White paper: the Therapeutic potential of CBD

Based on literature study
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This white paper discusses the therapeutic potential of CBD. The findings are a result of different sources of literature study (see references section).

Because of its promising therapeutic effects, cannabidiol is after THC, the most studied cannabinoid today. Despite this, little is still known about the pharmacodynamics due to the complexity of its function. Even though the affinity is low, many studies support the idea that CBD has an auto regulatory function through the CB_2 receptor and acts as a negative allosteric modulator of the CB_1 receptor (Morales et al., 2017).

Therapeutic potential

As all cannabinoids have affinity with the endocannabinoid system, either through endocannabinoid receptors, endocannabinoids, neurotransmitters and certain GPCRs, they influence the homeostatic role that the endocannabinoid system plays (Piscitelli et al., 2021).

This role includes regulating appetite, energy and metabolism, stress levels, nervous systems, analgesia, thermoregulation and sleep (Di marzo, 2009). While most of these mechanisms remain unclear, some target cells and their therapeutic results are better understood.

Many diseases involve TRP channel dysfunction, including neuropathic pain, inflammation, and respiratory disorders. In the pursuit of new treatments for these disorders, it was discovered that cannabinoids can modulate a certain subset of TRP channels (Muller et al., 2019). CBD and CBG were the most promising as agonists, showing therapeutic results against chronic pain and inflammation (Zagzoog et al., 2020).

CBD and CBG showed affinity for 5HT receptors, also known as serotonin receptors, and thus can influence stress and anxiety by regulating serotonin and dopamine uptake. CBG could also positively effect stress and anxiety disorders by regulating noradrenaline and adrenaline as potent agonist at the a_2-adrenoceptor (Levick, 2013).

As summarized in table 1, all researched cannabinoids show neuroprotective properties, often accompanied by potential use for movement disorders, chronic movement pains and even epilepsy as muscle signaling goes through the nervous system, for which the latter there are even multiple drugs approved globally (Fraguas-Sánchez et al., 2018), (Turner et al., 2017). Especially CBN and CBG were promising against neurodegeneration and movement disorders (Wong et al., 2019), (Maurya et al., 2018).

Kesner et al. (2020) did extensive research on sleeping disorders and found CBD, CBG and CBC potentially useful as a drug, whereas CBG as a remedy for sleeping disorders was supported by Cascio (2010), Rock (2011), and Granja et al. (2012).

CBD	CBG	CBN	CBC
• Epilepsy • Movement disorders • Neurodegenerative diseases (Fraguas-Sánchez et al., 2018) • Anti-inflammatory • Pain • Psychosis and anxiety • Addiction (Bih et al., 2015), (Grotenhermen, 2003) • Nausea (Grotenhermen, 2003) • Sleeping disorders (Kesner et al., 2020)	• Neuroprotection • Neuromodulation • Gastrointestinal diseases • Metabolic syndrome • Antibacterial agent • Sleeping disorders (Cascio et al., 2010), (Rock et al., 2011), (Granja et al., 2012)	• neuroprotective function, (Turner et al., 2017), • Chronic muscle disorders (Wong et al., 2019) • Sleeping disorders (Kesner et al., 2020)	• Antinociceptive effects (pain relief) • anti-inflammatory (Maurya et al., 2018) • Skin diseases (Pollastro et al, 2018) • Sleeping disorders

Table 1

Let's take a closer look at the functionalities of the different cannabinoids.

CBD

Bih et al. (2015) have identified a number of possible molecular targets of CBD which are likely to be of direct relevance to many of the therapeutic effects of this compound reported in the large number of preclinical and smaller numbers of clinical studies analyzed in this systematic search of existing literature. By judging if results were plausible to play a role in the therapeutic effects by virtue of potency and efficacy, a selection was made as illustrated in table 3. This was done by paying special attention to if in vitro outcomes could be obtained in vivo as well, and this affect was not caused by high micromolar nonspecific concentrations. Based on data derived on CBD plasma, brain pharmacokinetic profile, and possible administration routes, this led to certain supraphysiological concentrations that could most likely not be achieved in vivo and so these studies were seen as less potent.

Disease or disease group	Most plausible molecular targets of CBD
Epilepsy	VDAC1, CaV3.x, 5-HT_{1A}, GlyR, GPR55, adenosine modulation (ENT1)
Movement disorders	CaV3.x, 5-HT_{1A}, VDAC1
Neurodegenerative diseases	VDAC1, FABP, GPR55, NRF2, ENT1
Pain	TRPV1, TRPA1, TRPM8
Psychosis and anxiety	5-HT_{1A}, adenosine modulation (ENT1)
Addiction	CYP2D6, opioid receptors, ABCG2

VDAC1 = voltage-dependent anion channel 1; 5-HT = serotonin; GlyR = glycine receptor; GPR55 = G protein-coupled receptor 55; ENT1 = equilibrative nucleoside transporter 1; FABP = fatty acid binding protein; NRF2 = Nuclear factor erythroid 2-related factor 2; TRPV1 = transient receptor potential vanilloid-type 1; TRPA1 = transient receptor potential ankyrin type 1; TRPM8 = transient receptor potential subfamily M; CYP = cytochrome P

Table 3: most promising molecular targets of CBD per therapeutic indication (Bih et al., 2015)

Bih et al. also state that CBD most probably does not act through the endocannabinoid system, which is why they are not noted in table 3. This is most likely true for CB_1, but some mediation through CB_2 has been confirmed by many other studies, an assumption that Bih et al. dismiss. CBD has already been administered and used as a drug for epilepsy under the name of Epidiolex, as Sativex for neuropathic pain relief in MS (in combination 1:1 with THC) and other registrations are pending as well (Fraguas-Sánchez & Torres-Suárez, 2018). In earlier stages, antiepileptic, anti-dystonic,

antiemetic and anti-inflammatory effects have been observed (Grotenhermen, 2003). It reduced intraocular pressure, was neuroprotective and antagonized the psychotropic and several other effects of THC. Anxiolytic and antipsychotic properties might prove useful in psychiatry and other disease groups of interest are given in table 3 (Morales et al., 2017), (Bih et al, 2015). As the ECS plays a role in regulating sleep stability (Kesner & Lovinger, 2020), does binding to the CB receptors show therapeutic potential for sleeping disorders (Kesner et al., 2020).

CBG

Based on the receptor signaling of the a-2, 5-HT_{1A}, and PPARy receptors and the reported affinities of CBG at these receptors (in the tens of nanomolars to sub-nanomolar range), there are many reasons to believe that CBG will have therapeutic potential (Cascio et al., 2010), (Rock et al., 2011), (Granja et al., 2012). The most important areas of interest are neuroprotection and neuromodulation, gastrointestinal diseases, metabolic syndrome and acting as an antibacterial agent. Through the ECS, it also proves useful for sleeping disorders. Similarly, however, there are reasons to monitor high-dose CBG for untoward side effects beyond drug- drug interactions (Nachnani et al., 2021).

CBN

Apart from its neuroprotective function, (Turner et al., 2017), CBN could prove useful for chronic muscle disorders as Wong & Cairns (2019) state. Kesner et al (2020) also claim the role of the ECS in sleep stability so CBN could also be useful there. The effect on feeding behavior in rats has been studied but provided no clear outcome. There is little up to date literature on the pharmacology and possible application of Cannabinol and thus, further investigations need to take place to determine whether this phytocannabinoid has other therapeutic effects and how it modulates or enhances the physiological effects of whole cannabis-derived preparations (Turner et al., 2017).

CBC

Antinociceptive effects (pain relief) and anti-inflammatory through the desensitization of TRPA1 and the inhibition of endocannabinoid degradation effect were among the most promising therapeutic applications (Maurya & Velmurugan, 2018). Positive effects in animal trials with respect to certain gut inflammation diseases were discovered as well, yet none of the known targets were involved in this mechanism (Zagzoog et al., 2021). In a systematic screening of the nonnarcotic phytocannabinoids for the treatment of acne, CBC (along with other phytocannabinoids not discussed in this review) emerged as the best candidate (Pollastro et al, 2018). Like other phytocannabinoids showing affinity for the CB receptors, could CBC be used for sleeping disorders.

Entourage effect

The entourage effect was originally identified as a new way of endocannabinoid modulation where multiple endogenous compounds display a ‘higher power’ in eliciting a cellular response than the sum of the compounds by themselves. Now, it is used as the term to describe the polypharmacy effects of combined cannabinoids and other plant extracts such as terpenoids and flavonoids or the entire chemical profile of a cannabis plant. Because Finlay et al. (2020) could identify no interaction at the cannabinoid receptors and the mechanism remains unknown, there has been certain amounts of criticism. Yet, the entourage effect has shown promising results in the treatment of for example cancer and mood/anxiety disorders (Ferber et al., 2020), (Blasco-Benito et al., 2018). Russo (2019) reviews several studies, in which a whole plant extract had a superior effect to purified cannabinoid. The sum of the components might not be greater, but Russo states using the components together works better than isolates. Other studies found enhanced effects due to inactive compounds that prevented the degradation of the active compound, representing a novel mechanism for molecular regulation of endogenous cannabinoid activity (Anand, Pacchetti, Anand, & Sodergren, 2021)

All researched cannabinoids have certain mechanisms of action through the endocannabinoid system. This is mostly due to affinity with cannabinoid receptors CB1 and CB2, although almost all target molecules interact with the endocannabinoid system in one way or another. Most cannabinoids are not direct ligands for these receptors and depending on the interaction, they can have both enhancing, as inhibiting signaling (Ronan, Wongngamnit, & Beresford, 2016).

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