Author's Accepted Manuscript

The good face of Cannabis sativa: Cannabidiol

Cuneyt Evren, Gokhan Umut

To appear in: Dusunen Adam The Journal of Psychiatry and Neurological Sciences

DOI: 10.14744/DAJPNS.2019.00041

Cite this article as: Evren C, Umut G. The good face of Cannabis sativa: Cannabidiol, Dusunen Adam The Journal of Psychiatry and Neurological Sciences, DOI: 10.14744/DAJPNS.2019.00041

This is a PDF file of an unedited manuscript that has been accepted by the Dusunen Adam The Journal of Psychiatry and Neurological Sciences editor for publication. As a service to our researchers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable version. Please note that during the production process, typos or errors may be discovered which could affect the content, and all legal disclaimers pertaining to the manuscript.
The good face of Cannabis sativa: Cannabidiol

Cuneyt Evren, Gokhan Umut

Abstract

Cannabidiol (CBD) is the most common phytocannabinoid found in cannabis plants after tetrahydrocannabinol (THC). Unlike THC, no psychoactive effect has been demonstrated. Due to its effect on various neurotransmitter systems, it has been tried for treatment of many physical and psychiatric diseases due to its neuroprotective and antiinflammatory properties. In this letter, the characteristics of CBD and its place in various psychiatric disorders will be briefly mentioned.

Introduction

Cannabidiol (CBD) is a phytocannabinoid derived from the Cannabis sativa plant, such as tetrahydrocannabinol (THC), but with no psychoactive effect. Unlike THC, CBD does not activate the reward system and affects the opioid, serotonin and cannabinoid receptor systems. Therefore, it is thought to be promising for the treatment of drug addiction. Especially it acts as a non-competitive antagonist of CB1R within the cannabinoid system (1). However, CBD has been shown to be not acting directly on the CB1 receptor. It has been reported in most studies that it has no effect on the CB1 receptor at all, and in some studies it has weak agonistic or weak antagonistic effects. CBD also has low affinity on another cannabinoid receptor, the CB2 receptor (2). CBD can be converted to THC in some animal species and laboratory settings but does not convert to delta-9-THC in the human body (2,3).

Because of its effect on various receptors, cannabidiol's effect is being investigated in many physical or psychiatric diseases. Clinical studies for the treatment of epilepsy are ongoing and positive results have been reported. In some preclinical studies, although not as much as epilepsy, it has been shown to have neuroprotective, anxiolytic, antipsychotic, analgesic, anti-inflammatory, anti-asthmatic, and antitumor features (2). The therapeutic use of CBD has also been investigated in substance use disorders. Several preclinical studies have reported that CBD may have a therapeutic effect on opioid, cocaine, and psychostimulant addiction. Some studies have also obtained data that CBD may be beneficial in cannabis and tobacco addiction in humans (4).
Substance use causes dysregulation in the mesolimbic circuit. CBD weakens this dysregulation when administered regularly. Because of this feature, CBD was considered to be beneficial in substance use disorder. It is contemplated that its efficacy may depend on the dose and whether it is administered before or in combination with substance use (1). CBD is also thought to blunt the reward-facilitating effect of substance use through 5HT1A receptor agonism, which is effective in reducing stress and anxiety in the mesolimbic system. This suggestion is based on selective serotonin reuptake inhibitors and other antidepressants reducing substance use by alleviating mood symptoms. It has been suggested that CBD has a therapeutic effect on substance use disorder by alleviating stress, anxiety and depressive symptoms (1).

CBD has undesirable effects such as drowsiness, gastrointestinal disturbances, fatigue, and may also have drug interactions. It can cause an increase in liver function tests. Suicidal thoughts, which are rare in other anticonvulsant drugs, may also occur in CBD use. Therefore, its effect on suicidal ideation needs to be investigated (5).

The dependence potential of THC and CBD in mice has been compared, while tolerance to THC has improved but not to CBD. In addition, there are no clinical trials that report CBD has the potential for addiction or abuse (2). In one study, the potential for abuse of CBD compared to cannabis was shown to be placebo-like in humans (6). Polydrug users have shown low abuse potential at a therapeutic dose of CBD. High doses of CBD, however, have detectable subjective effects compared to placebo, significantly lower than those observed with alprazolam and dronabinol (7).

**Alcohol and CBD**

Alcohol has been shown to cause damage to the frontal and temporal lobes and hippocampus in particular by inducing neuroinflammatory mediators and / or oxidative stress. These brain regions are known to be associated with problem solving, attention, information processing, learning, and memory (8). Since CBD has neuroprotective effects that prevent oxidative damage, it has been considered for the treatment of cognitive impairments caused by alcohol. These effects of CBD have been hypothesized to be mediated by the 5HT1A or CB2 receptor (8). Although based on preclinical studies, the results have been reported to support the potential therapeutic benefits of CBD for AUD, particularly in the areas of neurodegeneration, hepatotoxicity, cognition, and recurrence risk (8). Additionally, CBD can have therapeutic
effect in alcoholic liver diseases characterized by inflammation, oxidative stress, and steatosis (9).

The study in male mice, a species that prefers ethanol, showed that CBD administration reduced reinforcing properties, motivation, and ethanol relapse. Based on these findings, authors suggest that CBD may be useful in the treatment of alcohol use disorders (10). In an animal study, co-administration of CBD and naltrexone has been found to be more effective than CBD or naltrexone alone in reducing ethanol consumption and drinking motivation. It has been stated that these effects are at least partially mediated by 5-HT1A receptors (11). In addition, it should be noted that there are a small number of these studies and that further clinical studies are needed.

Cannabis and CBD

The effectiveness of the agonist treatment approach in cannabis addiction is limited (12). Therefore, approaches other than pure agonist treatment are also being investigated. CBD administration has been shown to reduce behavior disorders associated with cannabinoid deprivation created in mice, suggesting that it supports CBD use in cannabis dependence (13). In a study of 20 cannabis users with an average of 5.5 years of cannabis use, CBD has been found to have positive effects on attention control and psychological symptoms caused by cannabis use. In addition, this study showed that CBD has greater benefits in dependent cannabis users than in non-dependent users. (14). In a case study, CBD was added to the treatment of a cannabis addict with bipolar disorder, while cannabis use was discontinued as well as improved sleep patterns (15). In another case report, CBD has been shown to be useful in cannabis withdrawal symptoms (16). However, it has been reported that CBD may have potential in reducing euphoria associated with cannabis use, despite not directly reducing cannabis use (14). No positive effects of oral CBD on the reinforcing, physiological or positive subjective characteristics of cannabis have been detected (17).

Opioids and CBD

Most studies on the effect of CBD on opioid use disorders are animal studies. In the recent research, CBD has been shown to block the reward-facilitating effect of morphine (18). CBD was also found to have some efficacy in heroin studies in rats. In the study exploring the effects of CBD on heroin self-administration and drug-seeking behavior in animal model, it
has been suggested that CBD may be a potential treatment for heroin craving and relapse (19). In this study, it was shown that heroin self-administration was not altered by CBD administration, but cues induced heroin seeking was clearly inhibited. (19). Moreover, even if administered during active heroin intake, CBD's ability to prevent relapse behavior was also seen in the weeks after recent exposure. Based on these findings, the authors suggested that CBD may affect the course of heroin addiction even following a potential lapse after a period of deprivation (19).

Cocaine, Psychostimulants and CBD

The results on CBD effectiveness for stimulus use are controversial (1). There have been studies showing that acute CBD administration does not block the reward-facilitating effect of cocaine (18), does not reduce self-administration of cocaine, or does not reduce clue-induced cocaine in rats (20). It has been reported that an acute CBD treatment has a minimal effect on a rat model of cocaine intake and relapse (20).

Although CBD could not reduce drug-related reinstatement, reduced voluntary consumption of cocaine (21). Since CBD has been shown to effectively prevent methamphetamine-induced conditional place preference (CPP) in rats even in the case of stress, it has been suggested that it could be used to reduce the risk of relaps (22). Different results were also revealed in studies on the relapse of psychostimulants and cocaine. CBD is able to attenuate reconsolidation of CPP for cocaine in mice (23), and effectively reduce cue and stress-induced reinstatement of cocaine seeking (24). Another study suggested no effect of CBD on drug-primed reinstatement post-extinction (25). These different results may be obtained depending on the dose (26). It has been shown that CBD can reduce the motivation to seek and consume methamphetamine, therefore might be used as a promising pharmacotherapy for methamphetamine dependence (26). The effect indicated in the previous study was seen at a dose of 80 mg/kg CBD, but not at 40 mg/kg and 20 mg/kg (26). In another study, it has been reported that CBD can be useful by blinding the acute rewarding effects of cocaine through a mechanism linked to DA (27).

Tobacco and CBD

As the endocannabinoid system has been thought to have the role in the nicotine dependence, the effectiveness of CBD in this regard has been investigated by various studies in dependent
smokers. In one of these studies, 24 smokers were divided into two groups to receive CBD (n = 12) or placebo (N = 12), during the treatment week. There was no difference in the number of cigarettes smoked in placebo group, while those who received CBD reduced the number of cigarettes smoked during treatment by approximately 40%. The results also showed some continuity in follow-up. With this preliminary data, it has been suggested that CBD is a potential treatment for nicotine addiction (28). In another study of 30 subjects, a single dose of CBD reduced the pleasantness and salience of cigarette cues compared to placebo after overnight abstinence in dependent smokers. However, CBD did not influence tobacco craving or withdrawal (29).

**Psychosis and CBD**

There are preclinical (30)(31) and clinical studies on the antipsychotic efficacy of CBD (32). First, in a single case report, CBD has been shown to improve in a treatment-resistant schizophrenia patient (33). A four-week randomized, double-blind clinical trial was conducted in 42 schizophrenia patients, comparing amisulprid and CBD. Patients received either CBD (600-800 mg / day) or amisulprid (600-800 mg / day), a very effective second-generation antipsychotic. Both drugs provided a marked improvement of both the positive and negative symptoms of psychosis. The effectiveness of cannabidiol was as good as amisulpride. Additionally, CBD's side effect profile was superior to amisulpride (34). CBD did not cause prolactin increase, weight gain, or extrapyramidal symptoms that could be seen in amisulpride. As decreased psychotic symptoms were associated with increased serum anandamide levels in patients receiving CBD treatment they suggested that inhibition of anandamide deactivation may contribute to the antipsychotic effects of CBD (34). In an fmRI study, it has been suggested that CBD may partially normalize changes in parahippocampal, striatal, and midbrain function that are important for the pathophysiology of psychosis, thus resulting in the therapeutic effects of CBD on psychotic symptoms. (35).

**Anxiety and CBD**

There are studies in the literature on the effect of CBD on anxiety (36). It has also been reported that although CBD has been shown to block anxiety triggered by delta 9-THC, this effect may be due to marijuana-like effects and other subjective changes caused by delta 9-THC. Because no changes were detected in the pulse measurements (37). The anxiolytic effect of CBD on anxiety induced by simulated public speaking (SPS) test has been shown in
a clinical study. The results suggested that CBD has anxiolytic properties in human volunteers submitted to a stressful situation (38). In a single-photon emission computed tomography (SPECT) study, CBD has been shown that significantly decreased subjective anxiety, while placebo did not induce significant changes. These results suggest that CBD has anxiolytic properties, and that these effects are mediated by an action on limbic and paralimbic brain areas (39). Using the same neuroimaging method, the effectiveness of CBD and placebo was compared in 10 subjects with social anxiety disorder, and CBD was shown to reduce anxiety in social anxiety disorder. This result was attributed to the effect of CBD on limbic and pralimbic brain regions (40). CBD has been found to increase the extinction of fear memories in 48 healthy volunteers, suggesting this may be useful in addition to extinction-based therapies for anxiety disorders (41). CBD has been reported to show an anxiolytic effect by reducing physiological rapid eye movement (REM) sleep and non-REM (NREM) sleep in normal rats. It has been suggested that this is an important outcome for patients with post-traumatic stress disorder, where sleep disorders such as REM sleep disorder and insomnia are common (42). According to the results obtained from preclinical and clinical studies, CBD also will be a promising treatment option in panic disorder (43).

**Depression and CBD**

In a study in mice, it has been suggested that CBD enhances both serotonergic and glutamatergic cortical signaling by a mechanism associated with the 5-HT1A receptor, so that it can be used as an antidepressant (44). Also, the results obtained from a genetic animal model of depression suggest that CBD may be potential treatment for clinical depression and other states with prominent anhedonia (45).

**Alzheimer Disease and CBD**

Since Alzheimer's disease (AD) is a neurological and psychiatric disease, it would be appropriate to mention the effect of CBD on this disease. Amyloid-β plaques and hyperphosphorylated taurine protein accumulate in the brain of AD patients. The brains of AD patients have neurodegeneration and high levels of oxidative stress and inflammation. As mentioned before, CBD have neuroprotective, antioxidant and anti-inflammatory properties and so reduces amyloid-β production and tau hyperphosphorylation in vitro. CBD is thought to be the new treatment option for AD disease, as it is also found effective in vivo in AD
disease. Lack of psychoactive or cognitive inhibitory properties makes CBD advantageous in this regard (46).

**Conclusion**

When the literature is considered, it is seen that CBD may have an effect in diseases such as substance use disorders, anxiety disorders, depression and Alzheimer's disease which is a neurodegenerative disease. These effects of CBD are mediated by various receptor systems. Unfortunately, most of the studies consist of preclinical studies which are animal models. More clinical trials are needed for the use of CBD in humans. Nevertheless, the available data show that there will be a promising treatment option for various diseases in the future.

**References**


27. Galaj E, Bi GH, Yang HJ, Xi ZX. Cannabidiol attenuates the rewarding effects of cocaine in rats by CB2, 5-TH1A and TRPV1 receptor mechanisms. Neuropsychopharmacology 2019; 107740.


