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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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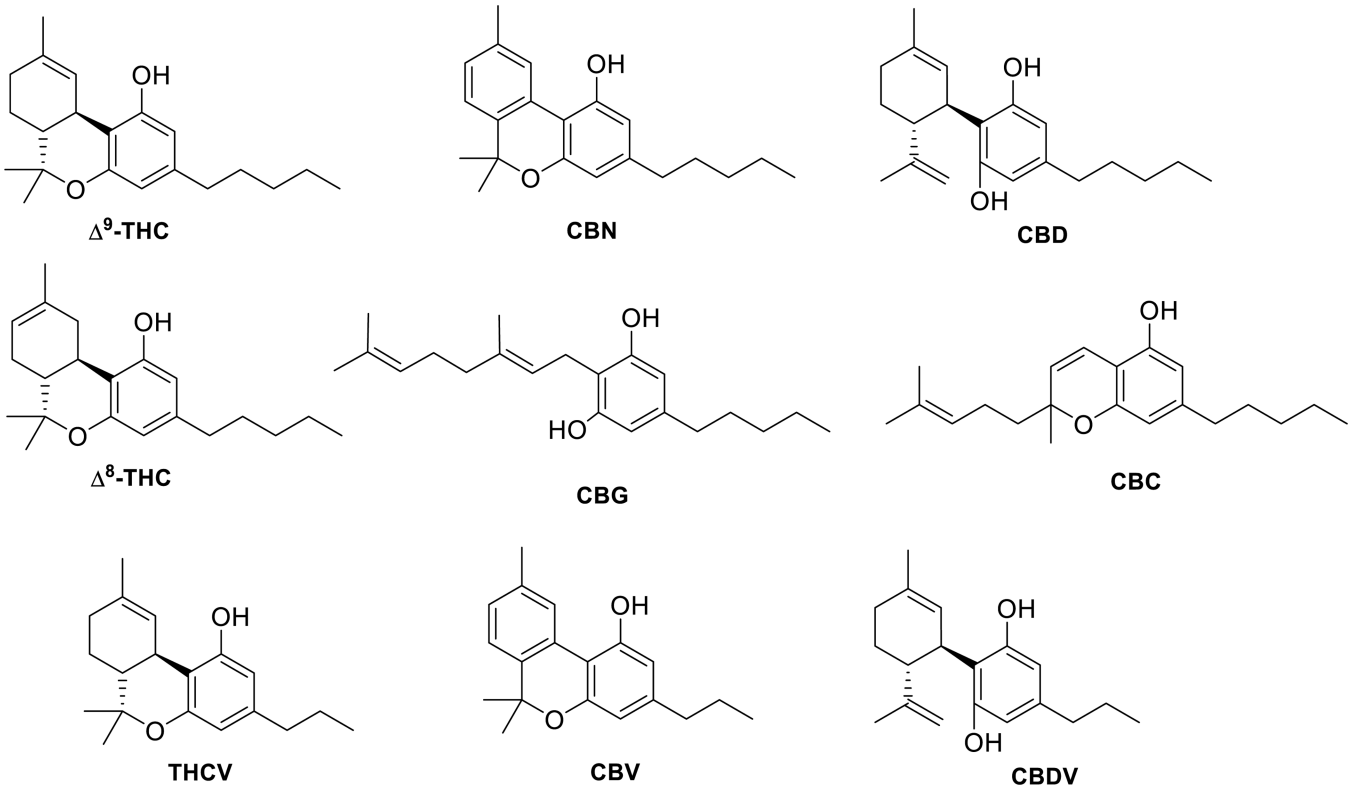


Fig. 1.
Structures of most abundant phytocannabinoids in *Cannabis sativa L.*

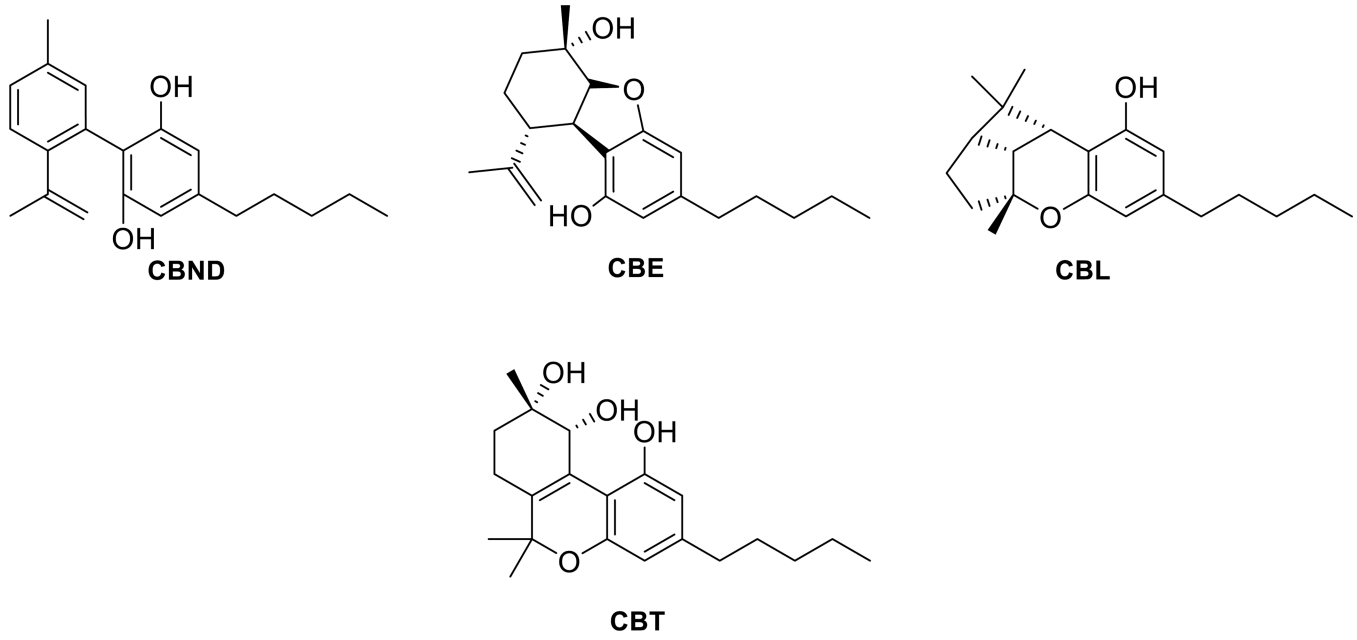
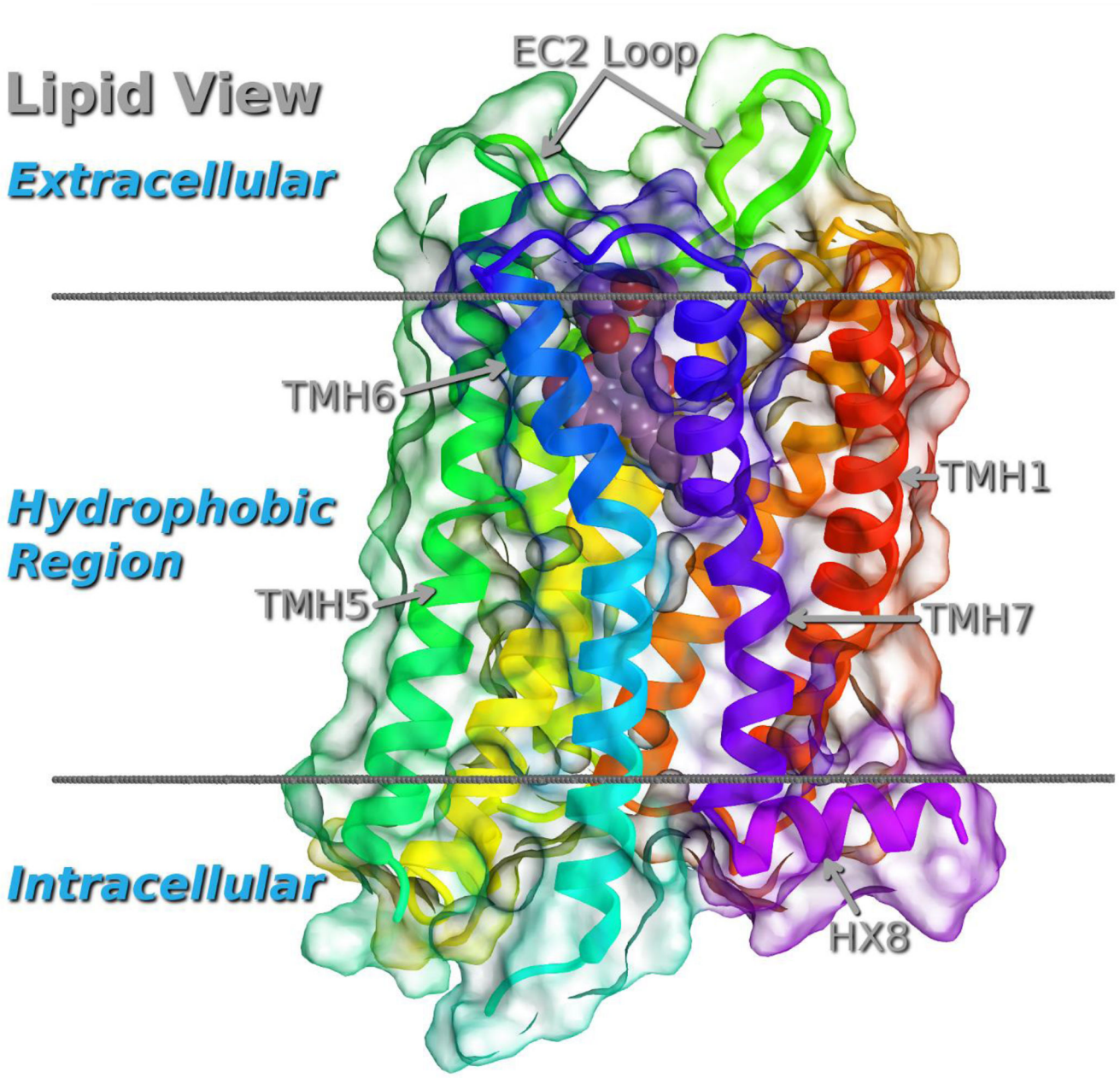


Fig. 2.
Structures of phytocannabinoids in lower abundance.

A



B

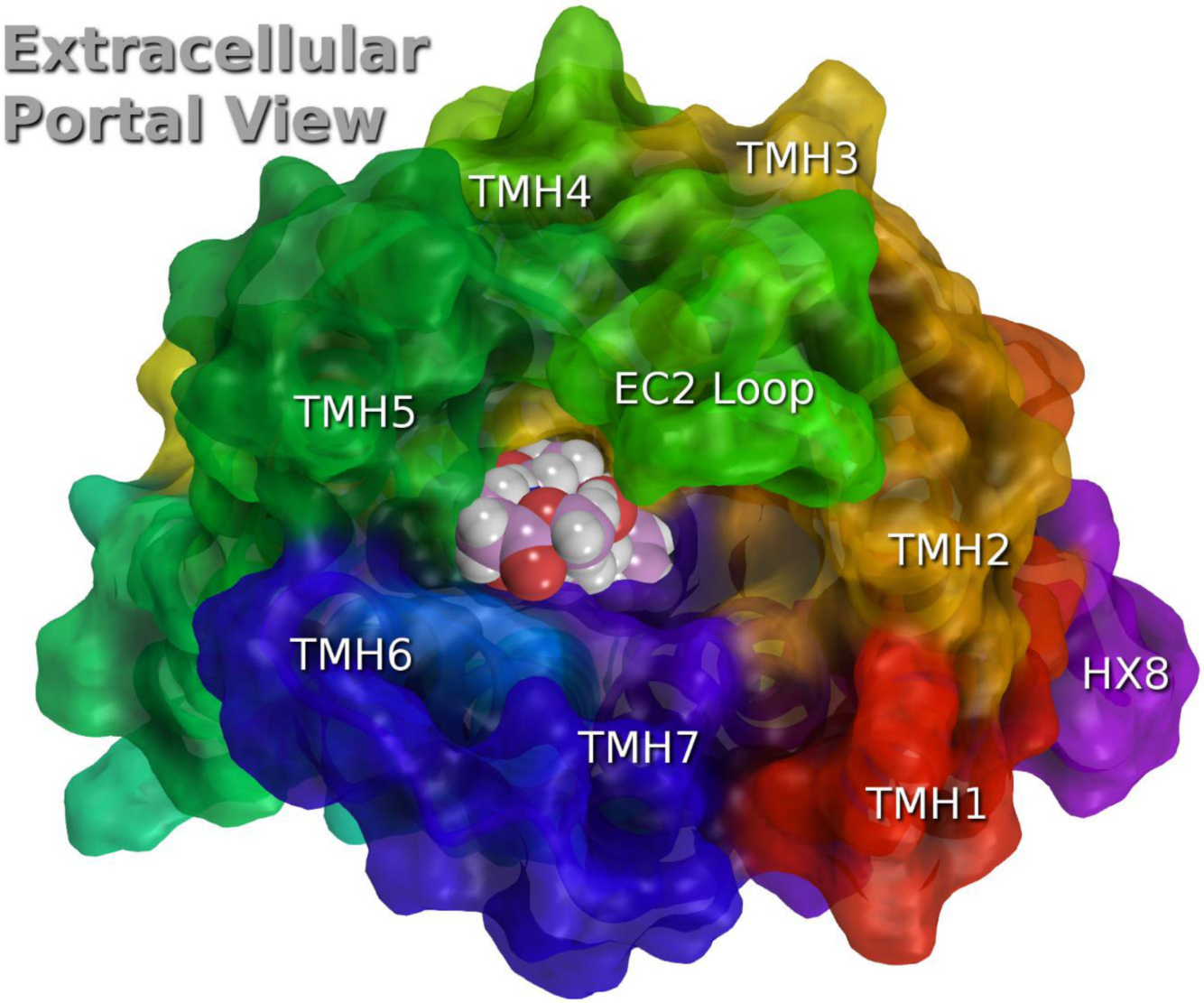


Fig. 3.

(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.

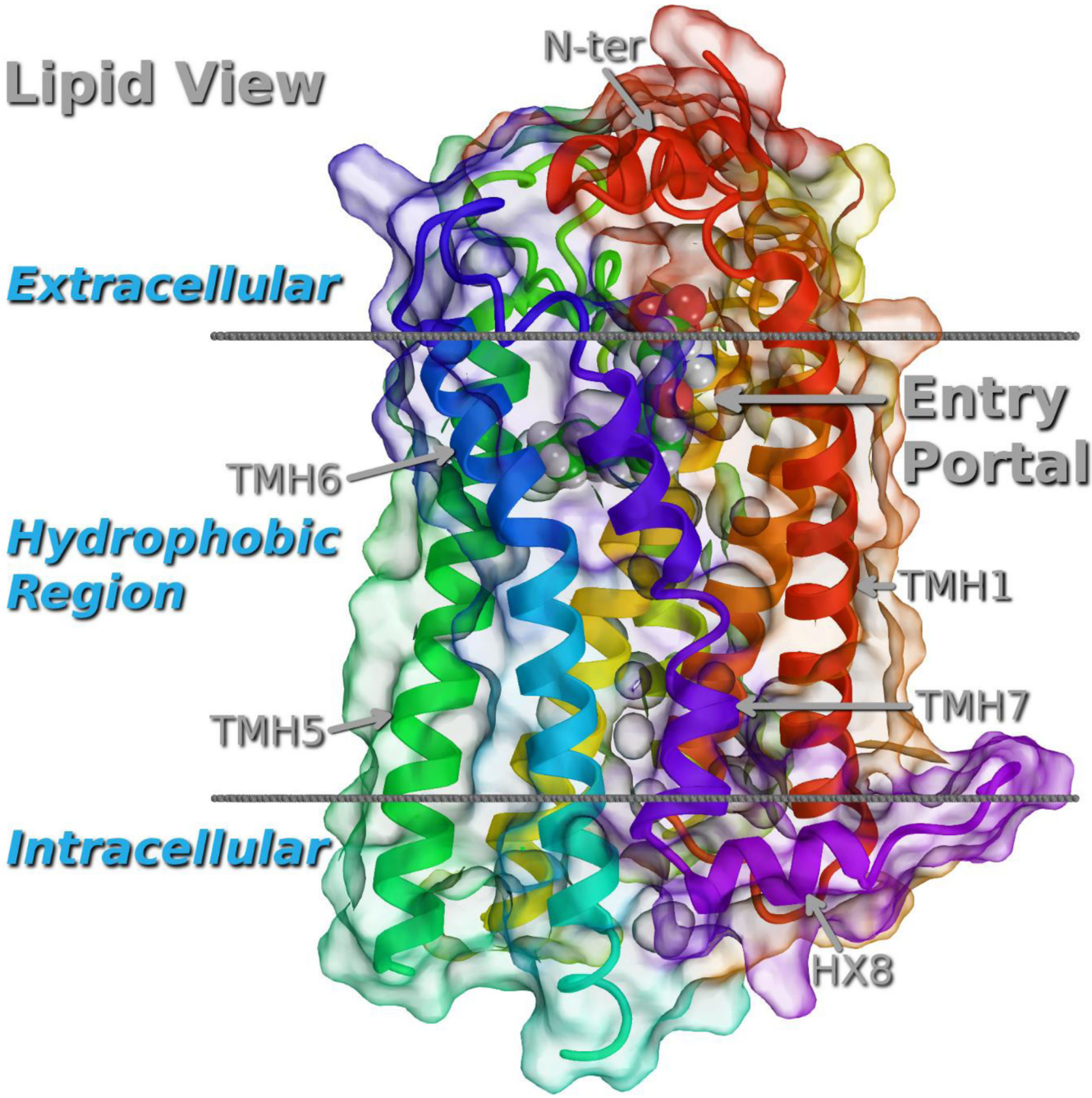


Fig. 4.

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.

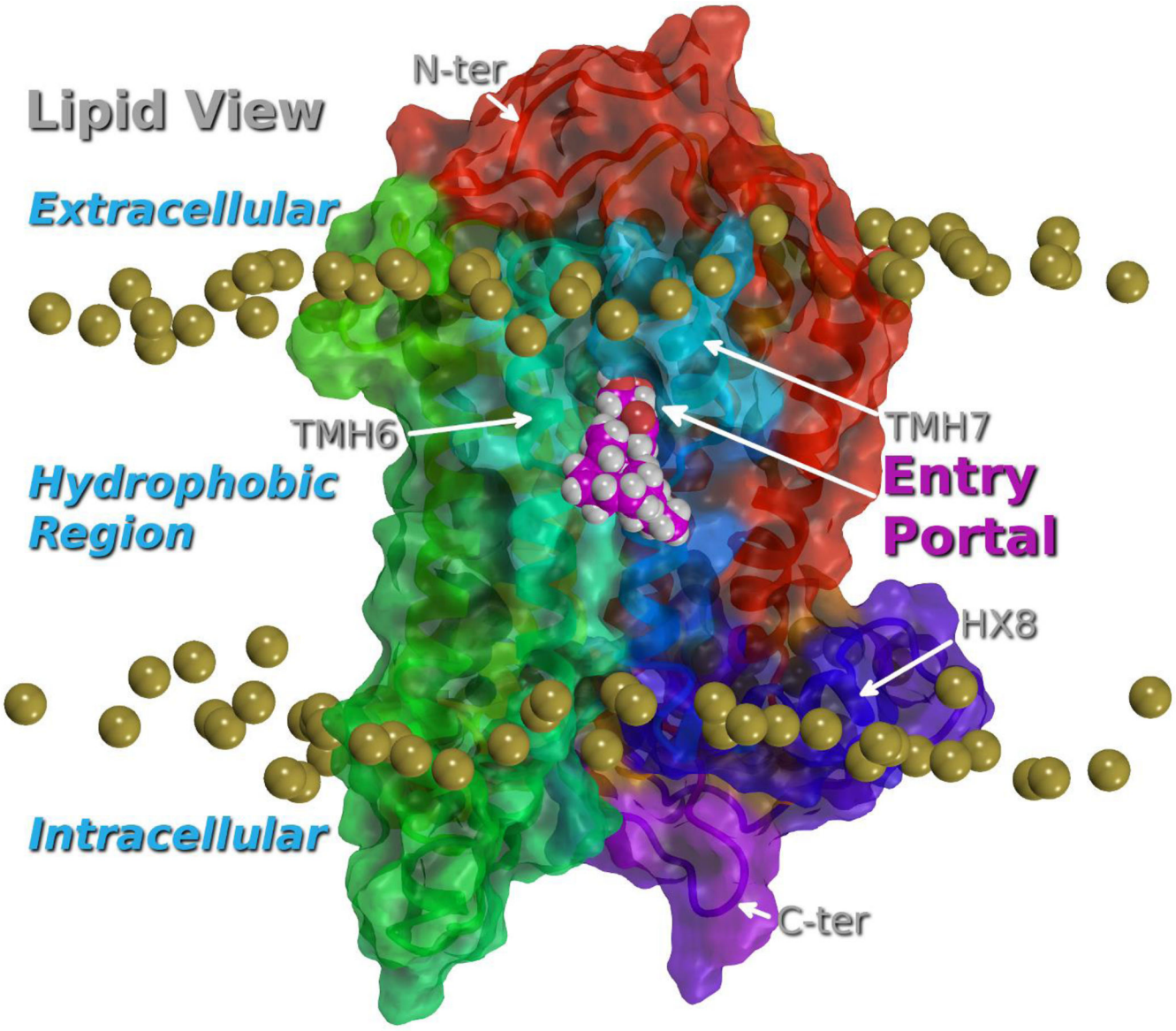


Fig. 5.

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.

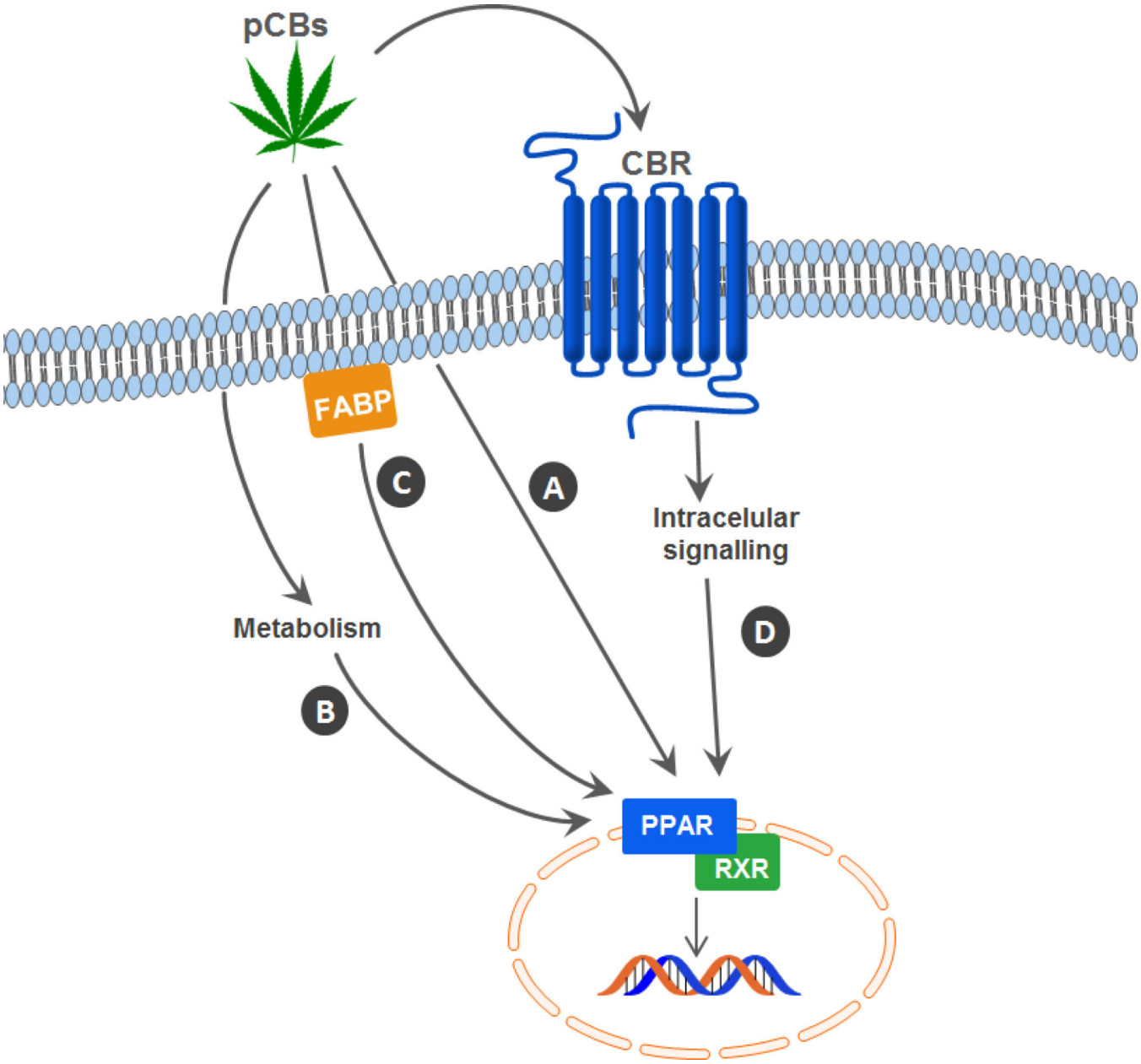


Fig. 6.

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.

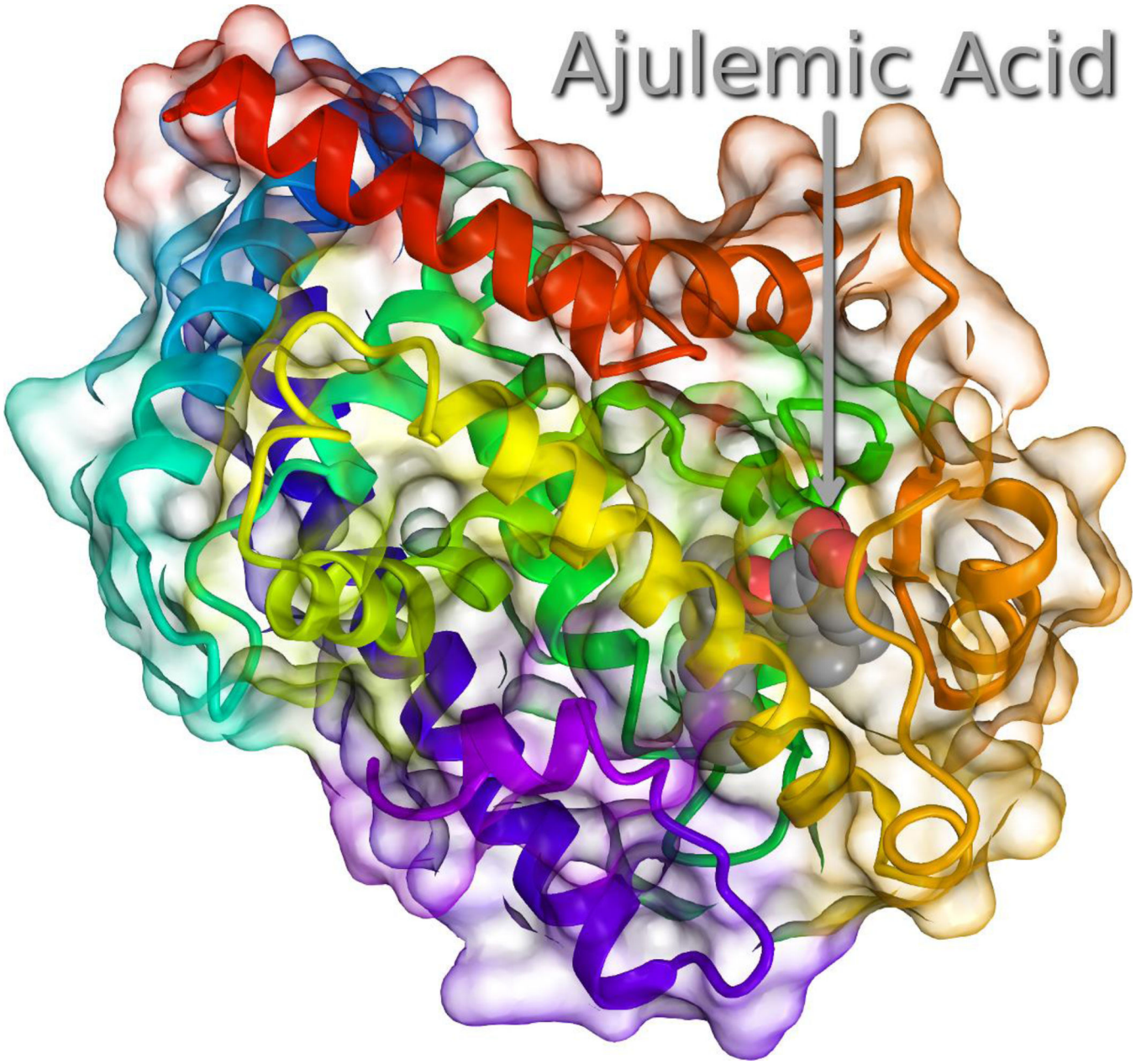


Fig. 7.
The 2.8 Å structure of PPARγ with ajulemic acid is illustrated here (PDB 2OM9).

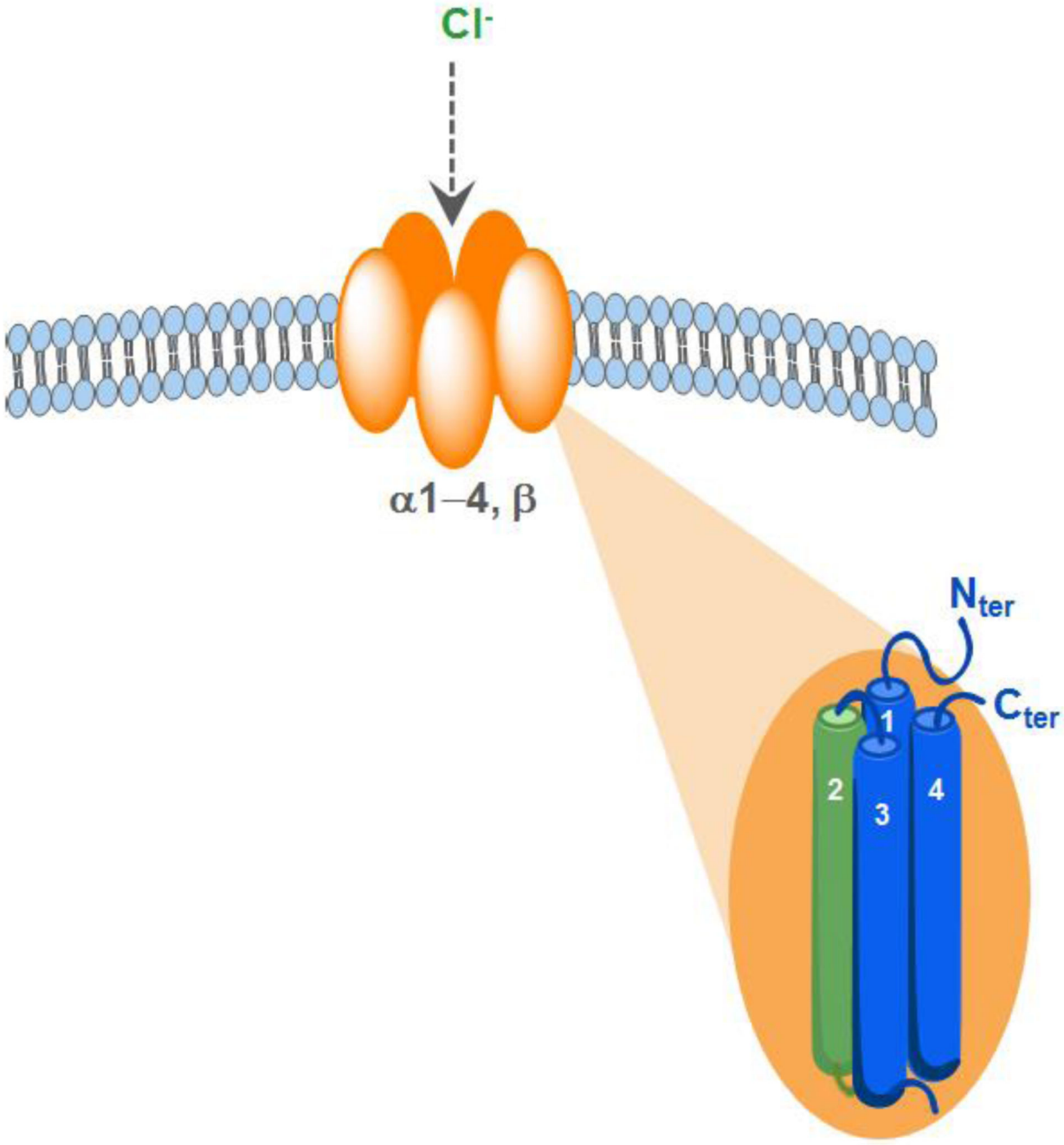


Fig. 8.

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.

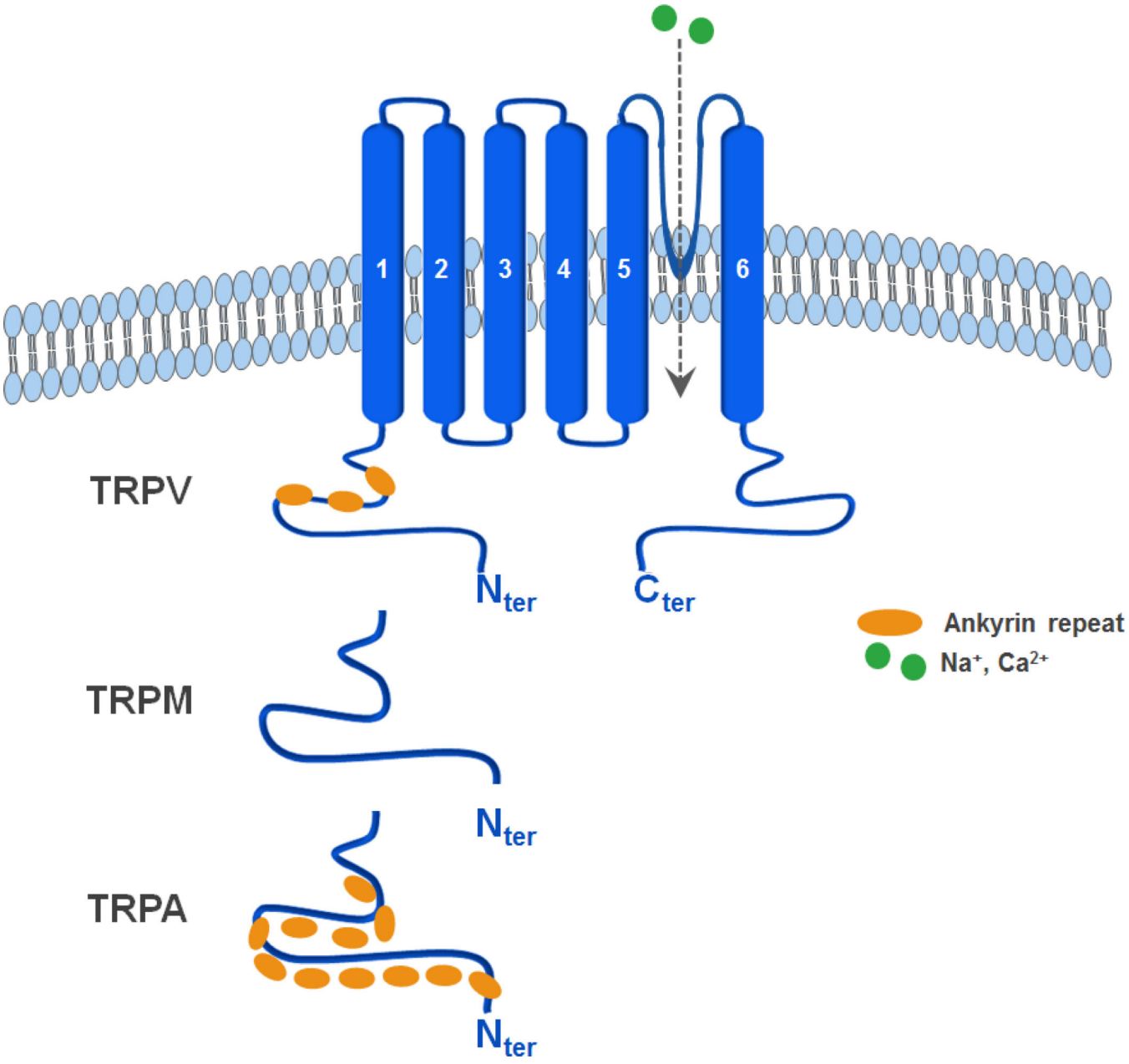


Fig. 9.
General structure of the TRP channels modulated by phytocannabinoids: TRPV, TRPM and TRPA.

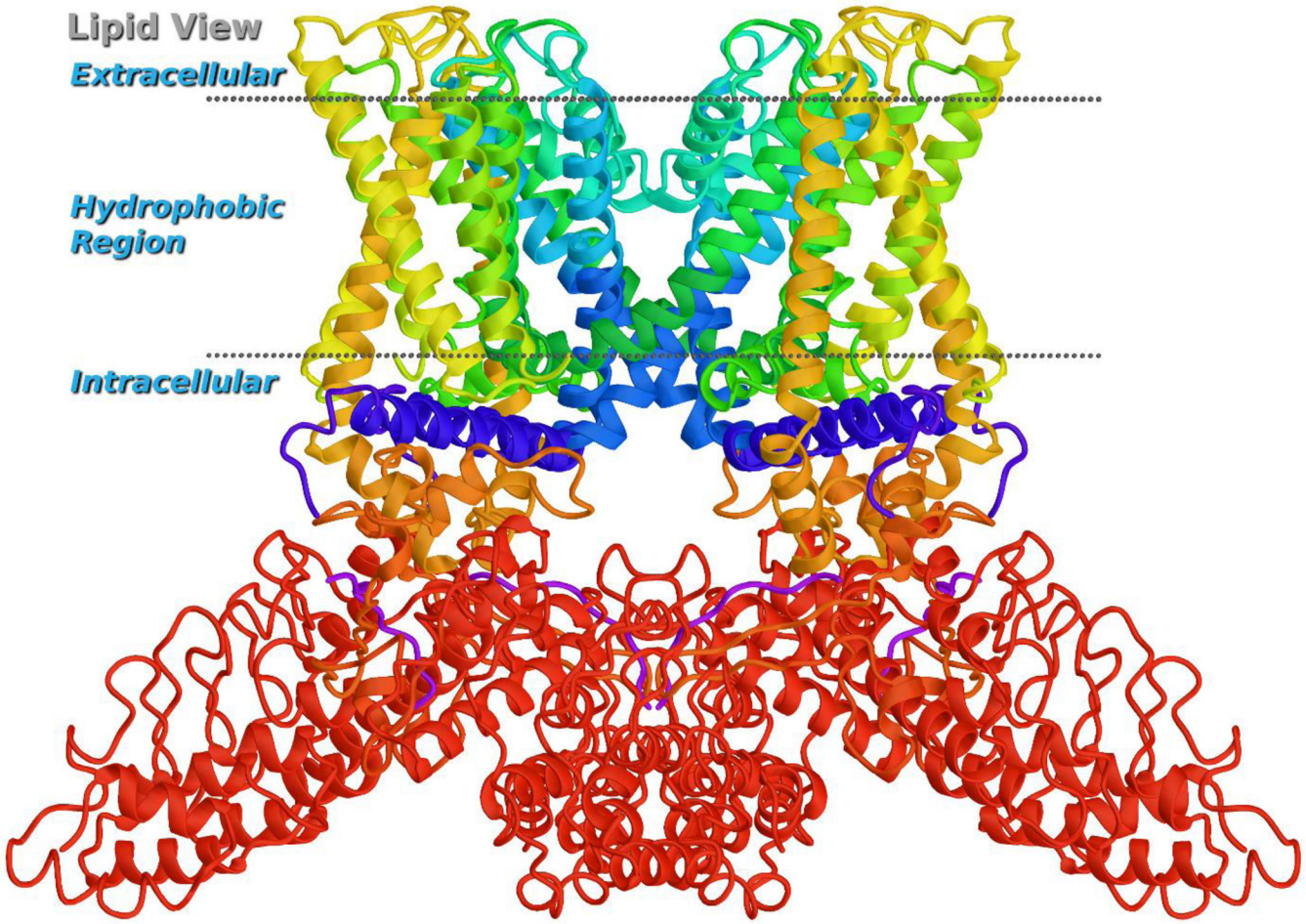


Fig. 10.
The 3.27 Å structure of the TRPV1 channel is illustrated here.

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]
				$GABA_A$	Positive Allosteric Modulator	[52]
	AEA uptake	Inhibitor	[23]	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]
				α_2-AR	Agonist	[56]
CBG	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]
	CB_2	Agonist*	[53]		TRPM8 Antagonist	[23]
CBC	AEA uptake	Inhibitor	[23]		TRPA1 Agonist	[23]
	CB_1	Antagonist	[57–59]	GPR55	Partial agonist/LPI inhibitor	[12]
				$5HT_{1A}$	Agonist	[62]
Δ^9-THCV	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