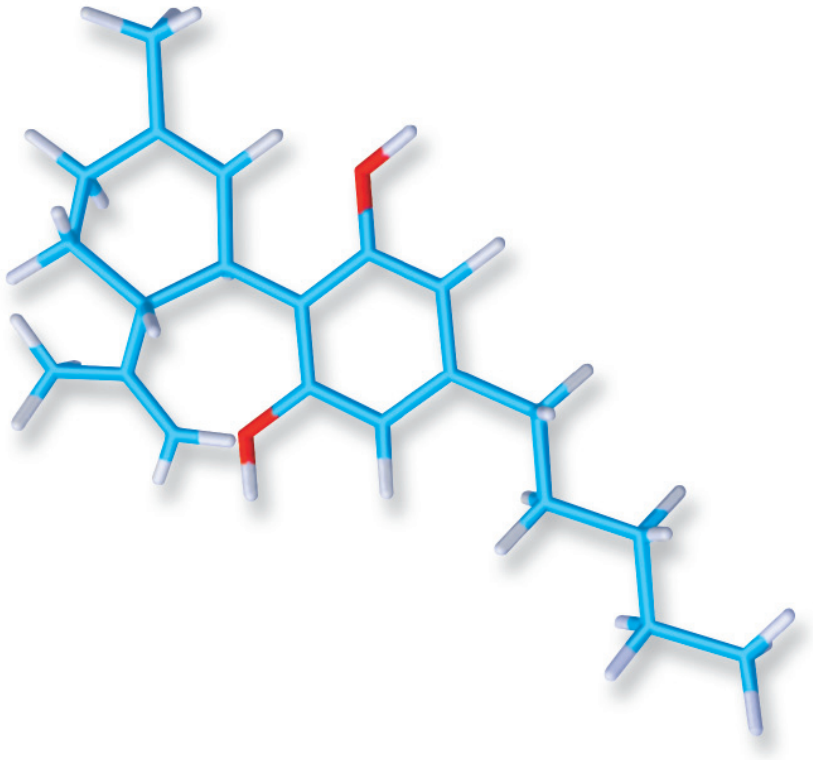
Bionorica® ethics

Cannabidiol

Information about the active ingredient



PATENT (WO 2009/039843 A2) for plant extract-CBD against skin diseases

Date: 05/2014

Cannabidiol is usually the primary cannabinoid of fibre or industrial hemp and the second most prevalent cannabinoid in drug types of the hemp plant. In fibre hemp Cannabidiol is present in concentrations in the range of about **0.5** *to* **2** *% in the upper third of the plant and the flowers. In recent years there is increasing interest in the therapeutic potential of CBD, which causes no psychotropic effects and even in high doses does not cause relevant side-effects. Only a few clinical studies have been conducted so far, but basic research suggests a potential therapeutic use in a large number of diseases like schizophrenia, epilepsy or skin diseases and different symptoms. Cannabinoids, including Cannabidiol are potent anti-oxidants, CBD has anxiolytic and strong anti-inflammatory properties too. A large number of products like CBD tinctures with very high CBD contents, CBD oils, CBD chewing gum and other products ready for use are available for example in US states.*

Content

1. INTRODUCTION

Cannabidiol (CBD) is usually the primary cannabinoid of fibre or industrial hemp/cannabis and the second most prevalent cannabinoid in drug types of the cannabis plant. In fibre cannabis CBD is present in concentrations in the range of about **0.5** to **2** % in the upper third of the plant and the flowers. In Germany and many other countries of the world farmers are allowed to grow fibre cannabis with high CBD and low THC concentrations (in the European Union below **0.2** % THC) for the production of fibre, which serves as raw material for industrial and other applications, and hemp seeds for the production of hemp seed oil, a high-quality vegetable oil. In recent years there is increasing interest in the therapeutic potential of CBD, which causes no psychotropic effects and even in high doses does not cause relevant side-effects. Only a few clinical studies have been conducted so far, but basic research suggests a potential therapeutic use in a large number of diseases and symptoms.

As with other cannabinoids, there are several cannabinoids of the CBD type, of which usually the phenolic (neutral) form is meant when we talk about CBD. There are also a few pharmacological effects of CBD acid, which may be of therapeutic interest, mainly the anti-emetic properties of this acid form.

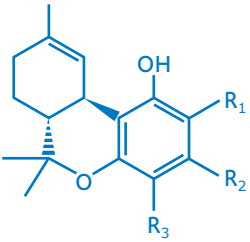


FIGURE **1**. Cannabinoids of the Δ^9-THC type. The most widespread cannabinoids are the Δ^9-THC with 21 carbon atoms and a C_5 side chain ($R_2 = C_5H_{11}$) and its two corresponding carboxylic acids A and B.

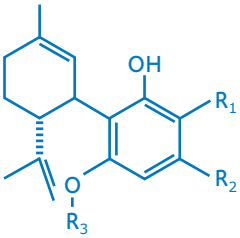


FIGURE **2**. Cannabinoids of the CBD type. The most widespread cannabinoids are the phenolic CBD ($R_1 = H$) with **21** carbon atoms and a C_5 side chain ($R_2 = C_5H_{11}$) and its corresponding carboxylic acid ($R_1 = COOH$) .

R_1 = H or COOH

R_2 = C_1, C_3, C_4, or C_5 side chain

R_3 = H or CH_3

2. PREPARATIONS

Bionorica Ethics produces and distributes the active pharmaceutical ingredient CBD for magistral preparations or other purposes. Details about quality etc. please find on page 22.

An Israeli company has developed a cannabis strain that contains 15.8 % CBD and less than one per cent of THC (Reuters of 3 July 2012) and does not cause psychological effects. Such strains could have a potential as anti-inflammatory drugs.

Recently, the U.S. Food and Drug Administration (FDA) has allowed the conduction of clinical studies with a new cannabis extract that contains cannabidiol as its active ingredient, for use in treating children with Dravet syndrome, a rare and severe form of infantile-onset, genetic, drug-resistant epilepsy syndrome. The pharmaceutical company hopes to start the trials in 2014. In addition to its clinical development program for the extract in Dravet syndrome, the company has also made arrangements to enable independent U.S. paediatric epilepsy specialists to treat high need paediatric epilepsy cases with cannabis extract immediately.

In the Netherlands a pharmaceutical company, which is producing several strains of cannabis flowers to be prescribed by Dutch physicians under the guidance of the Health Ministry of the Netherlands, intends to add a CBD rich variety to their four varieties currently available.

Currently 20 US states and the District of Columbia allow the medical use of cannabis. A large number of products, including CBD tinctures with very high CBD contents, CBD oils, CBD chewing gum, other products ready for use, and cannabis seeds, which yield cannabis plants with high CBD contents are available in these states.

3. PHARMACOKINETICS OF CBD

For an extended review on the pharmacokinetics of CBD please see: Grotenhermen (2003). 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 for 6 weeks in patients with Huntington's disease resulted in mean weekly plasma levels of 5.9-11.2 ng/ml.

33 metabolites were identified in the urine of a patient treated with CBD and further four metabolites were partially characterized. The metabolic pattern is similar to THC. However, unlike THC unchanged CBD is excreted in large percentages in the faeces.

The pharmacokinetics of cannabidiol (CBD), cannabidivarin (CBDV), delta-9-tetrahydrocannabivarin (delta-9-THCV) and cannabigerol (CBG) in mice and rats were recently investigated at the University of Aberdeen, UK (Deiana et al. 2012). Researchers determined concentrations in the brain after intraperitoneal (injection into the abdomen) and oral administration. The effects of CBD were further investigated in an animal model of obsessive compulsive behaviour. All phytocannabinoids readily penetrated the blood-brain barrier. In rats, oral administration offered higher brain concentrations for CBD and CBDV, but not for delta-9-THCV and CBG, for which the intraperitoneal route was more effective. CBD inhibited obsessive-compulsive behaviour in a time-dependent manner matching its concentration in the brain.

4. MECHANISM OF ACTION OF CBD

The mode of action of cannabidiol is not fully understood and several mechanisms have been proposed:

(1) CBD acts as antagonist at the central CB1 receptor and was able to inhibit several CB1 mediated THC effects (Zuardi et al. 1982). In a study by Petitet et al. (1998) CBD considerably reduced the receptor activation of a potent classical CB1 receptor agonist. CBD has a very low affinity for both known cannabinoid receptors. However, CBD antagonises CB1 and CB2 receptor agonists at doses considerably lower than those of CBD needed to activate cannabis receptors (Pertwee et al. 2002). CBD was also shown to display inverse agonism at the human CB2 receptor, which may be a rational basis for its anti-inflammatory properties.

(2) CBD stimulates the vanilloid receptor type 1 (VR1) with a maximum effect similar in efficacy to that of capsaicin (Bisogno et al. 2001, Costa et al. 1998).

(3) CBD inhibits the uptake and hydrolysis of the endocannabinoid anandamide, thus increasing its concentration (Bisogno et al. 2001, Mechoulam et al. 2002).

(4) Researchers investigated the mechanisms, by which CBD reduces inflammatory and neuropathic pain in animals (Xiong et al. 2012). They found that the cannabinoid-induced analgesic effect is absent in mice lacking glycine receptors and concluded that this receptor mediates suppression of chronic pain.

(5) CBD binds to the equilibrative nucleoside-transporter-1, thus enhancing endogenous adenosine signalling. Some immunosuppressive effects may be based on this mechanism. The treatment of mice with a low dose of CBD is known to decrease tumour necrosis factor alpha (TNF-alpha) production (Malfait et al. 2000). This effect was reversed with an A2A adenosine-receptor antagonist.

(6) CBD displaces an agonist (8-hydroxy-2-di-n-protylamino-tetralin) from the 5-HT1A receptor in a concentration-dependent manner (Russo et al. 2005). CBD is a modest-affinity agonist at this receptor in humans.

(7) 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, when administered concurrently with high ethanol exposure in rats prevented neurodegeneration and this effect was attributed to its anti-oxidative effects (Hamelink et al. 2005).

(8) 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.

5. ANTAGONISM OF DRONABINOL (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, 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).

In a study by Zuardi et al. (1982), eight volunteers received, in a double-blind design, either a high single oral dose of THC (0.5 mg THC per kg body weight, i.e. between 25 and 40 mg), or the same THC dose combined with twice that amount of CBD. The study demonstrated that CBD blocked the anxiety produced by THC. This antagonistic effect was also found with other symptoms caused by THC, among them difficulty concentrating and disconnected thoughts. Cannabidiol also blocks several physical effects of THC, among them tachycardia, i.e. an increase in heart rate (Karniol et al. 1974). 30 mg of oral THC caused, 50 minutes after ingestion, a maximum increase in pulse rate of 135 beats per minute, on average; in comparison, a placebo caused only 98 beats/min, while simultaneous ingestion of 30 mg of THC and 60 mg of CBD caused a maximum

pulse rate of **106** beats/min (Karniol et al. **1974**). Human volunteers were also asked to estimate the subjective duration of a time period of **60** seconds. After ingestion of a placebo, **30** mg THC, and a combination of **30** mg THC and **60** mg CBD, respectively, average estimates were **58** seconds (placebo), **34** seconds (THC), and **50** seconds (THC + CBD) (Karniol et al. **1974**).

According to a study with **94** cannabis users at the University College London, UK, the effects of cannabis vary according to the ratio of cannabidiol (CBD) and THC (Morgan et al. **2010**). Participants were tested **7** days apart, once while non-intoxicated and once while acutely under the influence of their own chosen smoked cannabis on the appetitive and reinforcing effects of the drug. A sample of cannabis was collected from each user and analysed for levels of cannabinoids. On the basis of CBD:THC ratios in the cannabis, individuals with a comparatively high and a low ratio were directly compared. When under the influence of cannabis, smokers of cannabis with a comparatively high CBD content showed reduced liking for drug and food stimuli compared with smokers of cannabis with a low CBD:THC ratio. Those smoking higher CBD:THC strains also showed lower self-rated liking of cannabis stimuli on both test days. Researchers concluded that their „findings suggest that CBD has potential as a treatment for cannabis dependence."

According to research at the University of Sydney, Australia, pre-treatment with CBD increased THC effects in rats (Klein et al. **2011**). With both acute and chronic administration, CBD pre-treatment potentiated blood and brain THC levels. Researcher concluded that „CBD can potentiate the psychoactive and physiological effects of THC in rats, most likely by delaying the metabolism and elimination of THC."

6. POSSIBLE INDICATIONS

6.1 ANXIETY DISORDERS AND POST-TRAUMATIC STRESS DISORDER

CBD was shown to have anxiolytic effects in animal models (Twardowschy et al. **2013**, Do Monte et al. **2013**, Campos et al. **2012**, Stern et al. **2012**, Elbatsh et al. **2012**) and humans (Zuardi et al. **1993**, Das et al. **2013**, Bergamaschi et al. **2011**, Crippa et al. **2010**).

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 and its physiological concomitants and is sensible to anxiolytic and anxiogenic com-

pounds. CBD (300 mg, P.O.) was compared, under a double-blind design, to ipsapirone (5-HT1A partial agonist, 5 mg), diazepam (anxiolytic benzodiazepine, 10 mg) or placebo. The results showed that both CBD and the two other anxiolytic compounds attenuated anxiety induced by the test. At this dosage CBD did not induce any significant sedative effects. The results, therefore, support the claim of anxiolytic properties of CBD.

In an experiment with 48 healthy participants who underwent a fear-conditioning test CBD enhanced consolidation of subsequent extinction learning and thus may be helpful in anxiety disorders (Das et al. 2013). Participants received 32 mg of CBD either following before or after extinction in a double-blind, placebo-controlled design. Successful conditioning and extinction were found in in the treatment groups. CBD given post-extinction enhanced consolidation of extinction learning. No acute effects of CBD were found on extinction.

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. The placebo group presented higher anxiety, cognitive impairment, discomfort, and alert levels when compared with the control group. No significant differences were observed between patients, who had received CBD, and healthy controls in anxiety cores or in the cognitive impairment, discomfort, and alert factors. This study confirmed previous research of the same group involving 10 patients with social anxiety disorder (Crippa et al. 2010).

Research with mice shows that the serotonin 5-HT1A receptor is involved in the anxiolytic effects of CBD (Twardowschy et al. 2013). Blocking of this receptor reduced the anti-panic effects of this natural cannabinoid. Repeated microinjections of CBD into the infralimbic cortex of mice facilitated fear extinction (Do Monte et al. 2013). This effect was mediated by the CB1 receptor. In a study with rats, which were exposed to cats, CBD reduced fear reactions one hour after the exposure to the predator (Campos et al. 2012). This effect was also mediated at least in part by the 5-HT1A receptor. Authors concluded: "Our results suggest that CBD has beneficial potential for PTSD [posttraumatic stress disorder] treatment and that 5-HT1A receptors could be a therapeutic target in this dis-

order." However, animal research at the University of Nottingham, UK, showed that chronic administration of cannabidiol increased anxiety in rats (Elbatsh et al. **2012**). Rats were treated for 14 days with CBD. Researchers concluded that „chronic administration of CBD produced an anxiogenic-like effect in clear opposition to the acute anxiolytic profile previously reported."

6.2 SCHIZOPHRENIA

The first investigation on the possible antipsychotic effects in humans was done in a schizophrenic patient who had significant hormonal side effects during treatment with a typical antipsychotic (Zuardi et al. **1995**). The patient, a **19**-year-old woman, was referred to the inpatient unit of the Clinical Hospital of Ribeirão Preto because of aggressiveness, self-injury, incoherent thoughts and auditory hallucinations. She received CBD in progressively increasing dosage, up to **1500** mg/day (in two divided doses) within four weeks. CBD was then stopped and replaced by placebo for **4** days. After that, haloperidol administration was started. Dosage adjustment was based on clinical evaluation. Diazepam was also administered in periods of great agitation. The mean daily dose of diazepam decreased after the beginning of CBD treatment from **16.3** to **5.7** mg/day. Two psychiatrists and two nurse auxiliaries evaluated the patient and the interviews were videotaped. At the end of the study the videotapes were analysed blindly and in a random sequence by another psychiatrist. Symptoms decreased after CBD treatment and there was a trend for worsening of the symptoms after drug withdrawal. The improvement obtained with CBD was not increased by haloperidol. This improvement was seen in all items of the rating scale employed, including those more closely related to psychotic symptoms, making it improbable that an anxiolytic action was the sole responsible for the antipsychotic effect.

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. CBD did not worsen the motor function. No adverse effect was observed during the treatment. Authors concluded that „these preliminary data suggest that CBD may be effective, safe and well tolerated for the treatment of the psychosis in PD."

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, in a double-blind manner. Either treatment was safe and led to significant clinical improvement, but CBD presented with significant less adverse effects. Moreover, cannabidiol treatment was accompanied by a significant increase in blood anandamide levels. "The results suggest that inhibition of anandamide deactivation may contribute to the antipsychotic effects of cannabidiol potentially representing a completely new mechanism in the treatment of schizophrenia," authors wrote.

6.3 CANCER

Several cell and animal experiments have shown that not only THC but also CBD possesses anti-cancer effects (Ligresti et al. **2006**, McKallip et al. **2006**, McAllister et al. **2007**, Marcu et al. **2010**, Solinas et al. **2013**, Scott et al. **2013**, Solinas et al. **2012,** De Petrocellis et al. **2013**, Ramer et al. **2012**, Shrivastava et al. **2011**, Torres et al. **2011**). So far, no clinical studies have been conducted and no conclusion can be drawn on it effects in humans.

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. CBD also reduced lung metastases deriving from human breast cancer cells that had been injected into the paws of the animals. Researchers found that the anti-tumour effects of CBD were caused by induction of apoptosis. They concluded that their data „support the further testing of cannabidiol and cannabidiol-rich extracts for the potential treatment of cancer."

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 living animals CBD caused a reduction in number of leukaemia cells. 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**. Id proteins play an important role in tumour cell biology. The researchers of the California Pacific Medical

Center Research Institute concluded that „CBD represents the first nontoxic exogenous agent that can significantly decrease Id-1 expression in metastatic breast cancer cells leading to the down-regulation of tumour aggressiveness."

Cannabidiol (CBD) also inhibits the formation of new blood vessels, called angiogenesis, in tumours by different mechanisms (Solinas et al. **2012**). Researchers concluded: "Its dual effect on both tumour and endothelial cells reinforces the hypothesis that CBD could represent a potential effective agent in cancer therapy."

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**). The two natural cannabinoids were tested on two glioblastoma cells lines. THC and CBD acted synergistically to inhibit cell proliferation. The treatment of glioblastoma cells with both compounds led to significant modulations of the cell cycle, induction of reactive oxygen species (free radicals) and apoptosis (programmed cell). There were specific changes that were not observed with either compound individually, indicating that the signal transduction pathways affected by the combination treatment were unique. Researchers concluded that these „results suggest that the addition of cannabidiol to delta-9-THC may improve the overall effectiveness of delta-9-THC in the treatment of glioblastoma in cancer patients."

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. The lead researcher said: "These agents are able to interfere with the development of cancerous cells, stopping them in their tracks and preventing them from growing. In some cases, by using specific dosage patterns, they can destroy cancer cells on their own. Used in combination with existing treatment, we could discover some highly effective strategies for tackling cancer."

CBD and several cannabis extracts reduced viability of prostate cancer cells (De Petrocellis et al. **2013**). 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**). Administration of submaximal doses of THC and CBD remarkably reduced the growth of gliomas. Moreover, treatment with TMZ and submaximal doses of THC and CBD produ-

ced a strong anti-tumoural action in both TMZ-sensitive and TMZ-resistant tumours. Authors suggested that „the combined administration of TMZ and cannabinoids could be therapeutically exploited for the management" of glioblastoma multiforme (glioma).

6.4 DYSTONIA AND DYSKINESIA

A few clinical investigations suggest a therapeutic potential of CBD in movement disorders (Consroe et al. 1986, Snider et al. 1984)

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 %. Side-effects of CBD were mild and included hypotension, dry mouth, psychomotor slowing, light-headedness, and sedation. In 2 patients with coexisting Parkinsonian features, CBD at doses over 300 mg/day exacerbated the hypokinesia and resting tremor.

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. Researchers noted that "these findings indicate that CBD can attenuate catalepsy caused by different mechanisms (...) via 5-HT1A receptors activation, suggesting that it could be useful in the treatment of striatal disorders." Among these disorders are Parkinson's disease and dyskinesia.

6.5 EPILEPSY

Animal research (Shirazizand et al. 2013, Jones et al. 2012, Jones et al. 2011), anecdotal evidence and one clinical study (Cunha et al. 1980) shows that CBD has anti-epileptic properties.

In phase 1 of the only clinical study conducted so far, 3 mg/kg daily of CBD was given for 30 days to 8 health human volunteers (Cunha et al. 1980). Another 8 volunteers received the same number of identical capsules containing

glucose as placebo in a double-blind setting. Neurological and physical examinations, blood and urine analysis, ECG and EEG were performed at weekly intervals. In phase 2 of the study, 15 patients suffering from secondary generalized epilepsy with temporal focus were randomly divided into two groups. Each patient received, in a double-blind procedure, 200-300 mg daily of CBD or placebo. The drugs were administered for along as 4 1/2 months. Throughout the experiment the patients continued to take the antiepileptic drugs prescribed before the experiment, although these drugs no longer controlled the signs of the disease. All patients and volunteers tolerated CBD very well and no signs of toxicity or serious side effects were detected on examination. 4 of the 8 CBD subjects remained almost free of convulsive crises throughout the experiment and 3 other patients demonstrated partial improvements in their clinical condition. CBD was ineffective in 1 patient. The clinical condition of 7 placebo patients remained unchanged whereas the condition of 1 patient clearly improved.

CBD reduced seizures in mice, in which seizures were caused by pentylenetetrazol (PTZ) and electroshocks (Shirazizand et al. 2013). CBD also showed antiepileptic effects in two other animal models of seizures (Jones et al. 2012). In the pilocarpine model CBD significantly reduced the percentage of animals experiencing the most severe seizures. In the penicillin model, CBD significantly decreased the percentage of mortality as a result of seizures; CBD also decreased the percentage of animals experiencing the most severe tonic-clonic seizures. According to research at the University of Reading, UK, CBD exerted anti-convulsant effects in animal models of temporal lobe and partial seizures (Jones et al. 2011).

6.6 DEPENDENCY AND WITHDRAWAL

Basic research (Justinova et al. 2013, Mahgoub et al. 2013, Katsidoni et al. 2013) and one case report (Crippa et al. 2013) suggest a therapeutic potential of CBD in dependency and withdrawal.

Basic research of two groups of researchers in the United Arab Emirates and the USA point to a possible mechanism, by which CBD has potential as a treatment for cannabis dependence. Scientists of the National Institute on Drug Abuse in Baltimore, USA, demonstrated that kynurenic acid, which inhibits the alpha-7-nicotinic acetylcholine receptors (alpha7-nACh receptor), reduced the rewarding effects of THC in rats and monkeys, who were dependent on THC (Justinova et al. 2013). Kynurenic acid is a product of the normal metabolism of the amino acid L-tryptophan. Researchers wrote that the modulation of

kynurenic acid "offers a pharmacological strategy for achieving abstinence from marijuana and preventing relapse."

A group from the College of Medicine and health Sciences of the University of Abu Dhabi in AL Ain, United Arab Emirates, showed that CBD inhibits acetylcholine-induced currents at the alpha-7-nicotinic acetylcholine receptors (Mahgoub et al. 2013). They concluded that their results "indicate that CBD inhibits the function of the alpha7-nACh receptor." Other mechanisms may be involved in these effects of CBD.

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."

6.7 DIABETES

Basic research suggests that CBD may be beneficial in diabetes and prevent complications of the disease, such as damage to the blood vessels (Weiss et al. 2006, Stanley et al. 2013, Liou et al. 2009, Ohki et al. 2010).

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). So-called NOD mice develop insulitis within 4 to 5 weeks of age followed by diabetes within a median of 14 weeks. Insulitis is an inflammation of the cells in the pancreas that produce insulin, and diabetes is a result of a destruction of these cells. NOD mice aged 6 to 12 weeks that were treated with 10 to 20 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. In addition, in the mice that developed diabetes in the treated group disease onset was a significantly delayed. Blood levels of two cytokines that promote inflammation, IFN-gamma and TFN-alpha, are usually increased in NOD mice. A treatment with CBD caused a significant reduction (more than 70 per cent) in levels

of both cytokines. In another experiment CBD-treated mice were observed for 26 weeks. While the 5 control mice all developed diabetes, 3 of 5 of the CBD-treated mice remained diabetes-free at 26 weeks. Scientists concluded that confirmation of the observed immunomodulatory effects of CBD „may lead to the clinical application of this agent in the prevention of type 1 diabetes" and possibly other autoimmune diseases. They note that many patients diagnosed with type 1 diabetes have sufficient residual cells that produce insulin at the time of diagnosis, and may be candidates for immunomodulation therapy.

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). Authors concluded that „these results coupled with the excellent safety and tolerability profile of CBD in humans, strongly suggest that it may have great therapeutic potential in the treatment of diabetic complications, and perhaps other cardiovascular disorders."

6.8 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).

6.9 OBESITY

CBD may be helpful in obesity (Farrimond et al. 2012, Ignatowska-Jankowska et al. 2010, Scopinho et al. 2011). Please see above the paragraph on "Antagonism of THC effects."

According to GW Pharmaceuticals four small clinical studies are underway to investigate the effects of two natural cannabinoids in obesity-related diseases (UPI of 8 July 2012). These cannabinoids are CBD and tetrahydrocannabivarin (THCV), which have shown to decrease appetite in animal studies. The compounds also had an impact on the level of fat in the body and its response to insulin.

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."

6.10 NEUROPROTECTION

In young rats the consequences of mechanical damage to the sciatic nerve was reduced by CBD (Perez et al. 2013). Authors concluded that "the present results show that CBD possesses neuroprotective characteristics that may, in turn, be promising for future clinical use."

6.11 BOVINE SPONGIFORME ENCEPHALOPATHY (MAD COW DISEASE)

According to basic research of scientists of the National Centre for Scientific Research in Valbonne, France, CBD may prevent the development of prion diseases, the most known being BSE (bovine spongiforme encephalopathy), which is often called mad cow disease (Dirikoc et al. 2007). It is believed that the BSE may be transmitted to human beings. In humans, it is known as Creutzfeldt-Jakob disease.

The infectious agent in prion diseases is believed to be a specific type of misfolded protein called prion. Misfolded prion proteins carry the disease between

individuals and cause deterioration of the brain. The French researchers reported that CBD inhibited the accumulation of prion proteins in both mouse and sheep prion-infected cells, whereas other cannabinoids were either weak or not effective. Moreover, after infection with mouse scrapie, a prion disease, CBD limited accumulation of the prion protein in the brain and significantly increased the survival time of infected mice. CBD inhibited the nerve damaging effects of prions in a concentration-dependent manner. Researchers noted that CBD may be a promising agent for the treatment of prion diseases.

6.12 ALZHEIMER'S DISEASE

According to research at the Sapienza University of Rome, Italy, CBD reduces inflammation in the brain caused by amyloid-beta in a rat model of Alzheimer's disease (Esposito et al. **2011**). CBD also stimulated the formation of new nerve cells in the hippocampus, a brain region important for memory. In research at the Cajal Institute in Madrid, Spain, CBD was able to modulate the function of microglia, immune cells in the brain, in a mouse model of Alzheimer's' disease (Martín-Moreno et al. **2011**). Scientists noted that „given that CBD lacks psychoactivity it may represent a novel therapeutic approach for this neurologic disease."

6.13 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. Researchers concluded that "Cannabidiol, via its antioxidant and anti-inflammatory properties, may represent a potential therapeutic option to protect" against damage to kidneys caused by temporarily reduced blood supply.

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**). Blood supply to the liver was interrupted for this reason and then restored. CBD significantly reduced the extent of liver inflammation and cell death. This effect was not mediated by cannabinoid receptors.

6.14 INFLAMMATION

CBD is a potent anti-inflammatory agent (Kozela et al. 2013, Mecha et al. 2013, Li et al. 2013, Ribeiro et al. 2012, Kozela et al. 2011, Buccellato et al. 2010).

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 substances, which increase inflammation (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). This effect may be mediated through the adenosine A2A receptor.

6.15 HEPATITIS

Scientists at the University of South Carolina in Columbia, USA, investigated the effects of CBD on acute hepatitis induced by concanavalin A (ConA) in mice (Hegde et al. 2011). CBD reduced inflammation by increasing the number of myeloid-derived suppressor cells through activation of TRPV1 vanilloid receptors.

6.16 LIVER AND BRAIN DAMAGE

According to scientists from Greece and Israel CBD improves brain and liver function in an animal model for brain damage (encephalopathy) caused by liver failure (Avraham et al. 2010).

6.17 SEPSIS

According to Spanish researchers CBD prevented from negative consequences of sepsis in a mouse model (Ruiz-Valdepeñas et al. **2011**). It prevented dilation of small arteries and veins.

6.18 SKIN DISEASES

The proliferation of human skin cells was influenced by the cannabinoids CBD and cannabigerol (CBG) (Pucci et al. **2013**). Authors concluded that this suggests "(especially for cannabidiol) a possible exploitation as lead compounds to be used in the development of novel therapeutics for skin diseases."

Endocannabinoid signalling has been shown to have a role in the control of epidermal physiology, whereby anandamide is able to regulate the expression of skin differentiation genes through DNA methylation. In this study CBD and CBG significantly reduced the expression of all the genes tested (keratins **1** and **10**, involucrin and transglutaminase **5**) in differentiated HaCaT cells, by increasing DNA methylation of keratin **10** gene, but cannabidivarin was ineffective. Remarkably, cannabidiol reduced keratin 10 mRNA through a CB**1** receptor-dependent mechanism, whereas cannabigerol did not affect either CB**1** or CB**2** receptors of HaCaT cells. In addition, CBD, but not CBG, increased global DNA methylation levels by selectively enhancing DNMT**1** expression, without affecting DNMT **3**a, **3**b or **3**L.

6.19 ALLERGIES AND ASTHMA

In a study with Guinea-pigs the inhalation of ovalbumin caused constriction of the airways and this was reduced by CBD (Dudášová et al. **2013**). Scientists concluded that CBD "may have beneficial effects in the treatment of obstructive airway disorders."

According to research at the Taipei medical University, Taiwan, the administration of CBD reduced delayed-type hypersensitivity reactions in mice to the protein ovalbumin (Liu et al. **2010**). Scientists found out that CBD curbs delayed-type hypersensitivity reactions by suppressing the infiltration and functional activity of certain immune cells (T cells and macrophages) in the inflammatory site, „suggesting a therapeutic potential for CBD for the treatment of type IV hypersensitivity", a certain type of allergic reaction.

6.20 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).

7. 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 and antiepileptic drugs, may be degraded slower if given together with CBD.

8. ADVERSE EFFECTS

According to a review of studies on CBD this non-psychotropic cannabinoid of the cannabis plant „may be safe in humans and animals" (Bergamaschi et al. 2011). „Several studies suggest that CBD is non-toxic in non-transformed cells and does not induce changes on food intake, does not induce catalepsy, does not affect physiological parameters (heart rate, blood pressure and body temperature), does not affect gastrointestinal transit and does not alter psychomotor or psychological functions."

In cell experiments CBD influenced the function of certain proteins (P-glycoprotein and Breast Cancer Resistance Protein), which play a role in the normal function of the placenta (Feinshtein et al. 2013). Authors concluded that the use of CBD during pregnancy "may reduce placental protective functions and change its morphological and physiological characteristics."

9. CHEMICAL, PHYSICAL PROPERTIES AND GENERAL INFORMATION

Product Name:	(-)-Cannabidiol (abbr. CBD)
IUPAC Name:	2-[(1*R*,6*R*)-3-Methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol
CAS Number:	13956-29-1
PubChem:	CID 644019
ChemSpider:	24593618
Molecular Formula:	$C_{21}H_{30}O_2$
Molecular Weight:	314,5
Appearance:	colourless to light yellow powder or colourless to light yellow crystals
Purity:	≥97,5 %
Stability:	24 months
Melting Point:	66 - 67 °C (150,8 - 152,6 °F)
Boiling Point:	188,5 °C (371,3 °F)
Storage:	between 15 - 25 °C (59 - 77 °F), tigthly closed and protected from light
Solubility:	practically insoluble in water or 10 % NaOH. Soluble in ethanol, methanol, ether, benzene, chloroform, per ether.
Legal status:	no narcotic drug (DE), Schedule I (US), Schedule II (Can)

NOTES:

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