CBD: A New Hope?

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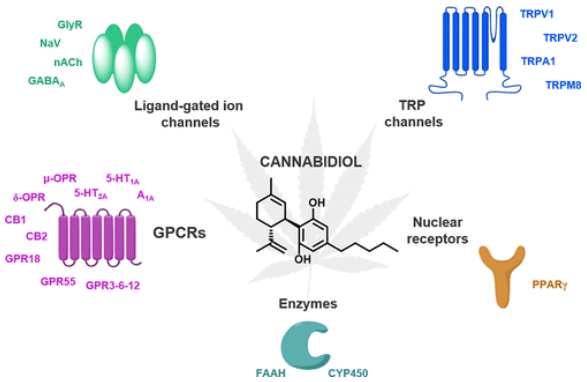
Abstract:



The nonpsychoactive phytocannabinoid, CBD, was recently approved by the Food and Drug Administration for the treatment of children with drug-resistant epilepsy. This milestone opens new avenues for cannabinoid research. In this Viewpoint, we provide an overview of recent progress in the field highlighting molecular insights into CBD's mechanism of action, as well as its therapeutic potential.

Keywords: Cannabidiol | phytocannabinoids, |epilepsy | CB1 | CB2 | GPCRs

Article:

Although the medicinal benefits of *Cannabis Sativa* have been known for centuries, research in the cannabinoid field did not enter its modern era until 1964, when Raphael Mechoulam published the structure and semisynthesis of Δ^9-THC, the major psychoactive component of *Cannabis Sativa*. Much of the cannabinoid compound development through the years has focused on the Δ^9-THC structure since Δ^9-THC binds to the cannabinoid receptors. However, today another phytocannabinoid, CBD (see Figure 1 for structure), is poised to lead the field. Among the over 120 phytogenic cannabinoids discovered so far, CBD stands out because of its promising effects in a wide variety of diseases. In addition, the lack of psychoactive effects exerted by this molecule confers on CBD a special relevance for drug development.

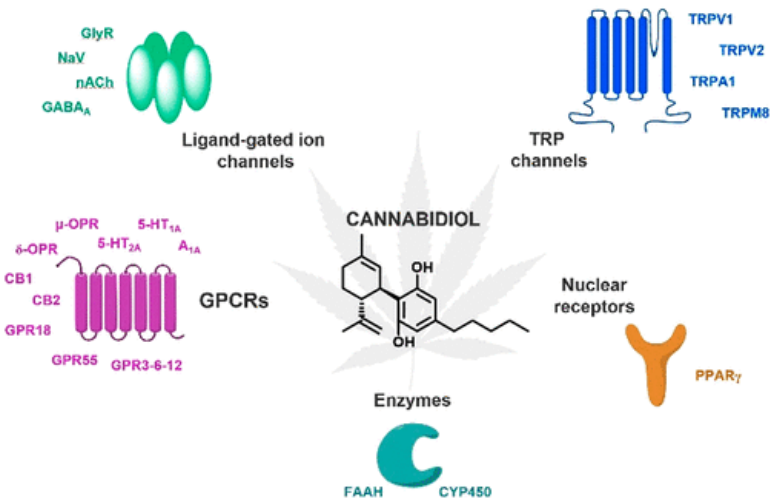


Figure 1. Molecular targets of CBD. Summary of the receptors that have been reported so far as targets of CBD.

Numerous *in vitro* and *in vivo* assays have demonstrated the therapeutic benefits of this phytocannabinoid, which exhibits anti-inflammatory, analgesic, anticonvulsant, anxiolytic, antiepileptic, neuroprotective, and antitumor properties, among others.[1] Indeed, the potential of this molecule to reduce seizures and convulsions has prompted the recent FDA approval of Epidiolex, a CBD oral solution, for the treatment of two severe forms of pediatric-onset epilepsies, Dravet and Lennox–Gastaut syndrome.[2,3]

The therapeutic potential of CBD has also been widely demonstrated in diverse types of cancer or neurodegenerative disorders such as multiple sclerosis. In fact, clinical trials to ascertain its potential for these patients are currently ongoing.[4] However, the molecular pharmacology of this nonpsychotropic cannabinoid chemotype is complex, and therefore, research efforts are currently focused on understanding its sites of action.

Diverse molecular targets have been proposed for this phytocannabinoid including G protein-coupled receptors (GPCRs) and nuclear and ionotropic receptors, among others.

CBD has been shown to modulate diverse GPCRs such as the cannabinoid receptors, CB1 and CB2, orphan GPCRs including GPR55, GPR18, GPR3, GPR6, and GPR12, as well as GPCRs from well-established families including serotonin, adenosine, and opioid receptors.[5]

Considering endocannabinoid-related targets such as the CB1 and CB2 receptors, CBD's pharmacology is rather puzzling. This is likely due to its complex functionality, along with experimental divergences. On the one hand, initial reports claimed that in binding assays, CBD exhibits very low affinity for CB1 and CB2,[6] whereas functional data revealed that it displays antagonistic properties at both cannabinoid receptors.[7] On the other hand, recent investigations have shown that this phytocannabinoid may act through allosteric mechanisms at these receptors.[8,9] Laprarie and co-workers reported that CBD behaves as a CB1 negative allosteric modulator (NAM) of Δ^9-THC and 2-AG (2-arachidonoylglicerol) signaling and as a partial agonist at CB2.[9] In contrast, Franco and collaborators suggested that CBD exerts allosteric properties at CB2.[8]

Regarding cannabinoid-related orphan GPCRs, diverse research groups have demonstrated the ability of CBD to modulate the putative CB receptors, GPR55 and GPR18. Interestingly, this nonpsychoactive phytocannabinoid has been recently proposed as an inverse agonist of the highly constitutively active receptors, GPR3, GPR6, and GPR12.[5] CBD's activity at these targets needs to be further explored to understand the structural basis of its action.

Besides GPCRs, transient receptor potential (TRP) channels, ligand-gated ion channels such as glycine (GlyR), sodium channels (NaV), nicotinic acetylcholine (nACh), $GABA_A$ receptors, and nuclear receptors such as PPARγ have also been reported to be CBD targets, adding molecular complexity to its pharmacology.[10]

CBD has been reported to alter the basal endocannabinoid system tone through blockcade of anandamide hydrolysis produced by FAAH (fatty acid amide hydrolase).[11] This way, CBD inhibits the cellular uptake of anandamide, the most abundant endocannabinoid.

In addition to the intrinsically complex pharmacology of CBD, its metabolism and interactions with other commercialized drugs need to be further considered in order to understand its clinical potential under particular physiopathological conditions. CBD has been reported to interact with several metabolic enzymes that define its ability to influence other drugs' metabolism through the inhibition of specific cytochrome P450 (CYP450) isoenzymes.[12]

Despite the current understanding of its therapeutic benefits, CBD should not be considered as a multisymptom panacea, and its medical potential in diverse pathologies should be appropriately studied taking into account possible interactions with other drugs commonly used as treatments for each particular disease. Moreover, further efforts need to determine its puzzling molecular pharmacology under different physiopathological conditions.

Above all, however, it is quite clear that the therapeutic profile of CBD offers novel prospects for the treatment of neurological, oncological, and inflammatory diseases.

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ABBREVIATIONS

THC tetrahydrocannabinol
CBD cannabidiol
CB1 cannabinoid receptor type 1
FDA Food and Drug Administration

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