, diabetes, obesity, as well as cardiovascular or neurodegenerative disorders.

How do phytocannabinoids reach the PPAR binding domain?: Several reports have revealed that certain phytocannabinoids, especially Δ^9-THC and CBD, can activate the transcriptional activity of PPARs and these effects can be blocked by PPAR antagonists. However, the mechanisms facilitating this activity are still under investigation [99, 101]. Based on different studies, direct binding of cannabinoids to the PPAR isoforms has been proposed [103, 104]. The PPAR ligand binding domain has an extensive secondary structure consisting of 13 alpha helices and a beta sheet. Many PPAR crystal structures, including a PPARγ complex with the THC acid synthetic analogue, ajulemic acid (AJA), have been already solved [104]. This crystallographic study revealed a low occupancy of the binding pocket explaining the structural basis for the weak PPAR activation produced by cannabinoids. On the other hand, metabolism of cannabinoids to active PPAR binders has also been suggested as a potential mechanism of interaction with these transcription factors

[105]. Another possible mechanism triggering cannabinoid-PPAR interaction is the active transport of cannabinoid to the nucleus by fatty acid binding proteins (FABPs). Recent findings have shown that Δ^9-THC and CBD can be transported to the interior of the cell by these proteins and therefore, they could be delivered for PPAR activation [106]. Finally, an indirect PPAR activation has been proposed that is triggered by the signaling cascades elicited by CB_1 and/or CB_2 receptors and a direct activation has also been proposed [107]. These four potential mechanisms has been summarized in Figure 6. The effects of phytocannabinoids at these receptors may be result of a combination of these pathways depending on the cell type, expression of receptors and experimental readout. Whether this activation is different depending on the PPAR isotype or why phytocannabinoids activate them differentially is a question to be further explored.

PPARα activation by phytocannabinoids: The alpha PPAR isoform is mainly expressed in liver, kidney, heart, muscle, and adipose tissue. Thus, PPARα activation by cannabinoids is involved in some of their central effects including memory, reward processing, food intake and lipid metabolism. There is little published data on the activity of phytocannabinoids at these nuclear receptor isoforms. In 2007, Sun and coworkers [108], reported that Δ^9-THC lacks PPARα binding, whereas a recent study demonstrates that this phytocannabinoid is able to increase PPARα transcriptional activity in triple-negative breast cancer cells [109].

PPARγ activation by phytocannabinoids: The gamma isoform of these nuclear receptors is predominantly expressed in heart, muscle, colon, kidney, pancreas, and spleen. These transcription factors are implicated in the regulation of fatty acid storage, glucose metabolism, cell growth and cell differentiation. Activation of PPARγ plays a role in the apoptotic effects of cannabinoids [25, 102].

The phytocannabinoids Δ^9-THC and CBD have extensively been shown to bind PPARγ enhancing their transcriptional activity. In addition, their effects have been selectively inhibited by PPARγ antagonists in different experimental *in vitro* and *in vivo* models [25, 110–112]. Other phytocannabinoids such as CBG and CBC are also PPARγ agonists [111], whereas THCV was not able to increase the transcriptional activity of PPARγ [24]. It is interesting to note that in spite of their ability to activate these nuclear receptors, phytocannabinoids do not modulate PPARs to the same extent as other reported PPAR ligands, and therefore are considered weak agonists. Table 3 provides a summary of the PPAR isotypes that are activated by individual phytocannabinoids.

Synthetic cannabinoids such as abnormal CBD, cannabigerol quinone and ajulemic acid (AJA), also modulate PPARγ increasing transcriptional activity [104, 111]. Figure 7 illustrates the 2.8 Å structure of PPARγ with ajulemic acid bound (PDB 2OM9).

Despite all of this data, PPAR-activation was not reproduced in certain experimental models where Δ^9-THC and CBD failed to activate either PPARα or PPARγ on an intestinal permeability study [113, 114].

To the best of our knowledge, the PPAR activity of many of the phytocannabinoids discussed in this chapter has not been explored yet. In fact, to date there is little direct

evidence of the effects of phytocannabinoids at PPARα, and the potential involvement of the PPARβ/δ isotype on cannabinoid properties remains unknown.

3.2.2 Glycine Receptors (GlyR)—Over the last years, consistent evidence has shown that glycine receptors (GlyR) are relevant targets for CNS cannabinoid action [26, 55, 115, 116]. Glycine receptors mediate synaptic inhibitory neurotransmission involved in crucial physiological and pathological processes [117]. These ionotropic receptors consist of five subunits, each of them composed of a four transmembrane helical segment, surrounding a central chloride-selective ion channel opened by the inhibitory neurotransmitter glycine [118] (Figure 8). Direct interaction of phytocannabinoids with GlyR has been proposed in the literature [26, 56, 119]. Using mutagenesis and NMR studies, Xiong and coworkers have demonstrated that certain phytocannabinoids can hydrogen bond with the polar residue S296 in the third transmembrane domain of purified α1 and α3 GlyR subunits [26, 56, 120].

The anti-inflammatory and antinociceptive properties of phytocannabinoids are in part mediated by their ability to target glycine receptors. Different cannabinoids, including Δ^9-THC and CBD, can potentiate glycine currents in native neurons, hippocampus, amygdala or spinal cord [27, 55]. *In vivo* studies in a rodent model have also demonstrated that CBD and Δ^9-THC analgesic effects are significantly decreased in mice lacking α3-GlyR, but not in mice lacking CB_1 and CB_2 receptors [26, 56]. Therefore, these receptors likely contribute to the therapeutic effects of phytocannabinoids in the treatment of inflammatory and neuropathic pain.

3.2.3 Transient receptor potential channels (TRP channels)—Transient receptor potential (TRP) channels are a group of membrane proteins involved in the transduction of a significant range of chemical and physical stimuli. These channels modulate ion entry mediating a variety of neural signalling processes. They are involved in numerous physiological functions such as temperature sensation, smell, taste, vision, pressure or pain perception among others [122, 123].

Phytocannabinoids have shown activity at TRP channels from three different subfamilies: TRPV (Vanilloid), TRPA (Ankyrin) and TRPM (Melastatin). These receptors are formed by six transmembrane helixes, a cation-permeable pore (between helix 5 and 6), and intracellular C- and N-termini. The general topology of TRP channels is depicted in Figure 9. The most striking structural divergence among these three subfamilies is the number of ankyrin repeat domains present in the N-terminus of the receptor. Ankyrin type channels (TRPA) bear a high number of repeats, whereas the TRPM subfamily lacks ankyrin domains. The vanilloid subfamily present a variable number of ankyrin repeats, depending on the TRPV type.

To date, six types of TRP channels of the aforementioned three subfamilies have been reported to affect phytocannabinoid activity: TRPV1, TRPV2, TRPV3, TRPV4, TRPM8 and TRPA1 [29, 30, 124]. The increasing data regarding cannabinoid interactions with these receptors has prompted some research groups to consider certain TRP channels as the "ionotropic cannabinoid receptors" [125–127]. Therefore, these receptors represent

potentially attractive targets for the therapeutic use of phytocannabinoids in the treatment of sensory, inflammatory or dermatological pathologies [128].

TRPV1 channel activation by phytocannabinoids: TRPV1 was first cloned in 1997 as a receptor for the natural product capsaicin. Its structure has been determined in a recent study by a combination of electron cryomicroscopy and lipid nanodisc technology (Figure 10) [129]. This receptor is widely expressed in brain and sensory neurons (mainly in dorsal root and trigeminal ganglia), being involved in pain, nociception, and temperature sensing among other physiological and pathological conditions [130]. TRPV1 colocalizes with CB_1 receptors and CB_2 receptors in sensory and brain neurons respectively [131, 132]. Endocannabinoids and synthetic derivatives have been considered putative endovanilloids based on their high potency towards TRPV1. In fact, anandamide and *N*-arachidonoyl dopamine have been proposed to interact at the same binding site as capsaicin (TMH3–4 region) [133]. Although with less potency and efficacy, many phytocannabinoids, are able to activate TRPV1 [29, 125, 134]. As summarized in Table 1, CBD, CBN, CBG, CBC, Δ^9-THCV, and CBDV are agonists of this ion channel.

TRPV2, TRPV3 and TRPV4 channel activation by phytocannabinoids: Phytocannabinoids can also modulate other non capsaicin-sensitive TRPV channels such as TRPV2, TRPV3 and TRPV4. These receptors are directly involved in the modulation of nociception and temperature perception. As demonstrated through diverse functional outcomes, the phytocannabinoids Δ^9-THC, CBD, CBG, Δ^9-THCV, and CBDV are agonists of TRPV2 [29, 125]. In addition, strong data suggests that some of the analgesic and antiproliferative properties of CBD may be mediated by TRPV2 activation [28, 135].

The activity of phytocannabinoids has also been evaluated in TRPV3- and TRPV4-expressing HEK-293 cells [30]. In this study, phytocannabinoids were not only able to modulate, but also alter the expression of these TRP channels. These results highlight the therapeutic potential of phytocannabinoids for the treatment of diseases such as gastrointestinal inflammation.

Other TRP channels affecting phytocannabinoid activity: TRPA1 and TRPM8: TRPA1 and TRPM8 belong to the ankyrin and melastatin subfamilies of TRP channels respectively. These receptors are also involved in thermosensation, but they are activated by cold temperatures, as well as by different molecules such as menthol. TRPA1 and TRPM8 play a role in cold hypersensitivity associated with inflammatory and neuropathic pain [136]. Therefore, these ion channels may be a potential targets for the treatment of pathophysiological cold pain.

In HEK293 cells expresssing TRPA1, diverse plant-derived cannabinoids were able to efficaciously activate this ion channel. Among others, THC, CBC and CBG can induce TRPA1-mediated Ca^{2+} elevation in these cells [29, 31]. Although with lower potecy, the activation effect of CBC was also confirmed in DGR neurons. In addition, CBD and CBC were further observed to potently desensitize TRPA1 [31], thus supporting the hypothesis that phytocannabinoids may exert analgesic effects via TRPA1 activation/desensitization.

De Petrocelli and coworkers have characterized phytocannabinoid effects on TRPM8 channels (see Table 1). Studies on intracellular Ca^{2+} increase in HEK293 cells transfected with rat recombinant TRPM8, as well as in DRG neurons, have demonstrated that certain phyocannabinoids can efficaciously antagonize the effect of TRPM8 agonists [31, 125]. Interestingly, this activity was shown to be cannabinoid receptor-independent. Even though more studies, especially *in vivo*, need to be done to fully determine the role of TRP channels in the activity triggered by phytocannabinoids, there is definitely evidence that these molecules are highly involved in the modulation of these receptors.

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References

1. Mechoulam R, Gaoni Y. The absolute configuration of delta-1-tetrahydrocannabinol, the major active constituent of hashish. Tetrahedron Lett. 1967; 12:1109. [PubMed: 6039537]
2. Pomorska DK, do-Rego J-C, do-Rego J-L, Zubrzycka M, Janecka A. Opioid and Cannabinoid System in Food Intake. Curr Pharm Des. 2016; 22:1361. [PubMed: 26806346]
3. Boychuk DG, Goddard G, Mauro G, Orellana MF. The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. J oral facial pain headache. 2015; 29:7. [PubMed: 25635955]
4. Novack GD. Cannabinoids for treatment of glaucoma. Curr Opin Ophthalmol. 2016; 27:146. [PubMed: 26840343]
5. Phillips RS, Friend AJ, Gibson F, Houghton E, Gopaul S, Craig JV, Pizer B. Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. Cochrane database Syst Rev. 2016; 2:CD007786. [PubMed: 26836199]
6. Mechoulam R, Peters M, Murillo-Rodriguez E, Hanus LO. Cannabidiol--recent advances. Chem Biodivers. 2007; 4:1678. [PubMed: 17712814]
7. ElSohly, Mahmoud, A., Gul, W. Constituents of Cannabis Sativa. Pertwee, RG., editor. Oxford: Handb. Cannabis, Oxford Uni.; 2014. p. 3-22.
8. Howlett A, Barth F, Bonner T, Cabral G, Casellas P, Devane W, Felder CC, Herkenham M, Mackie K, Martin BR, Mechoulam R, Pertwee RG. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev. 2002; 54:161. [PubMed: 12037135]
9. Pertwee RG. Pharmacological actions of cannabinoids. Handb Exp Pharmacol. 2005; 168:1.
10. Pertwee RG. Pharmacology of cannabinoid receptor ligands. Curr Med Chem. 1999; 6:635. [PubMed: 10469884]
11. Bolognini D, Cascio MG, Parolaro D, Pertwee RG. AM630 behaves as a protean ligand at the human cannabinoid CB2 receptor. Br J Pharmacol. 2012; 165:2561. [PubMed: 21615724]
12. Lauckner JE, Jensen JB, Chen H-Y, Lu H-C, Hille B, Mackie K. GPR55 is a cannabinoid receptor that increases intracellular calcium and inhibits M current. Proc Natl Acad Sci U S A. 2008; 105:269.
13. Drmota, P., Greasley, P., Groblewski, T. Screening assays for cannabinoid- ligand type modulators. AstraZeneca Patent. WO2004074844. 2004.
14. Ryberg E, Larsson N, Sjögren S, Hjorth S, Hermansson N-O, Leonova J, Elebring T, Nilsson K, Drmota T, Greasley PJ. The orphan receptor GPR55 is a novel cannabinoid receptor. Br J Pharmacol. 2007; 152:1092. [PubMed: 17876302]
15. Yin H, Chu A, Li W, Wang B, Shelton F, Otero F, Nguyen DG, Caldwell JS, Chen YA. Lipid G protein-coupled receptor ligand identification using beta-arrestin PathHunter assay. J Biol Chem. 2009; 284:12328. [PubMed: 19286662]

16. Oka S, Nakajima K, Yamashita A, Kishimoto S, Sugiura T. Identification of GPR55 as a lysophosphatidylinositol receptor. Biochem Biophys Res Commun. 2007; 362:928. [PubMed: 17765871]
17. Kapur A, Zhao P, Sharir H, Bai Y, Caron MG, Barak LS, Abood ME. Atypical responsiveness of the orphan receptor GPR55 to cannabinoid ligands. J Biol Chem. 2009; 284:29817. [PubMed: 19723626]
18. Anavi-Goffer S, Baillie G, Irving AJ, Gertsch J, Greig IR, Pertwee RG, Ross RA. Modulation of L-α-lysophosphatidylinositol/GPR55 mitogen-activated protein kinase (MAPK) signaling by cannabinoids. J Biol Chem. 2012; 287:91. [PubMed: 22027819]
19. McHugh D, Page J, Dunn E, Bradshaw HB. Δ9-Tetrahydrocannabinol and N-arachidonyl glycine are full agonists at GPR18 receptors and induce migration in human endometrial HEC-1B cells. Br J Pharmacol. 2012; 165:2414. [PubMed: 21595653]
20. McHugh D, Roskowski D, Xie S, Bradshaw HB. Δ9-THC and N-arachidonoyl glycine regulate BV-2 microglial morphology and cytokine release plasticity: Implications for signaling at GPR18. Front Pharmacol. 2014; 4:1.
21. Barann M, Molderings G, Brüss M, Bönisch H, Urban BW, Göthert M. Direct inhibition by cannabinoids of human 5-HT3A receptors: probable involvement of an allosteric modulatory site. Br J Pharmacol. 2002; 137:589. [PubMed: 12381672]
22. Shi B, Yang R, Wang X, Liu H, Zou L, Hu X, Wu J, Zou A, Liu L. Inhibition of 5-HT3 receptors-activated currents by cannabinoids in rat trigeminal ganglion neurons. J Huazhong Univ Sci Technol. 2012; 32:265.
23. Kathmann M, Flau K, Redmer A, Tränkle C, Schlicker E. Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors. Naunyn Schmiedebergs Arch Pharmacol. 2006; 372:354. [PubMed: 16489449]
24. O'Sullivan SEO, Kendall Da, Randall MD. Further Characterization of the Time-Dependent Vascular Effects of D9 -Tetrahydrocannabinol. J Pharmacol Exp Ther. 2006; 317:428. [PubMed: 16352700]
25. Vara D, Morell C, Rodríguez-Henche N, Diaz-Laviada I. Involvement of PPARγ in the antitumoral action of cannabinoids on hepatocellular carcinoma. Cell Death Dis. 2013; 4:e618. [PubMed: 23640460]
26. Xiong W, Cheng K, Cui T, Godlewski G, Rice KC, Xu Y, Zhang L. Cannabinoid potentiation of glycine receptors contributes to cannabis-induced analgesia. Nat Chem Biol. 2011; 7:296. [PubMed: 21460829]
27. Hejazi N, Zhou C, Oz M, Sun H, Ye JH, Zhang L. Delta9-tetrahydrocannabinol and endogenous cannabinoid anandamide directly potentiate the function of glycine receptors. Mol Pharmacol. 2006; 69:991. [PubMed: 16332990]
28. Qin N, Neeper MP, Liu Y, Hutchinson TL, Lubin M Lou, Flores CM. TRPV2 is activated by cannabidiol and mediates CGRP release in cultured rat dorsal root ganglion neurons. J Neurosci. 2008; 28:6231. [PubMed: 18550765]
29. De Petrocellis L, Ligresti A, Moriello AS, Allar M, Bisogno T, Petrosino S, Stott CG, Di Marzo V. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Br J Pharmacol. 2011; 163:1479. [PubMed: 21175579]
30. De Petrocellis L, Orlando P, Moriello AS, Aviello G, Stott C, Izzo AA, di Marzo V. Cannabinoid actions at TRPV channels: Effects on TRPV3 and TRPV4 and their potential relevance to gastrointestinal inflammation. Acta Physiol. 2012; 204:255.
31. De Petrocellis L, Vellani V, Schiano-Moriello A, Marini P, Magherini PC, Orlando P, Di Marzo V. Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyrin type-1 and melastatin type-8. J Pharmacol Exp Ther. 2008; 325:1007. [PubMed: 18354058]
32. Leighty EG, Fentiman AF, Foltz RL. Long-retained metabolites of Δ9- and Δ8-tetrahydrocannabinols identified as novel fatty acid conjugates. Res Commun Chem Pathol Pharmacol. 1976; 14:13. [PubMed: 935647]

33. Razdan RK, Dalzell HC, Herlihy P, Howes JF. Hashish. Unsaturated side-chain analogues of delta8-tetrahydrocannabinol with potent biological activity. J Med Chem. 1976; 19:1328. [PubMed: 1003411]
34. Huffman JW, Liddle J, Yu S, Aung MM, Abood ME, Wiley JL, Martin BR. 3-(1',1'-Dimethylbutyl)-1-deoxy-Δ8-THC and related compounds: Synthesis of selective ligands for the CB2 receptor. Bioorganic Med Chem. 1999; 7:2905.
35. Razdan RK. Structure-activity relationships in cannabinoids. Pharmacol Rev. 1986; 38:75. [PubMed: 3018800]
36. Järbe TU, Henriksson BG. Acute effects of two tetrahydrocannabinols (Δ9-THC and Δ8-THC) on water intake in water deprived rats: implications for behavioral studies on marijuana compounds. Psychopharmacologia. 1973; 30:315–322. [PubMed: 4722202]
37. Järbe TU, Henriksson BG. Effects of Δ8-THC, and Δ9-THC on the acquisition of a discriminative positional habit in rats. The transitions between normal and tetrahydrocannabinol-induced states on reversal learning. Psychopharmacologia. 1973; 31:321. [PubMed: 4795349]
38. Harvey DJ. Stability of cannabinoids in dried samples of cannabis dating from around 1896–1905. J Ethnopharmacol. 1990; 28:117. [PubMed: 2314109]
39. Rhee MH, Vogel Z, Barg J, Bayewitch M, Levy R, Hanus L, Breuer A, Mechoulam R. Cannabinol derivatives: binding to cannabinoid receptors and inhibition of adenylylcyclase. J Med Chem. 1997; 40:3228. [PubMed: 9379442]
40. MacLennan SJ, Reynen PH, Kwan J, Bonhaus DW. Evidence for inverse agonism of SR141716A at human recombinant cannabinoid CB1 and CB2 receptors. Br J Pharmacol. 1998; 124:619. [PubMed: 9690851]
41. McPartland JM, Glass M, Pertwee RG. Meta-analysis of cannabinoid ligand binding affinity and receptor distribution: interspecies differences. Br J Pharmacol. 2007; 152:583. [PubMed: 17641667]
42. Pertwee RG, Ross RA, Craib SJ, Thomas A. (−)-Cannabidiol antagonizes cannabinoid receptor agonists and noradrenaline in the mouse vas deferens. Eur J Pharmacol. 2002; 456:99. [PubMed: 12450575]
43. Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. Br J Pharmacol. 2007; 150:613. [PubMed: 17245363]
44. Laprairie RB, Bagher AM, Kelly MEM, Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the type 1 cannabinoid receptor. Br J Pharmacol. 2015; 20:4790.
45. Morales P, Goya P, Jagerovic N, Hernandez-Folgado L. Allosteric Modulators of the CB1 Cannabinoid Receptor: A Structural Update Review. Cannabis Cannabinoid Res. 2016; 1:22.
46. Ford LA, Roelofs AJ, Anavi-Goffer S, Mowat L, Simpson DG, Irving AJ, Rogers MJ, Rajnicek AM, Ross RA. A role for L-alpha-lysophosphatidylinositol and GPR55 in the modulation of migration, orientation and polarization of human breast cancer cells. Br J Pharmacol. 2010; 160:762. [PubMed: 20590578]
47. Whyte LS, Ryberg E, Sims NA, Ridge SA, Mackie K, Greasley PJ, Ross RA, Rogers MJ. The putative cannabinoid receptor GPR55 affects osteoclast function in vitro and bone mass in vivo. Proc Natl Acad Sci U S A. 2009; 106:16511. [PubMed: 19805329]
48. Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem Res. 2005; 30:1037. [PubMed: 16258853]
49. Rock EM, Bolognini D, Limebeer CL, Cascio MG, Anavi-Goffer S, Fletcher PJ, Mechoulam R, Pertwee RG, Parker La. Cannabidiol, a nonpsychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT 1A somatodendritic autoreceptors in the dorsal raphe nucleus. Br J Pharmacol. 2012; 165:2620. [PubMed: 21827451]
50. Yang K-H, Galadari S, Isaev D, Petroianu G, Shippenberg TS, Oz M. The nonpsychoactive cannabinoid cannabidiol inhibits 5-hydroxytryptamine3A receptor-mediated currents in Xenopus laevis oocytes. J Pharmacol Exp Ther. 2010; 333:547. [PubMed: 20160007]
51. Gonca E, Darıcı F. The Effect of Cannabidiol on Ischemia/Reperfusion-Induced Ventricular Arrhythmias: The Role of Adenosine A1 Receptors. J Cardiovasc Pharmacol Ther. 2014; 1:76.

52. O'Sullivan SE, Sun Y, Bennett AJ, Randall MD, Kendall DA. Time-dependent vascular actions of cannabidiol in the rat aorta. Eur J Pharmacol. 2009; 612:61. [PubMed: 19285060]
53. Esposito G, Scuderi C, Valenza M, Togna GI, Latina V, de Filippis D, Cipriano M, Carratù MR, Iuvone T, Steardo L. Cannabidiol reduces Aβ-induced neuroinflammation and promotes hippocampal neurogenesis through PPARγ involvement. PLoS One. 2011; 6:e28668. [PubMed: 22163051]
54. Scuderi C, Steardo L, Esposito G. Cannabidiol promotes amyloid precursor protein ubiquitination and reduction of beta amyloid expression in SHSY5YAPP+ cells through PPARg involvement. Phyther Res. 2014; 28:1007.
55. Ahrens J, Demir R, Leuwer M, De La Roche J, Krampfl K, Foadi N, Karst M, Haeseler G. The nonpsychotropic cannabinoid cannabidiol modulates and directly activates alpha-1 and alpha-1-beta glycine receptor function. Pharmacology. 2009; 83:217. [PubMed: 19204413]
56. Xiong W, Cui T, Cheng K, Yang F, Chen SR, Willenbring D, Guan Y, Pan HL, Ren K, Xu Y, Zhang L. Cannabinoids suppress inflammatory and neuropathic pain by targeting alpha3 glycine receptors. J Exp Med. 2012; 209:1121. [PubMed: 22585736]
57. Bakas, T., Devenish, S., Van Nieuwenhuizen, P., Arnold, J., McGregor, I., Collins, M. The actions of cannabidiol and 2-arachidonyl glicerol on GABA-A receptors. 26th Annu. Symp. Cannabinoids, Int. Cannabinoid Res. Soc; Bukovina, Poland. 2016. p. 28
58. Rosenthaler S, Pöhn B, Kolmanz C, Nguyen Huu C, Krewenka C, Huber A, Kranner B, Rausch WD, Moldzio R. Differences in receptor binding affinity of several phytocannabinoids do not explain their effects on neural cell cultures. Neurotoxicol Teratol. 2014; 46:49. [PubMed: 25311884]
59. Izzo A, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci. 2009; 30:515. [PubMed: 19729208]
60. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol. 2008; 153:199. [PubMed: 17828291]
61. Cascio MG, Gauson LA, Stevenson LA, Ross RA, Pertwee RG. Evidence that the plant cannabinoid cannabigerol is a highly potent α 2-adrenoceptor agonist and moderately potent 5HT 1A receptor antagonist. Br J Pharmacol. 2010; 159:129. [PubMed: 20002104]
62. Thomas A, Stevenson LA, Wease KN, Price MR, Baillie G, Ross RA, Pertwee RG. Evidence that the plant cannabinoid Delta9-tetrahydrocannabivarin is a cannabinoid CB1 and CB2 receptor antagonist. Br J Pharmacol. 2005; 146:917. [PubMed: 16205722]
63. Pertwee RG, Thomas A, Stevenson LA, Ross RA, Varvel SA, Lichtman AH, Martin BR, Razdan RK. The psychoactive plant cannabinoid, Delta9-tetrahydrocannabinol, is antagonized by Delta8- and Delta9-tetrahydrocannabivarin in mice in vivo. Br J Pharmacol. 2007; 150:586. [PubMed: 17245367]
64. McPartland JM, Duncan M, Di Marzo V, Pertwee RG. Are cannabidiol and Δ 9 - tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. Br J Pharmacol. 2015; 172:737. [PubMed: 25257544]
65. Pertwee RG. The ring test: a quantitative method for assessing the"cataleptic" effect of cannabis in mice. Br J Pharmacol. 1972; 46:753. [PubMed: 4655271]
66. Bolognini D, Costa B, Maione S, Comelli F, Marini P, Di Marzo V, Parolaro D, Ross RA, Gauson LA, Cascio MG, Pertwee RG. The plant cannabinoid Delta9-tetrahydrocannabivarin can decrease signs of inflammation and inflammatory pain in mice. Br J Pharmacol. 2010; 160:677. [PubMed: 20590571]
67. Cascio MG, Zamberletti E, Marini P, Parolaro D, Pertwee RG. The phytocannabinoid, Δ9-Tetrahydrocannabivarin, can act through 5-HT1A receptors to produce antipsychotic effects. Br J Pharmacol. 2015; 172:1305. [PubMed: 25363799]
68. Merkus FW. Cannabivarin, a new constituent of hashish. Pharm Weekbl. 1971; 106:69. [PubMed: 5546952]
69. Merkus FW. Cannabivarin and tetrahydrocannabivarin, two new constituents of hashish. Nature. 1971; 232:579. [PubMed: 4937510]

70. Bailey K, Gagné D. Distinction of synthetic cannabidiol, cannabichromene, and cannabivarin by GLC using on-column methylation. J Pharm Sci. 1975; 64:1719. [PubMed: 1185546]
71. Hill TDM, Cascio MG, Romano B, Duncan M, Pertwee RG, Williams CM, Whalley BJ, Hill AJ. Cannabidivarin-rich cannabis extracts are anticonvulsant in mouse and rat via a CB1 receptor-independent mechanism. Br J Pharmacol. 2013; 170:679. [PubMed: 23902406]
72. Robert JJ, Ch L, Ludwig Bercht CA, van Ooyen R, Spronck HJW. Cannabinodiol: Conclusive identification and synthesis of a new cannabinoid from Cannabis sativa. Phytochemistry. 1977; 16:595.
73. ElSohly MA, Slade D. Chemical constituents of marijuana: The complex mixture of natural cannabinoids. Life Sci. 2005; 78:539. [PubMed: 16199061]
74. Shani A, Mechoulam R. Cannabielsoic acids: isolation and synthesis by a novel oxidative cyclization. Tetrahedron. 1974; 30:2437.
75. Ujváry I, Hanuš L. Human Metabolites of Cannabidiol: A Review on Their Formation, Biological Activity, and Relevance in Therapy. Cannabis Cannabinoid Res. 2016; 1:90.
76. Hartsel SC, Loh WH, Robertson LW. Biotransformation of Cannabidiol to Cannabielsoin by Suspension Cultures of Cannabis sativa and Saccharum officinarum. Planta Med. 1983; 48:17. [PubMed: 17404934]
77. Yamamoto I, Gohda H, Narimatsu S, Watanabe K, Yoshimura H. Cannabielsoin as a new metabolite of cannabidiol in mammals. Pharmacol Biochem Behav. 1991; 40:541. [PubMed: 1806944]
78. Crombie L, Ponsford R, Shani A, Yagnitinsky B, Mechoulam R. Hashish components. Photochemical production of cannabicyclol from cannabichromene. Tetrahedron Lett. 1968; 9:5771.
79. Vree TB, Breimer DD, van Ginneken CAM, van Rossum JM. Identification of cannabicyclol with a pentyl or propyl side-chain by means of combined as chromatography—mass spectrometry. J Chromatogr A. 1972; 74:124.
80. Obata Y, Ishikawa Y. Studies on the Constituents of Hemp Plant (Cannabis sativa L.). Agric Biol Chem. 1966; 30:619.
81. Elsohly MA, El-Feraly FS, Turner CE. Isolation and characterization of (+)-cannabitriol and (−)-10-ethoxy-9-hydroxy-delta 6a[10a]-tetrahydrocannabinol: two new cannabinoids from Cannabis sativa L. extract. Lloydia. 1977; 40:275. [PubMed: 895385]
82. Brogan AP, Eubanks LM, Koob GF, Dickerson TJ, Janda KD. Antibody-Catalyzed Oxidation of Δ 9 -Tetrahydrocannabinol. JACS. 2007; 129:3698.
83. Bayewitch M, Rhee MH, Avidor-Reiss T, Breuer A, Mechoulam R, Vogel Z. (−)-Delta9-tetrahydrocannabinol antagonizes the peripheral cannabinoid receptor-mediated inhibition of adenylyl cyclase. J Biol Chem. 1996; 271:9902. [PubMed: 8626625]
84. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature. 1990; 346:561. [PubMed: 2165569]
85. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature. 1993; 365:61. [PubMed: 7689702]
86. Hurst DP, Schmeisser M, Reggio PH. Endogenous lipid activated G protein-coupled receptors: Emerging structural features from crystallography and molecular dynamics simulations. Chem Phys Lipids. 2013; 169:46. [PubMed: 23485612]
87. Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, Gopher A, Almog S, Martin BR, Compton DR. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol. 1995; 50:83. [PubMed: 7605349]
88. Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K, Yamashita A, Waku K. 2-Arachidonoylgylcerol: A Possible Endogenous Cannabinoid Receptor Ligand in Brain. Biochem Biophys Res Commun. 1995; 215:89. [PubMed: 7575630]
89. Devane W, Hanus L, Breuer A, Pertwee R, Stevenson L, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science. 1992; 258:1946. [PubMed: 1470919]
90. Di Marzo V. Endocannabinoids: synthesis and degradation. Rev Physiol Biochem Pharmacol. 2008; 160:1. [PubMed: 18481028]

91. Dinh TP, Freund TF, Piomelli D. A role for monoglyceride lipase in 2-arachidonoylglycerol inactivation. Chem Phys Lipids. 2002; 121:149. [PubMed: 12505697]
92. Bracey MH, Hanson MA, Masuda KR, Stevens RC, Cravatt BF. Structural adaptations in a membrane enzyme that terminates endocannabinoid signaling. Science. 2002; 298:1793. [PubMed: 12459591]
93. Diana MA, Marty A. Endocannabinoid-mediated short-term synaptic plasticity: depolarization-induced suppression of inhibition (DSI) and depolarization-induced suppression of excitation (DSE). Br J Pharmacol. 2004; 142:9. [PubMed: 15100161]
94. Hanson MA, Roth CB, Jo E, Griffith MT, Scott FL, Reinhart G, Desale H, Clemons B, Cahalan SM, Schuerer SC, Sanna MG, Han GW, Kuhn P, Rosen H, Stevens RC. Crystal structure of a lipid G protein-coupled receptor. Science. 2012; 335:851. [PubMed: 22344443]
95. Srivastava A, Yano J, Hirozane Y, Kefala G, Gruswitz F, Snell G, Lane W, Ivetac A, Aertgeerts K, Nguyen J, Jennings A, Okada K. High-resolution structure of the human GPR40 receptor bound to allosteric agonist TAK-875. Nature. 2014; 513:124. [PubMed: 25043059]
96. Hurst DP, Grossfield A, Lynch DL, Feller S, Romo TD, Gawrisch K, Pitman MC, Reggio PH. A lipid pathway for ligand binding is necessary for a cannabinoid G protein-coupled receptor. J Biol Chem. 2010; 285:17954. [PubMed: 20220143]
97. Picone RP, Khanolkar AD, Xu W, Ayotte LA, Thakur GA, Hurst DP, Abood ME, Reggio PH, Fournier DJ, Makriyannis A. (−)-7'-Isothiocyanato-11-hydroxy-1',1'-dimethylheptylhexahydrocannabinol (AM841), a high-affinity electrophilic ligand, interacts covalently with a cysteine in helix six and activates the CB1 cannabinoid receptor. Mol Pharmacol. 2005; 68:1623. [PubMed: 16157695]
98. Pei Y, Mercier RW, Anday JK, Thakur G, Zvonok AM, Hurst D, Reggio PH, Janero DR, Makriyannis A. Ligand-Binding Architecture of Human CB2 Cannabinoid Receptor: Evidence for Receptor Subtype-Specific Binding Motif and Modeling GPCR Activation. Chem Biol. 2008; 15:1207. [PubMed: 19022181]
99. O'Sullivan SE. An update on peroxisome proliferator-activated receptor (PPAR) activation by cannabinoids. Br J Pharmacol. 2016; 173:1899. [PubMed: 27077495]
100. O'Sullivan SE. Cannabinoid activation of peroxisome proliferator-activated receptors: An update and review of the physiological relevance. Wiley Interdiscip Rev Membr Transp Signal. 2013; 2:17.
101. O'Sullivan SE. Cannabinoids go nuclear: evidence for activation of peroxisome proliferator-activated receptors. Br J Pharmacol. 2007; 152:576. [PubMed: 17704824]
102. Burstein S. PPAR-gamma: a nuclear receptor with affinity for cannabinoids. Life Sci. 2005; 77:1674. [PubMed: 16005906]
103. Sun Y, Alexander SPH, Kendall DA, Bennett AJ. Cannabinoids and PPARalpha signalling. Biochem Soc Trans. 2006; 34:1095. [PubMed: 17073758]
104. Ambrosio ALB, Dias SMG, Polikarpov I, Zurier RB, Burstein SH, Garratt RC. Ajulemic acid, a synthetic nonpsychoactive cannabinoid acid, bound to the ligand binding domain of the human peroxisome proliferator-activated receptor. J Biol Chem. 2007; 282:18625. [PubMed: 17462987]
105. Kozak KR, Gupta RA, Moody JS, Ji C, Boeglin WE, DuBois RN, Brash AR, Marnett LJ. 15-Lipoxygenase metabolism of 2-arachidonylglycerol. Generation of a peroxisome proliferator-activated receptor alpha agonist. J Biol Chem. 2002; 277:23278. [PubMed: 11956198]
106. Hughes MLR, Liu B, Halls ML, Wagstaff KM, Patil R, Velkov T, Jans DA, Bunnett NW, Scanlon MJ, Porter CJH. Fatty acid-binding proteins 1 and 2 differentially modulate the activation of peroxisome proliferator-activated receptor? in a ligand-selective manner. J Biol Chem. 2015; 290:13895. [PubMed: 25847235]
107. Yano M, Matsumura T, Senokuchi T, Ishii N, Murata Y, Taketa K, Motoshima H, Taguchi T, Sonoda K, Kukidome D, Takuwa Y, Kawada T, Brownlee M, Nishikawa T, Araki E. Statins activate peroxisome proliferator-activated receptor gamma through extracellular signal-regulated kinase 1/2 and p38 mitogen-activated protein kinase-dependent cyclooxygenase-2 expression in macrophages. Circ Res. 2007; 100:1442. [PubMed: 17463321]

108. Sun Y, Alexander SP, Garle MJ, Gibson CL, Hewitt K, Murphy SP, Kendall DA, Bennett AJ. Cannabinoid activation of PPAR alpha; a novel neuroprotective mechanism. Br J Pharmacol. 2007; 152:734. [PubMed: 17906680]
109. Takeda S, Ikeda E, Su S, Harada M, Okazaki H, Yoshioka Y, Nishimura H, Ishii H, Kakizoe K, Taniguchi A, Tokuyasu M, Himeno T, Watanabe K, Omiecinski CJ, Aramaki H. Δ(9)-THC modulation of fatty acid 2-hydroxylase (FA2H) gene expression: possible involvement of induced levels of PPARα in MDA-MB-231 breast cancer cells. Toxicology. 2014; 326:18. [PubMed: 25291031]
110. O'Sullivan SE, Tarling EJ, Bennett AJ, Kendall DA, Randall MD. Novel time-dependent vascular actions of Delta9-tetrahydrocannabinol mediated by peroxisome proliferator-activated receptor gamma. Biochem Biophys Res Commun. 2005; 337:824. [PubMed: 16213464]
111. Granja AG, Carrillo-Salinas F, Pagani A, Gomez-Canas M, Negri R, Navarrete C, Mecha M, Mestre L, Fiebich BL, Cantarero I, Calzado MA, Bellido ML, Fernandez-Ruiz J, Appendino G, Guaza C, Munoz E. A cannabigerol quinone alleviates neuroinflammation in a chronic model of multiple sclerosis. J Neuroimmune Pharmacol. 2012; 7:1002. [PubMed: 22971837]
112. Hind WH, England TJ, O'Sullivan SE. Cannabidiol protects an in vitro model of the blood-brain barrier from oxygen-glucose deprivation via PPARγ and 5-HT1A receptors. Br J Pharmacol. 2016; 173:815. [PubMed: 26497782]
113. Alhamoruni A, Wright KL, Larvin M, O'Sullivan SE. Cannabinoids mediate opposing effects on inflammation-induced intestinal permeability. Br J Pharmacol. 2012; 165:2598. [PubMed: 21745190]
114. Alhamoruni A, Lee AC, Wright KL, Larvin M, Sullivan SEO. Pharmacological Effects of Cannabinoids on the Caco-2 Cell Culture Model of Intestinal Permeability. Pharmacology. 2010; 335:92.
115. Ahrens J, Leuwer M, Demir R, Krampfl K, De La Roche J, Foadi N, Karst M, Haeseler G. Positive allosteric modulatory effects of ajulemic acid at strychnine-sensitive glycine α1- and α1β- receptors. Naunyn Schmiedebergs Arch Pharmacol. 2009; 379:371. [PubMed: 18985319]
116. Demir R, Leuwer M, De La Roche J, Krampfl K, Foadi N, Karst M, Dengler R, Haeseler G, Ahrens J. Modulation of glycine receptor function by the synthetic cannabinoid HU210. Pharmacology. 2009; 83:270. [PubMed: 19307742]
117. Dutertre S, Becker CM, Betz H. Inhibitory glycine receptors: An update. J Biol Chem. 2012; 287:40216. [PubMed: 23038260]
118. Betz H, Laube B. Glycine receptors: Recent insights into their structural organization and functional diversity. J Neurochem. 2006; 97:1600. [PubMed: 16805771]
119. Foadi N, Leuwer M, Demir R, Dengler R, Buchholz V, De La Roche J, Karst M, Haeseler G, Ahrens J. Lack of positive allosteric modulation of mutated α1S267I glycine receptors by cannabinoids. Naunyn Schmiedebergs Arch Pharmacol. 2010; 381:477. [PubMed: 20339834]
120. Christie MJ, Vaughan CW. Receptors: Cannabis medicine without a high. Nat Chem Biol. 2011; 7:249. [PubMed: 21502945]
121. Moss SJ, Smart TG. Constructing inhibitory synapses. Nat Rev Neurosci. 2001; 2:240. [PubMed: 11283747]
122. Wu L, Sweet T, Clapham DE. International Union of Basic and Clinical Pharmacology. LXXVI. Current Progress in the Mammalian TRP Ion Channel Family. Pharmocol Rev. 2010; 62:381.
123. Moran MM, McAlexander MA, Bíró T, Szallasi A. Transient receptor potential channels as therapeutic targets. Nat Rev Drug Discov. 2011; 10:601. [PubMed: 21804597]
124. De Petrocellis L, Vellani V, Schiano-Moriello A, Marini P, Magherini PC, Orlando P, Di Marzo V. Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyrin type-1 and melastatin type-8. J Pharmacol Exp Ther. 2008; 325:1007. [PubMed: 18354058]
125. Di Marzo V, De Petrocellis L. Endocannabinoids as regulators of transient receptor potential (TRP) channels: A further opportunity to develop new endocannabinoid-based therapeutic drugs. Curr Med Chem. 2010; 17:1430. [PubMed: 20166923]

126. Akopian AN, Ruparel NB, Jeske NA, Patwardhan A, Hargreaves M. Role of ionotropic cannabinoid receptors in peripheral antinociception and antihyperalgesia. Trends Pharmacol Sci. 2009; 30:79. [PubMed: 19070372]

127. Pertwee RG, Howlett AC, Abood ME, Alexander SPH, Marzo V Di, Elphick MR, Greasley PJ, Hansen HS, Kunos G. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid Receptors and Their Ligands : Beyond CB 1 and CB 2. Pharmacol Rev. 2010; 62:588. [PubMed: 21079038]

128. Caterina MJ. TRP channel cannabinoid receptors in skin sensation, homeostasis, and inflammation. ACS Chem Neurosci. 2014; 5:1107. [PubMed: 24915599]

129. Gao Y, Cao E, Julius D, Cheng Y. TRPV1 structures in nanodiscs reveal mechanisms of ligand and lipid action. Nature. 2016; 534:347. [PubMed: 27281200]

130. Venkatachalam K, Montell C. TRP channels. Annu Rev Biochem. 2007; 76:387. [PubMed: 17579562]

131. Anand U, Otto WR, Sanchez-Herrera D, Facer P, Yiangou Y, Korchev Y, Birch R, Benham C, Bountra C, Chessell IP, Anand P. Cannabinoid receptor CB2 localisation and agonist-mediated inhibition of capsaicin responses in human sensory neurons. Pain. 2008; 138:667. [PubMed: 18692962]

132. Price TJ, Patwardhan A, Akopian AN, Hargreaves KM, Flores CM. Modulation of trigeminal sensory neuron activity by the dual cannabinoid-vanilloid agonists anandamide, N-arachidonoyl-dopamine and arachidonyl-2-chloroethylamide. Br J Pharmacol. 2004; 141:1118. [PubMed: 15006899]

133. Jordt SE, Julius D. Molecular basis for species-specific sensitivity to"hot" chili peppers. Cell. 2002; 108:421. [PubMed: 11853675]

134. Iannotti FA, Hill CL, Leo A, Alhusaini A, Soubrane C, Mazzarella E, Russo E, Whalley BJ, Di Marzo V, Stephens GJ. Nonpsychotropic plant cannabinoids, cannabidivarin (CBDV) and cannabidiol (CBD), activate and desensitize transient receptor potential vanilloid 1 (TRPV1) channels in vitro: potential for the treatment of neuronal hyperexcitability. ACS Chem Neurosci. 2014; 5:1131. [PubMed: 25029033]

135. Nabissi M, Morelli MB, Santoni M, Santoni G. Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents. Carcinogenesis. 2013; 34:48. [PubMed: 23079154]

136. McKemy DD. How cold is it? TRPM8 and TRPA1 in the molecular logic of cold sensation. Mol Pain. 2005; 1:16. [PubMed: 15847696]

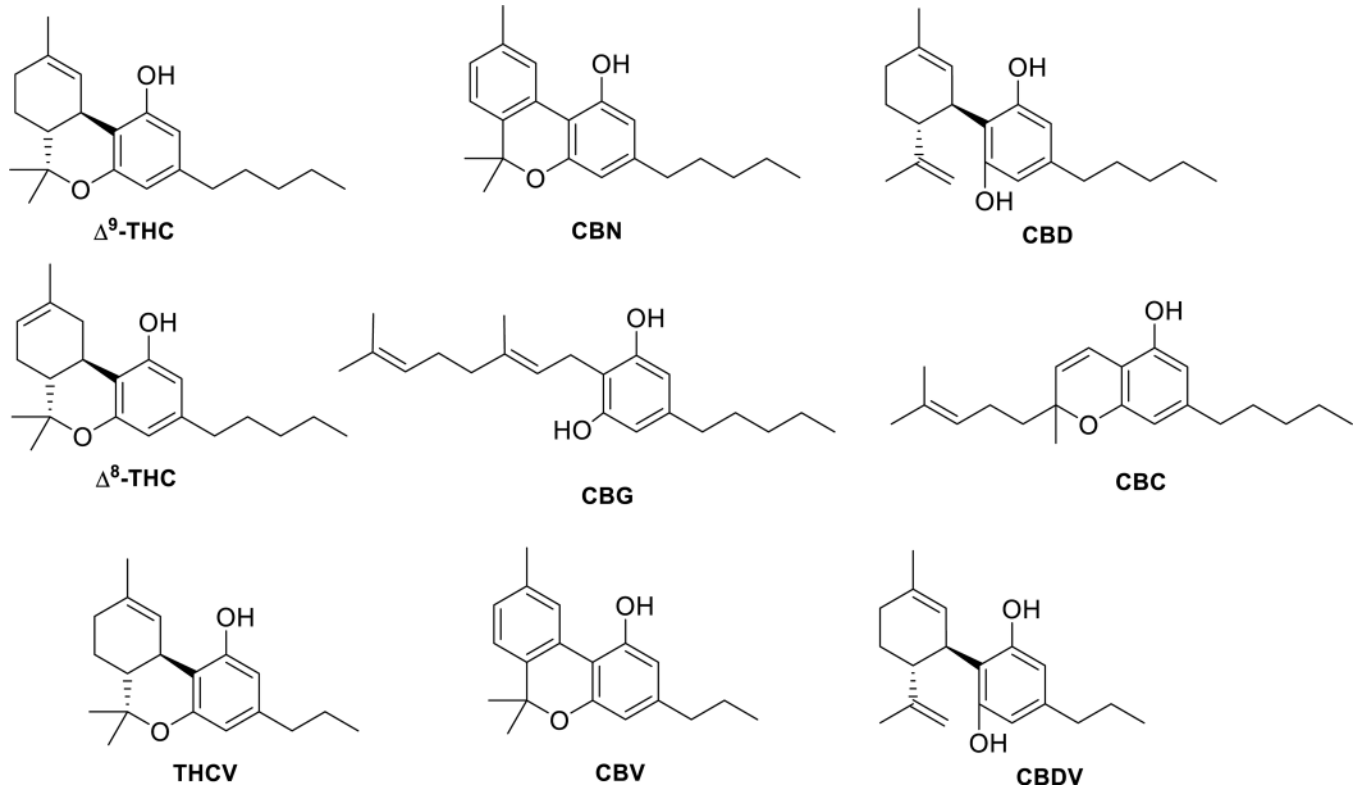


Fig. 1.
Structures of most abundant phytocannabinoids in *Cannabis sativa L.*

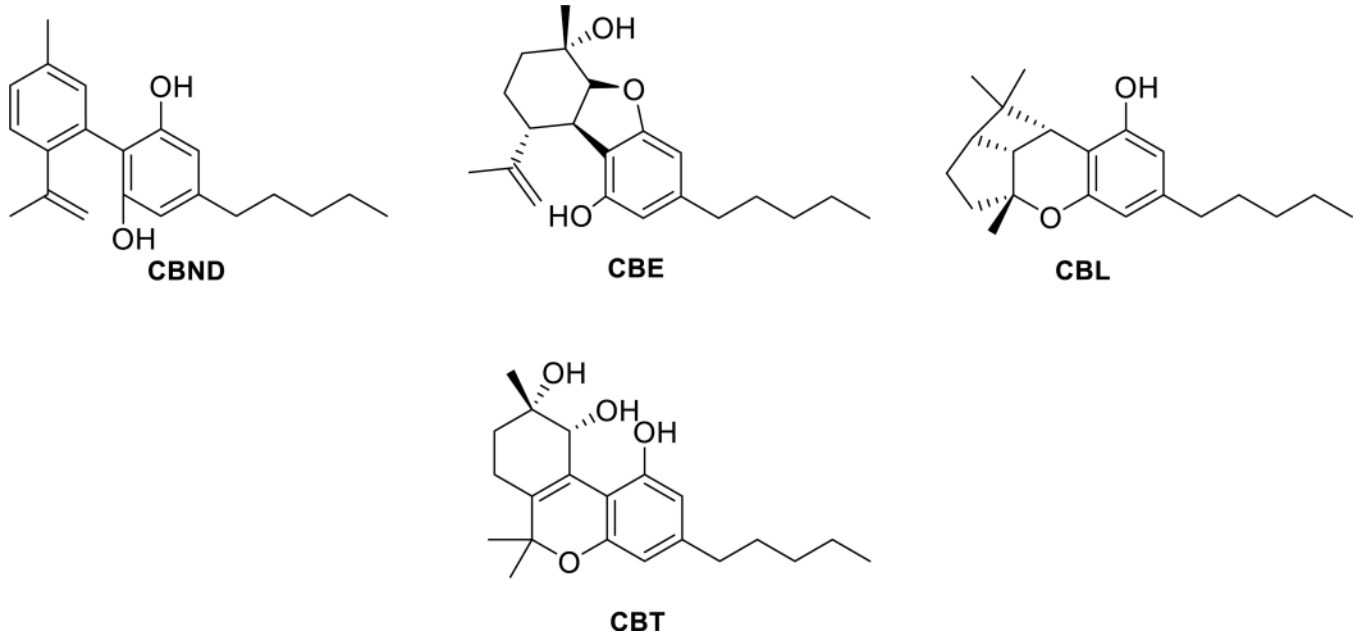
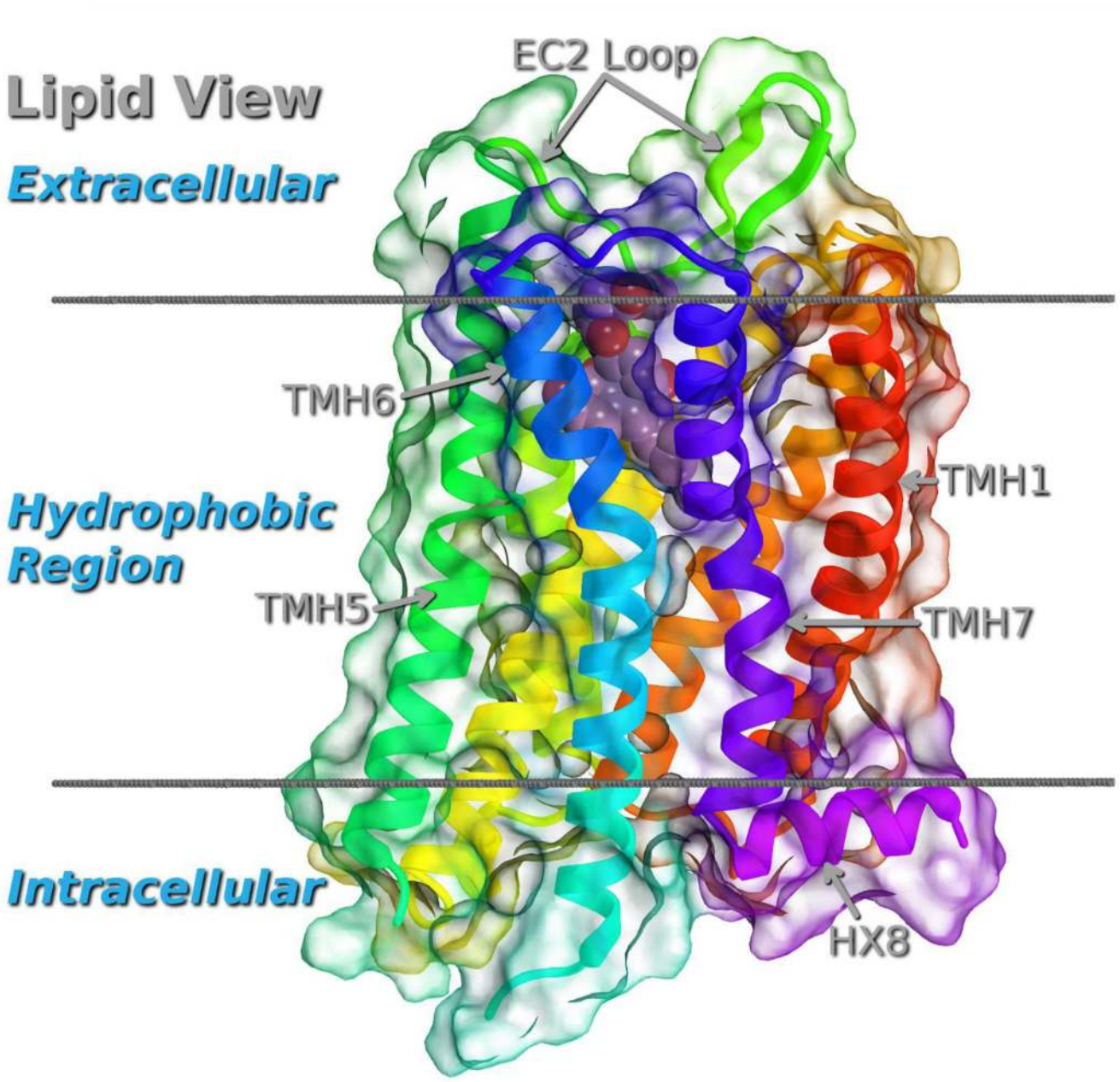


Fig. 2.
Structures of phytocannabinoids in lower abundance.

A



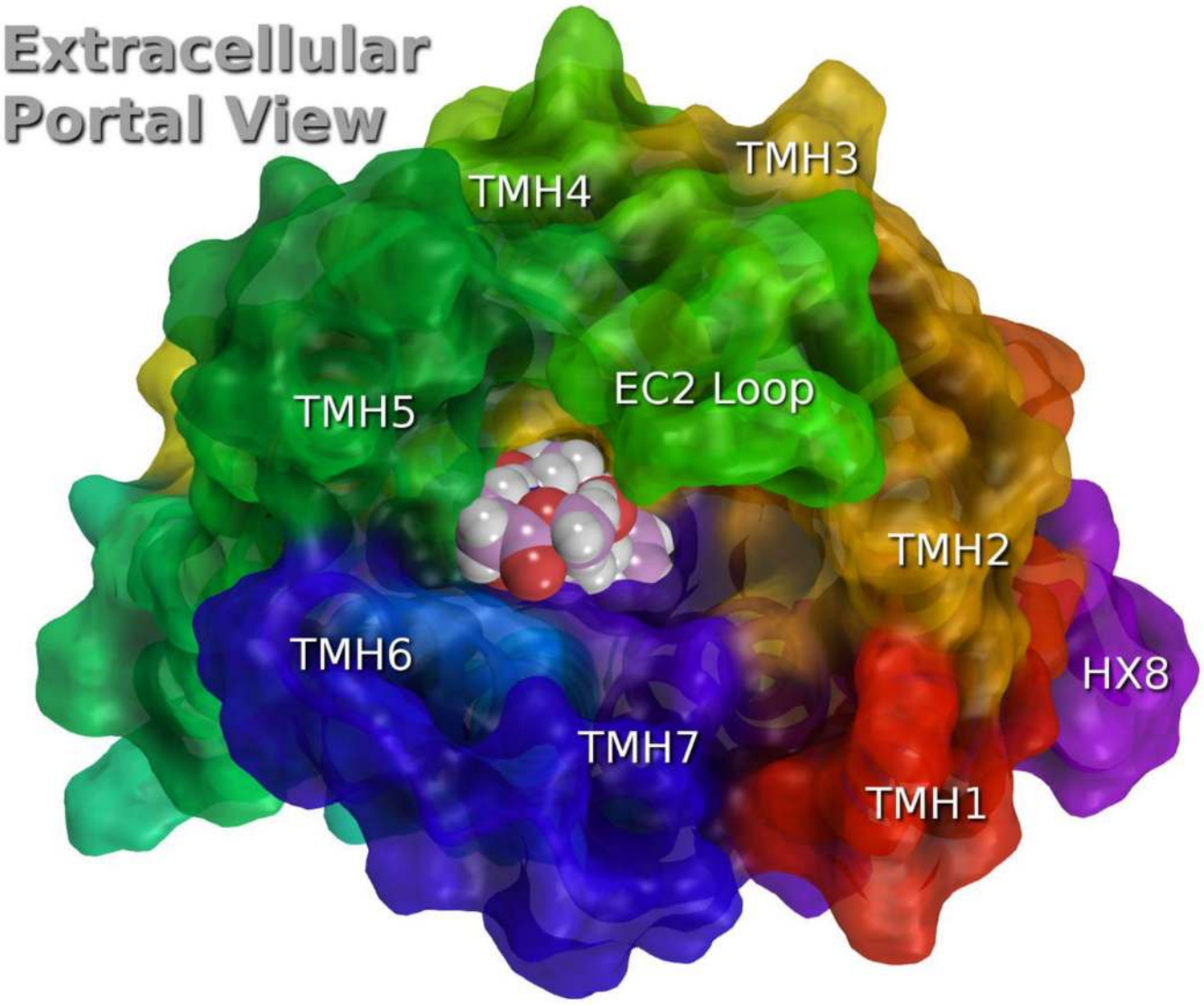


Fig. 3.

(A) The typical Class A G-protein coupled receptor structure is illustrated here by the 2.8 Å structure of the mu opioid receptor (MOR; PDB entry 4DKL) (B) An extracellular view of the MOR structure is illustrated here. In MOR, the extracellular loops of the receptor are splayed open, making ligand access from the extracellular milieu possible. Here the covalent ligand, beta-funaltrexamine is bound.

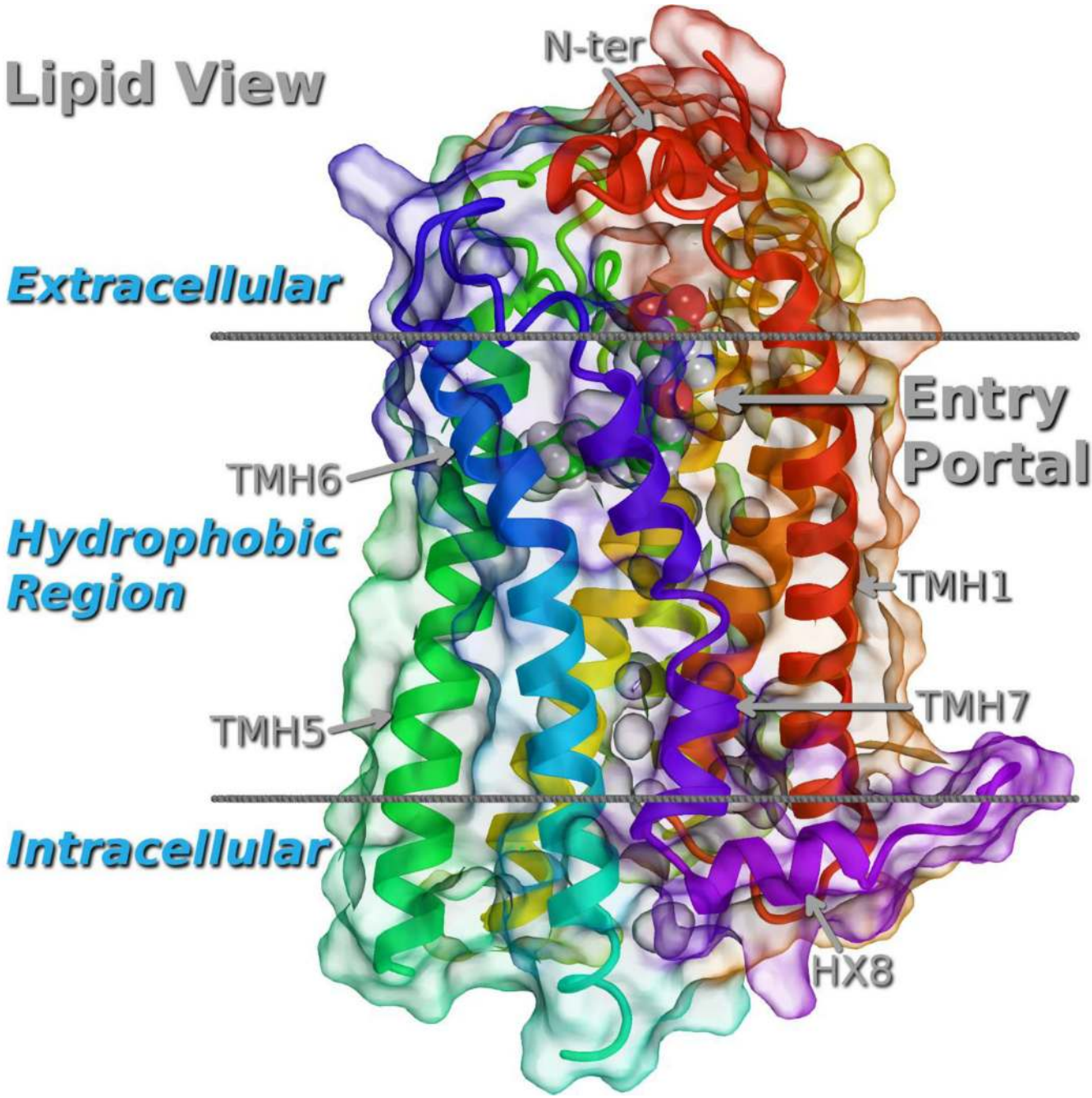


Fig. 4.

The 2.8 Å structure of the S1P1 receptor is illustrated here (PDB 3V2Y with antagonist, ML056). In this receptor, the N-terminus covers the EC side of the receptor, permitting no ligand access from the EC milieu. Instead, there is a portal between THH1 and TMH7 that allows ligand access from the lipid bilayer.

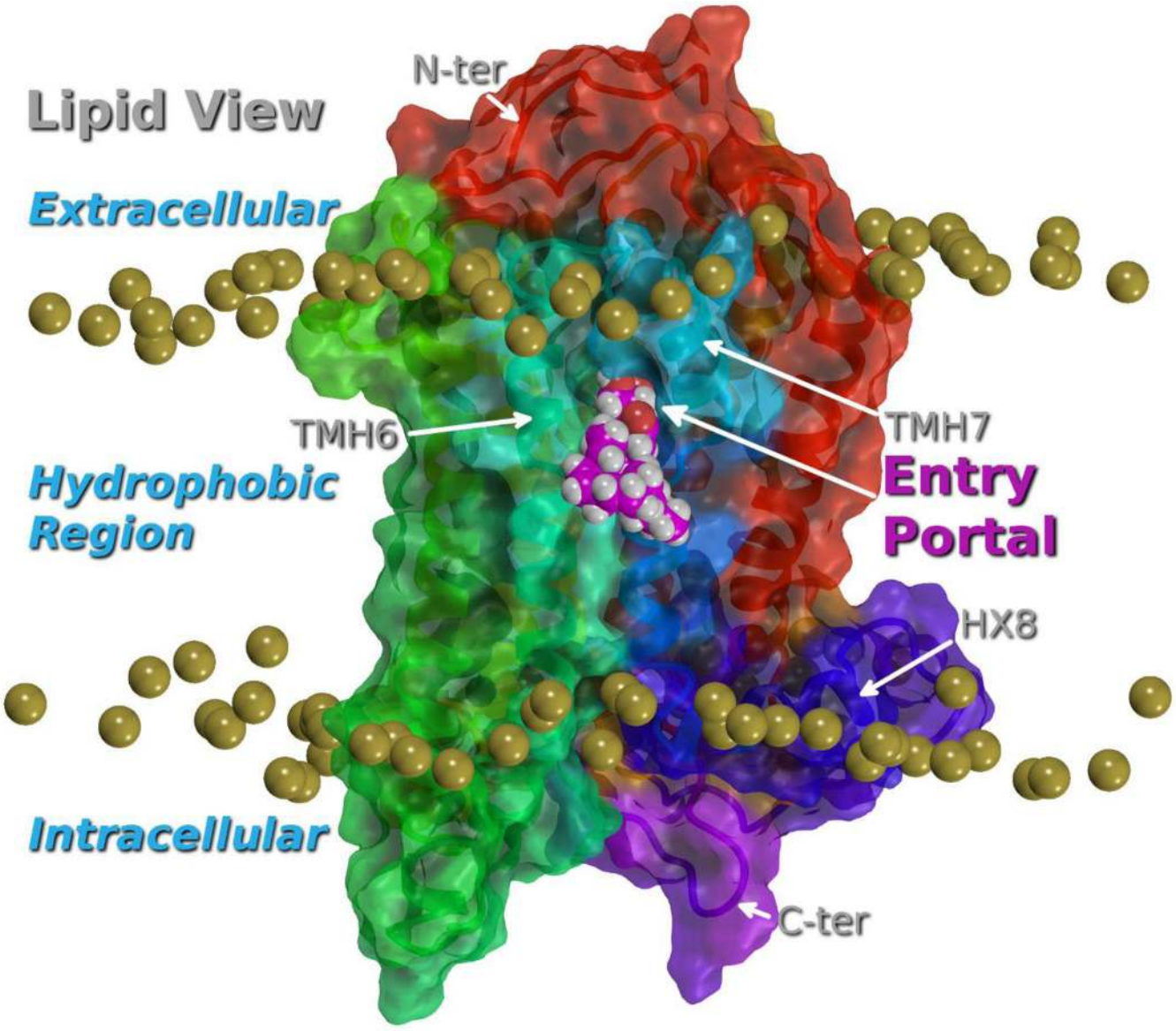


Fig. 5.

This figure shows results from molecular dynamics simulations in which the CB endogenous ligand, 2-AG enters the CB2 receptor from the lipid bilayer via a TMH6–TMH7 portal.

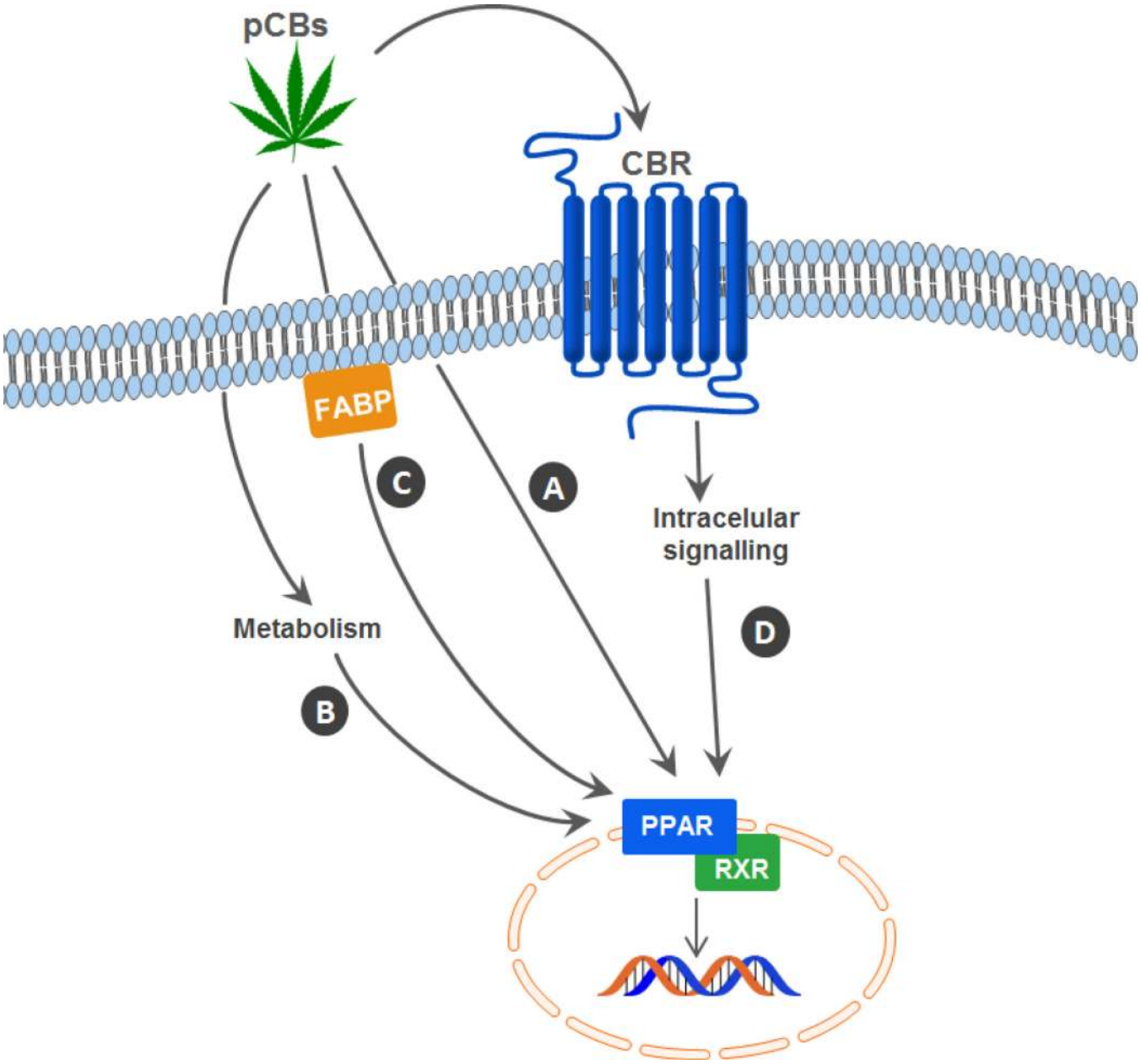


Fig. 6.

Potential mechanisms of PPAR-phytocannabinoids interactions: **A**) Direct binding of phytocannabinoids to these nuclear receptors; **B**) Possible conversion of phytocannabinoids into metabolites that may activate PPARs; C) Phytocannabinoid transported to the nucleus by FABPs; D) Another possibility is that phytocannabinoids modulate CBR triggering intracellular signalling pathways that may lead to the activation of PPARs.

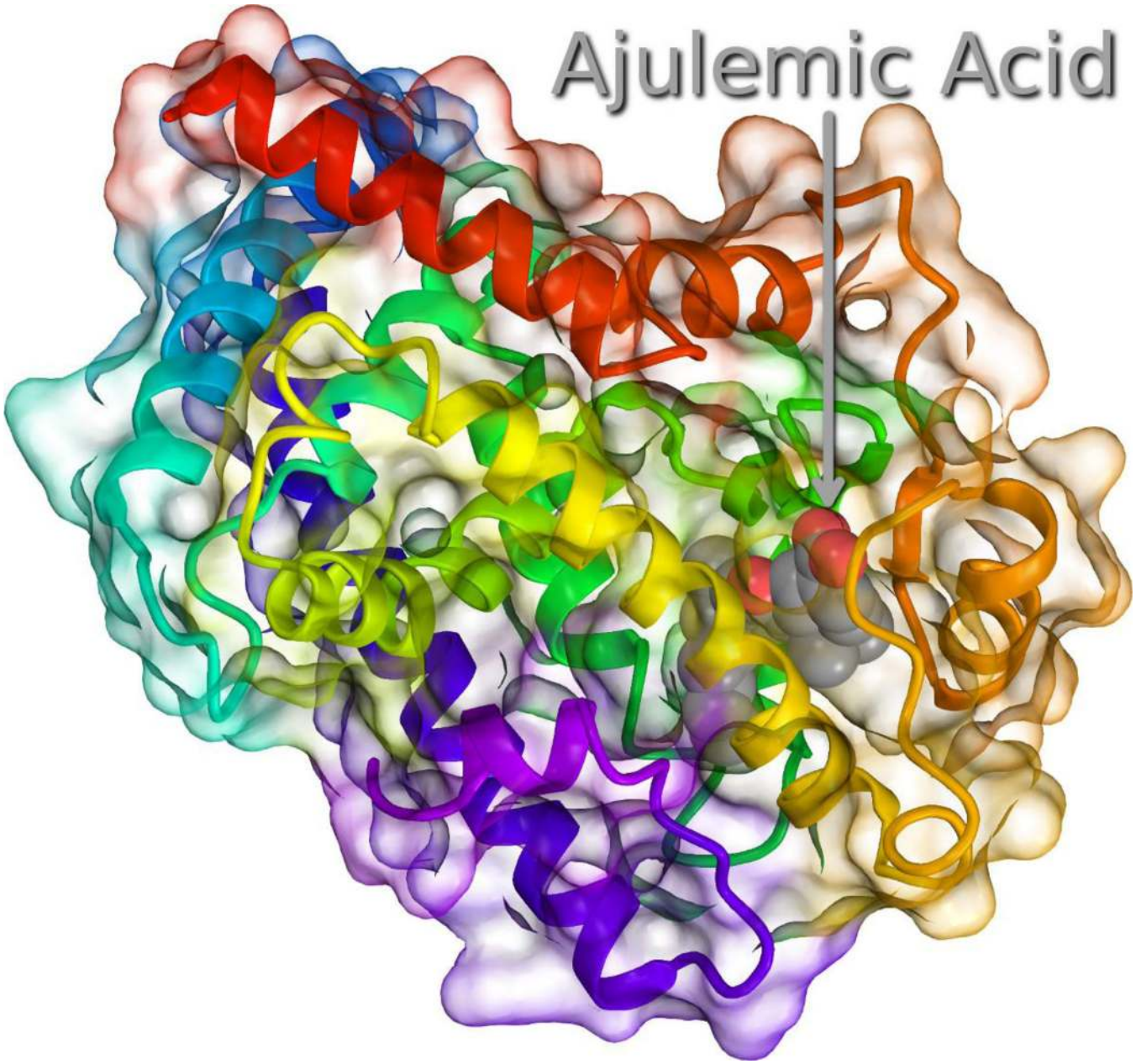


Fig. 7.
The 2.8 Å structure of PPARγ with ajulemic acid is illustrated here (PDB 2OM9).

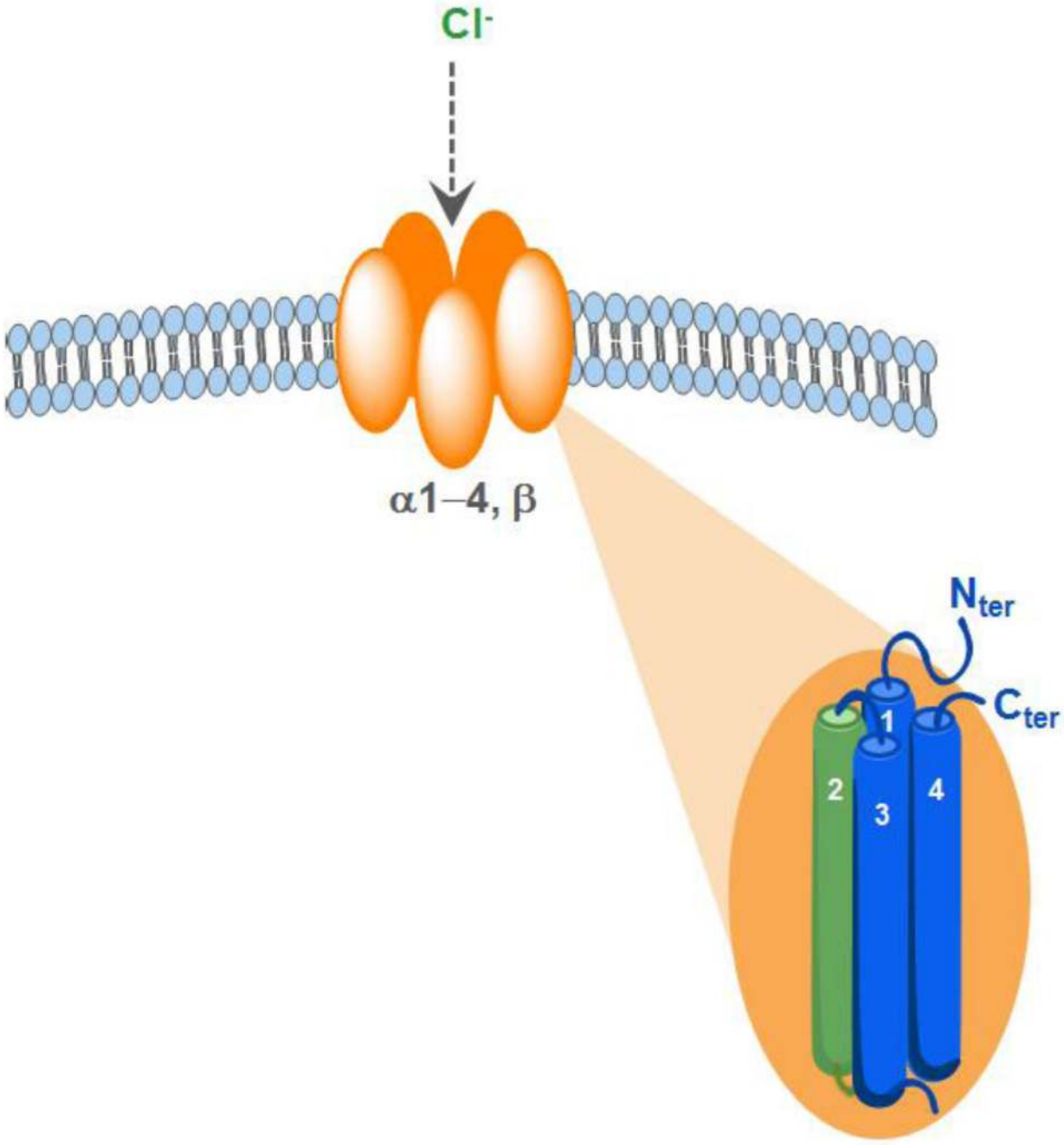


Fig. 8.

Structure of glycine receptors: pentamers formed by α and β subunits in a ratio of 2α:3β [116], each subunit consists of four transmembrane segments, the second transmembrane helix of each subunit forms the lining of the ion pore of these ligand-gated ion channels.

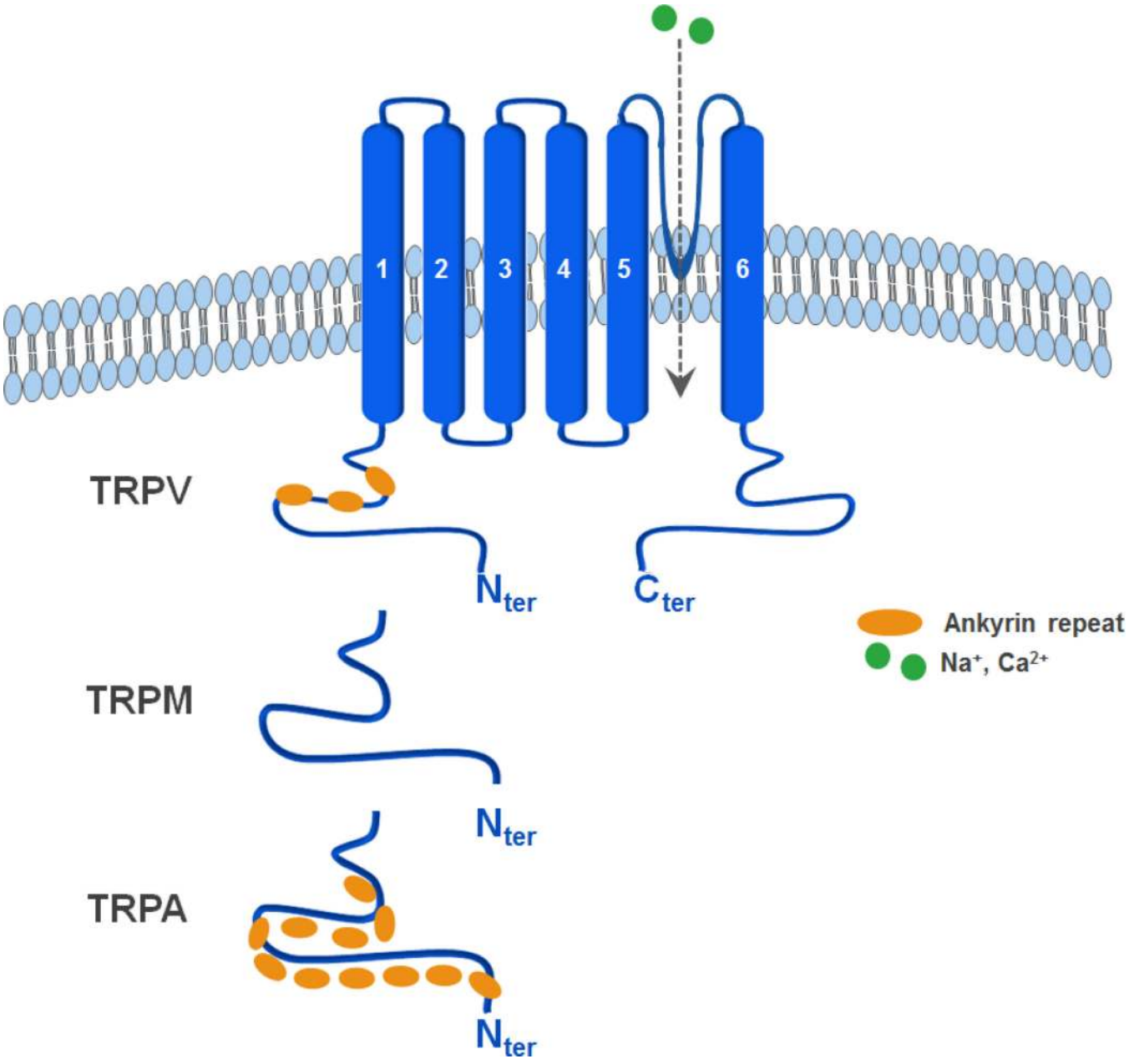


Fig. 9.
General structure of the TRP channels modulated by phytocannabinoids: TRPV, TRPM and TRPA.

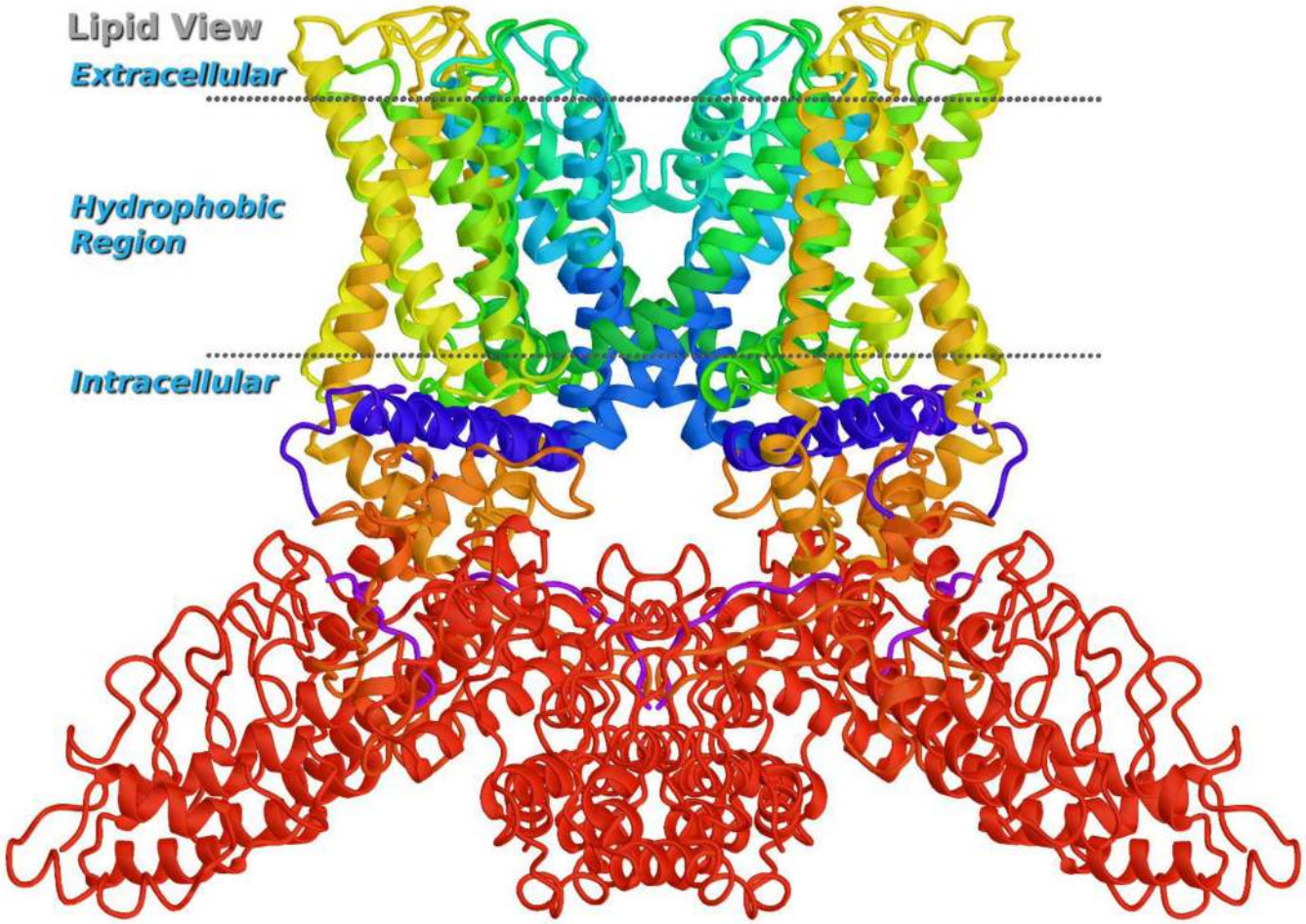


Fig. 10.
The 3.27 Å structure of the TRPV1 channel is illustrated here.

Table 1

Cannabinoid and non-cannabinoid molecular targets of selected phytocannabinoids.

pCBs	CB activity			Non-CB_1/Non-CB_2 activity			
	Target	Functionality	References	Target		Functionality	References
Δ^9-THC	CB_1	Partial Agonist	[2–4]	GPR55		Agonist	[8]
						NR	[11]
						LPI inhibitor	[12]
				GPR18		Agonist	[13, 14]
				$5HT_{3A}$		Antagonist	[15, 16]
	CB_2	Partial Agonist	[3, 4, 78]	μ– and δ-OPR		Allosteric Modulator	[17]
				PPARγ		Agonist	[18]
				GlyR	α_1	Positive Allosteric Modulator	[21]
					α_2	NR	[20]
					α_3	Positive Allosteric Modulator	[20]
				TRP channels		TRPV1 NR	[22]
						TRPV2, 3, 4 Agonist	[22–24]
						TRPM8 Antagonist	[25]
						TRPA1 Agonist	[22, 25]
Δ^8-THC	CB_1	Partial Agonist	[28, 29]	-		-	-
	CB_2	Partial Agonist	[28, 29]				
CBN	CB_1	Agonist	[4]	TRP channels		TRPA1 Agonist	[23]
	CB_2	Agonist	[33]			TRPM8 Antagonist	[23]
		Inverse agonist	[34]				
CBD	CB_1	Antagonist *	[37, 38]	GPR55		Antagonist	[8, 42]
				GPR18		Antagonist	[13, 14]
		Negative Allosteric Modulator	[39]	$5\text{-}HT_{1A}$		Agonist	[43, 44]
				$5\text{-}HT_{2A}$		Partial agonist *	[43]
				$5\text{-}HT_{3A}$		Antagonist	[45]

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pCBs	CB activity			Non-CB_1/Non-CB_2 activity			
	Target	Functionality	References	Target	Functionality	References
				A_{1A}	Agonist	[46]
	CB_2	Antagonist*	[38]	μ– and δ-OPR	Allosteric Modulator	[17]
				PPARγ	Agonist	[47–49]
				GlyR α_1	Positive Allosteric Modulator	[50]
				GlyR α_2	ND	-
				GlyR α_3	Positive Allosteric Modulator	[51]
	AEA uptake	Inhibitor	[23]	$GABA_A$	Positive Allosteric Modulator	[52]
				TRP channels	TRPV1, 2, 3 Agonist	[23, 24]
					TRPA1 Agonist	[23]
	CB_1	Partial Agonist*	[53–55]	GPR55	LPI inhibitor*	[12]
				5-HT_{1A}	Antagonist	[56]
CBG				α_2-AR	Agonist	[56]
	CB_2	Partial Agonist*	[53–55]	TRP channels	TRPV1, 2 Agonist	[23]
					TRPM8 Antagonist	[25]
	AEA uptake	Inhibitor	[23]		TRPA1 Agonist	[23]
	CB_1	Agonist*	[53]	TRP channels	TRPV3, 4 Agonist	[24]
CBC	CB_2	Agonist*	[53]		TRPM8 Antagonist	[23]
	AEA uptake	Inhibitor	[23]		TRPA1 Agonist	[23]
	CB_1	Antagonist	[57–59]	GPR55	Partial agonist/LPI inhibitor	[12]
Δ^9-THCV				$5HT_{1A}$	Agonist	[62]
	CB_2	Partial agonist	[61]	TRP channels	TRPV2 Agonist	[23]
					TRPM8 Antagonist	[23]
					TRPA1 Agonist	[23]
CBV	CB_1	ND	-	-	-	-

pCBs	CB activity			Non-CB_1/Non-CB_2 activity		
	Target	Functionality	References	Target	Functionality	References
	CB_2	ND	-			
CBDV	CB_1	NR	[66]	GPR55	LPI inhibitor	[12]
	CB_2	NR	[53]	TRP channels	TRPV1, 2, 3 Agonist	[23, 24]
					TRPA1 Agonist	[23]
CBND	CB_1	ND	-	-	-	-
	CB_2	ND	-			
CBE	CB_1	ND	-	-	-	-
	CB_2	ND	-			
CBL	CB_1	ND	-	-	-	-
	CB_2	ND	-			
CBT	CB_1	ND	-	-	-	-
	CB_2	ND	-			

NR: No response; ND: Not determined;

*: weak effect

Table 2

Physicochemical QlogP descriptor of phytocannabinoids Δ^9-THC, Δ^8-THC, CBN, CBD, CBG, CBC, Δ^9-THCV, CBV, CBDV, CBDN, CBE, CBL, and CBT calculated with QikProp 3.5 integrated in Maestro (Schrödinger, LLC, New York, USA).

pCB	QPlogP[a]
Δ^9-THC	5.627
Δ^8-THC	5.630
CBN	5.576
CBD	5.414
CBG	5.790
CBC	5.954
Δ^9-THCV	4.901
CBV	4.855
CBDV	4.648
CBDN	5.299
CBE	4.859
CBL	5.575
CBT	3.997

[a]Predicted octanol/water partition coefficient [−2.0/6.5]; [range of 95% of drugs].

Table 3

Activation of PPAR isotypes by phytocannabinoids.

pCBs	PPARα	PPARβ/δ	PPARγ
Δ^9-THC	Transcriptional activity [104]	-	Binding assays [106] Transcriptional activity [105] Inhibition by PPARγ antagonists [19, 105]
CBD	-	-	Binding assays [106] Transcriptional activity [47] Inhibition by PPARγ antagonists[47–49]
CBG	-	-	Binding assays [106]
CBC	-	-	Binding assays [106]
THCV	-	-	NR [18]

NR: No response