The therapeutic potential of CBD

An overview of the state of scientific knowledge from basic research and clinical trials

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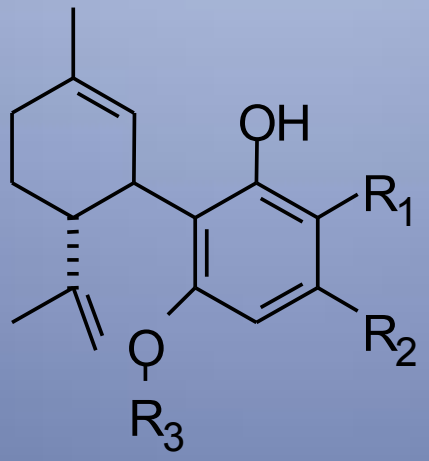
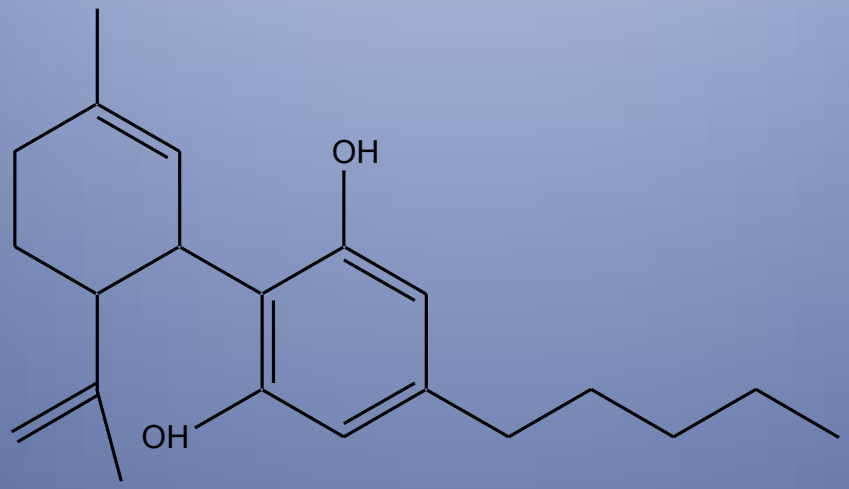
Cannabinoids of the CBD type



R_1 = H or COOH
R_2 = C_1, C_3, C_4, or C_5 side chain
R_3 = H or CH_3

Cannabinoids of the CBD type. The most widespread cannabinoids are the phenolic CBD (R1 = H) with 21 carbon atoms and a C5 side chain (R2 = C5H11) and its corresponding carboxylic acid (CBDA) (R1 = COOH) .

Phenolic CBD



cannabidiol

Most of the pharmacological effects of CBD are attributed to the phenolic CBD gained from CBDA by heating.

Pharmacokinetics of CBD

Average systemic bioavailability of inhaled CBD in a group of cannabis users was 31% (range: 11-45%).

The plasma pattern is similar to that of THC with high levels of about 100 ng/mL within minutes after smoking and a fast decrease to a concentration of about 10 ng/mL after one hour.

After oral administration of 40 mg CBD the plasma course over 6 h was in the same range as the course after 20 mg THC.

Daily oral doses of 10 mg/kg CBD per day (or 700 mg for a person of 70 kg) for 6 weeks in patients with Huntington's disease resulted in mean weekly plasma levels of 5.9-11.2 ng/ml. In an animal study such plasma levels were effective in killing cancer cells.

Mechanism of action of CBD

- CBD acts as antagonist at the central CB1 receptor (Zuardi et al. 1982).
- CBD stimulates the vanilloid receptor type 1 (VR_1) with a maximum effect similar in efficacy to that of capsaicin (Bisogno et al. 2001).
- It also binds to VR_2, which is involved in anti-cancer effects (Nabissiet al. 2015).
- CBD inhibits the uptake and hydrolysis of the endocannabinoid anandamide, thus increasing its concentration (Mechoulam et al. 2002) .
- Some analgesic effects were mediated by the glycine receptor (Xiong et al. 2012).
- CBD binds to the equilibrative nucleoside-transporter-1, thus enhancing endogenous adenosine signalling. Some immunosuppressive effects may be based on this mechanism (Malfait et al. 2000).
- CBD binds to the $5\text{-}HT_{1A}$ receptor, which is involved in the anxiolytic effects (Russo et al. 2005).
- Cannabinoids, including CBD are potent anti-oxidants. It was demonstrated that CBD prevents oxidative damage caused by H_2O_2 equally well or better than ascorbate (vitamins C) or tocopherol (vitamin E) (Hampson et al. 1998).
- CBD binds to the GPR55 receptor, a putative cannabinoid receptor (Li et al. 2013). This effect is involved in the anti-inflammatory action of the cannabinoid.

Antagonism of THC effects

It has been demonstrated that CBD acts as a weak antagonist to all agonists at the CB1 cannabinoid receptor, including THC (Petitet et al. 1998). CBD has been shown to antagonize in humans the psychotropic, other subjective, and several physical effects of THC including increase of heart rate and appetite enhancement, mediated by the CB1 receptor (Karniol et al. 1974). In several studies simultaneous administration of CBD antagonized the characteristic psychotropic effects of THC (Zuardi et al. 1982, Dalton et al. 1976, Karniol et al. 1974).

13 possible medical uses of CBD

… and a few others

Epilepsy

- 15 patients suffering from secondary generalized epilepsy with temporal focus were randomly divided into two groups (Cunha et al. 1980). Each patient received, in a double-blind procedure, 200-300 mg daily of CBD or placebo. 4 of the 8 CBD subjects remained almost free of convulsive crises throughout the experiment and 3 other patients demonstrated partial improvement.
- Today clinical studies are conducted with the CBD extract Epidiolex of the British company GW Pharmaceuticals in the USA in children with treatment resistant genetic epilepsy forms, such as Dravet syndrome.
- One study was presented at the 68th Annual Meeting of the American Epilepsy Society. Patients received CBD at a constant dose of 5mg per kg body weight in addition to their current epilepsy medication. The daily dose was gradually increased until intolerance occurred or a maximum dose of 25 mg per kg body weight was achieved. After three months of therapy, 39% of patients had a greater than 50% reduction in seizures.

Anxiety Disorders

- In a clinical study subjects were asked to perform a speech in front of a video camera (Zuardi et al. 1993). The procedure increases subjective anxiety. The results showed that both CBD and two other anxiolytic compounds (diazepam, ipsapirone) attenuated anxiety induced by the test.
- Scientists at the University of Sao Paulo, Brazil, investigated the effects of CBD on patients with generalized social anxiety disorder in a simulation public speaking test (Bergamaschi et al. 2011). Three groups were compared, 12 healthy controls without any medication, 12 patients with anxiety disorder, who received a single dose of CBD (600 mg) and a group of 12 patients, who received a placebo in a double-blind design. Pre-treatment with CBD significantly reduced anxiety, cognitive impairment and discomfort in the speech performance of patients with social anxiety disorder, and significantly decreased alert in their anticipatory speech. This study confirmed previous research of the same group involving 10 patients with social anxiety disorder (Crippa et al. 2010).

Schizophrenia

- In an open pilot study at the University of Sao Paulo CBD was effective in the treatment of psychotic symptoms of patients with Parkinson's disease (Zuardi et al. 2008). Six consecutive patients (four men and two women) with the diagnosis of Parkinson's disease and who had psychosis for at least 3 months were selected for the study. All patients received CBD in flexible doses (starting with an oral dose of 150 mg/day) for 4 weeks, in addition to their usual therapy. The psychotic symptoms showed a significant decrease under CBD treatment.
- The first controlled clinical study of CBD in schizophrenia was connected at the University of Cologne with 42 patients suffering from acute schizophrenia. It demonstrated that CBD significantly reduced psychopathological symptoms, when compared to the initial status (Leweke et al. 2012). Half of them received 800 mg of oral CBD daily for four weeks and the other half the standard medicinal drug amisulpride, a potent antipsychotic. Either treatment was safe and led to significant clinical improvement, but CBD presented with significant less adverse effects.

Inflammation

- In studies with mice both THC and CBD dose-dependently suppressed the production and secretion of the cytokine interleukin 17 (IL-17) (Kozela et al. 2013). This pro-inflammatory substance is increased in inflammatory diseases such as multiple sclerosis. Pre-treatment with CBD also resulted in increased levels of the anti-inflammatory cytokine IL-10.
- In a viral model of multiple sclerosis with mice CBD reduced inflammation and this effect was long-lasting, ameliorating motor deficits in the chronic phase of the disease in conjunction with reduced production of pro-inflammatory cytokines (Mecha et al. 2013).
- CBD also reduced inflammation in acute pancreatitis of mice (Li et al. 2013). It reduced the concentration of pro-inflammatory substances (interleukin-6, tumour necrosis factor alpha).
- Research at the University of São Paulo, Brazil, demonstrated that CBD reduced inflammation in a mouse model of acute lung injury (Ribeiro et al. 2012).

Pain

- Some patients use CBD against pain. This can easily be explained if pain is associated with inflammation. There are several forms of pain, where the inflammatory aspect is not visible at first glance, but where inflammation plays a role for example bone pain in cancer (Lu et al. 2015).
- The effects of morphine, CBD, and morphine/CBD combinations were assessed in three assays (Neelakantan et al. 2005). Morphine alone produced antinociceptive effects in all three models of acute nociception, whereas CBD alone produced antinociception only in the acetic acid-stimulated stretching assay. Combinations of CBD and morphine produced synergistic effects in reversing acetic acid-stimulated stretching behavior, but subadditive effects in the hot plate thermal nociceptive assay and the acetic acid-decreased operant responding for palatable food assay.

Cancer I

- Italian researchers investigated the anti-tumour effects of five natural cannabinoids of the cannabis plant (cannabidiol, cannabigerol, cannabichromene, cannabidiol-acid and THC-acid) in breast cancer (Ligresti et al. 2006). Cannabidiol was the most potent cannabinoid in inhibiting the growth of human breast cancer cells that had been injected under the skin of mice.
- These observations are supported by investigations of US scientists who found out that exposure of leukaemia cells to CBD led to a reduction in cell viability and induction of apoptosis (McKallip et al. 2006).
- In a mouse model of metastatic breast cancer CBD reduced the aggressiveness of breast cancer cells (McAllister et al. 2007). CBD inhibited a protein called Id-1.
- Cannabidiol (CBD) also inhibits the formation of new blood vessels, called angiogenesis, in tumours by different mechanisms (Solinas et al. 2012).
- CBD and several cannabis extracts reduced viability of prostate cancer cells (De Petrocellis et al. 2013).

Cancer II

- According to research at the California Pacific Medical Center Research Institute in San Francisco CBD increased the inhibitory effects of dronabinol (THC) on human brain cancer cell proliferation and survival (Marcu et al. 2010). THC and CBD acted synergistically to inhibit cell proliferation.
- Other groups confirmed anti-cancer effects of CBD in glioma (Solinas et al. 2013) and leukaemia cells (Scott et al. 2013). In the research on leukaemia a combination of several cannabinoids also increased the effect on cancer.
- According to cell experiments at the University of Rostock, Germany, CBD inhibits lung cancer metastasis by increasing the concentration of a certain protein (ICAM-1) (Ramer et al. 2012).
- At the Complutense University in Madrid, Spain, the effects of a combination of cannabinoids and temozolomide (TMZ) were investigated in the treatment of glioblastoma multiforme in animals (Torres et al. 2011). Treatment with TMZ and submaximal doses of THC and CBD produced a strong anti-tumoural action.

Dystonia and Dyskinesia

- In 1984 a case report of a patient with Meige syndrome was published (Snider et al. 1984). The patient profited from the treatment with 200 mg CBD. Meige syndrome is a form of dystonia affecting the eyelid and muscles of the face.
- CBD was given to 5 patients with dystonic movement disorders in a preliminary open pilot study (Consroe et al. 1986). Oral doses of CBD rising from 100 to 600 mg/day over a 6 week period were administered along with standard medication. Dose-related improvement in dystonia was observed in all patients and ranged from 20 to 50%.
- In studies with mice the natural cannabinoid CBD attenuated catalepsy, characterized by muscular rigidity and fixity of posture (Gomes et al. 2013). Catalepsy was caused by the anti-psychotic drug haloperidol, by L-nitro-N-arginine (L-NOARG) or by the synthetic cannabinoid WIN55,212-2, which acts similar to THC.

Dependency and Withdrawal

- In a study with rats CBD inhibited the reward-facilitating effect of morphine (Katsidoni et al. 2013). These effects were mediated by activation of 5-HT1A receptors in a certain brain region (dorsal raphe). Scientists concluded that “cannabidiol may be clinically useful in attenuating the rewarding effects of opioids.”
- In a study at the Ribeirão Preto Medical School of the University of São Paulo, Brazil, a 19-year-old woman with withdrawal symptoms after cessation of cannabis use profited from a treatment with CBD (Crippa et al. 2013). Daily symptom assessments demonstrated the absence of significant withdrawal, anxiety and other symptoms during the treatment. Authors concluded that “CBD can be effective for the treatment of cannabis withdrawal syndrome.”

Reduction of Appetite and Obesity

- GW Pharmaceuticals is conducting clinical studies to investigate the effects of CBD and THCV in obesity-related diseases.
- CBD significantly reduced total chow consumption in animals (Farrimond et al. 2012). According to research of the University of Gdansk, Poland, CBD decreased body weight gain in rats in a dose-dependent manner (Ignatowska-Jankowska et al. 2010). This effect was at least in part mediated by the CB2 receptor.
- Researchers at the University of Sao Paulo, Brazil, demonstrated that CBD inhibited the increased appetite induced by CB1 receptor agonists (Scopinho et al. 2011). They suggest "that its role as a possible food intake regulator should be further investigated."
- Research with zebra fish and obese mice shows that the cannabinoids CBD (cannabidiol) and THCV (tetrahydrocannabivarin) reduce fat levels in liver cells and inhibit the development of fatty liver (Silvestri et al. 2015).

Sleep

- The effects of CBD on sleep may depend on dose with lower doses having alerting properties and high doses being sedative.
- In a clinical study 8 volunteers received four treatments before sleep (at 10 p.m.): placebo, 15 mg THC, 5 mg THC combined with 5 mg CBD, and 15 mg THC combined with 15 mg CBD (Nicholson et al. 2004). Fifteen milligrams THC would appear to increase sleepiness, while 15 mg CBD appears to have alerting properties.
- CBD increased total sleep time and increased sleep latency, the time needed to fall asleep, in the light period of the day in rats (Chagas et al. 2013). In the animals that received the highest dose the phase of deepest sleep (so-called slow-wave sleep) was increased. Sedation was noted as a side effect in some clinical studies (e.g. Consroe et al. 1986).

Ischemia

- CBD given intravenously one hour before and 12 hours after reducing blood supply to the kidneys for 30 minutes in rats reduced damage to the organs (Fouad et al. 2012).
- According to research at the National Institute on Alcohol Abuse and Alcoholism in Bethesda, USA, CBD reduced the consequences of reduced blood supply to the liver in a mouse model of hepatic ischemia injury (Mukhopadhyay et al. 2011). CBD significantly reduced the extent of liver inflammation and cell death.
- The British company GW Pharmaceuticals has been granted orphan drug designation for cannabidiol (CBD) by the U.S. Food and Drug Administration for use in treating new-born children with neonatal hypoxic-ischemic encephalopathy. This is an acute or sub-acute brain injury due to suffocation caused during the birth process and resulting from deprivation of oxygen during birth (hypoxia). GW has developed an intravenous CBD formulation for use in this patient population. The company wants to commence a Phase 1 trial in the second half of 2015.

Diabetes

- Researchers of the Hadassah University Hospital of Jerusalem investigated the effects of CBD on the development of diabetes in mice, which develop diabetes due to genetic causes (Weiss et al. 2006). NOD mice that were treated with injections of CBD (5 mg per kilogram body weight) presented with a significantly reduced incidence of diabetes of 30 per cent compared to 86 per cent in untreated control mice.
- Studies suggest that increased circulating endocannabinoids may alter the function of blood vessels both positively and negatively in type 2 diabetes, and “that part of the beneficial effect of cannabidiol in diabetes may be due to improved endothelium-dependent vasorelaxation” (Stanley et al. 2013).
- Scientists at the Medical College of Georgia in Augusta, USA, suggested that CBD may be a useful novel treatment option for the damage of the retina in diabetes (diabetic retinopathy) (Liou et al. 2009).
- According to research at the National Institutes of Health in Bethesda, USA, CBD attenuates cardiac dysfunction, oxidative stress, fibrosis, inflammation and cell death in animal models of diabetic cardiomyopathy (Ohki et al. 2010).

Nausea and Vomiting

- Anecdotal evidence and basic research suggest a potential of CBD acid (CBDA) to reduce nausea and vomiting induced by different causes (Rock et al. 2013, Rock et al. 2013b, Rock et al. 2012, Parker et al. 2011).
- In rats the effects of metoclopramide, a medicinal drug used in the treatment of nausea and vomiting, were increased by cannabidiolic acid (CBDA) (Rock et al. 2013). Scientists concluded that “CBDA could be a powerful adjunct treatment to anti-emetic regimens for chemotherapy-induced nausea.” CBDA also acted synergistically in combination with very low doses of the highly effective anti-nausea drug ondansetron (Rock et al. 2013b).
- In a study with rats and shrews cannabidiolic acid (CBDA) reduced nausea and vomiting by enhancing 5-HT1A receptor activation (Rock et al. 2012).

Possible Further Medical Uses

- Neuroprotection after nerve injury
- Bovine Spongiforme Encephalopathy (mad cow disease)
- Alzheimer‘s Disease
- Parkinson‘s Disease
- Hepatitis
- Liver and Brain Damage
- Sepsis
- Bone Fracture Healing
- Skin Diseases
- Allergies and Asthma
- Side Effects of Doxorubicin
- Malaria

Drug Interactions

CBD inhibits the activity of the enzyme cytochrome P450 2C19 (Jiang et al. 2013). Enzymes of the cytochrome P450 complex are responsible for the degradation of medicinal drugs. Medicines that are degraded by the 2C19 enzyme of the complex, including many proton pump inhibitors such as Pantoprazol and antiepileptic drugs such as Clobazam, may be degraded slower if given together with CBD.

It also inhibits the activity of CYP2D6, which may cause interactions with the proton pump inhibitor Ondansetron and the antiepileptic drug Risperidon.

According to research at Hokuriku University in Kanazawa, Japan, several phytocannabinoids (THC, CBN, CBD) reduce the degradation of warfarin and of diclofenac increasing their effect and duration of action. Warfarin is a medicinal drug used to reduce blood clotting and diclofenac reduces pain and inflammation. This cannabinoid effect was due to the inhibition of an enzyme (CYP2C9) in the liver, which is mainly responsible for the degradation of THC and CBD (Yamaori et al. 2012).

Many thanks for your attention!