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Cannabis/Cannabinoids as Medicine: Are we there?

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Abstract:

Cannabis remains the most used illicit drug in the world today. There is a fierce debate ongoing in the US and elsewhere whether to approve cannabis and or its products as a medicine. Despite the lack of enough scientific and clinical evidence to support cannabis as medicine, many parts of the US and other countries have legalized it as medicine. Currently, based on pre-clinical and clinical research, products such as synthetic THC alone, e.g., dronabinol and nabilone and in combination with cannabidiol (Sativex) have been approved as medicine. Furthermore, cannabidiol also has been recently approved for the treatment of epilepsy in children. Research also shows that cannabidiol appears to have a great potential for developing as a medicine to be able to treat a wide range of clinical conditions ranging from neuropathic pain to Alzheimer's and Parkinson's diseases, muscular sclerosis, anxiety, depression to inflammatory conditions of the gastrointestinal system. However, currently available research does not support the use of smoked cannabis as a medicine to treat any of the above-mentioned health conditions. Other cannabinoids such as cannabichromene, tetrahydro-cannabivarin, cannabigerol and others, although studied in many pre-clinical and clinical studies, research so far suggests that much work is still needed before any of them can be individually approved as medicine by a regulatory body of a country like the US Food and Drug Administration.

Introduction

Cannabis remains the most used illicit drug in the world with an estimated 2.5% of the world's population (180 million) using it regularly[1] and its use is associated with significant social and health consequences.[2] Unequivocally, one of the most pressing and important controversies worldwide is the movement toward legalization of cannabis as medicine. Questions about the medicinal value of cannabis are now being fiercely debated, and despite the lack of enough clinical evidence to support the use of cannabis as medicine, 30 states and Washington, DC., in the United States and countries around the globe like Canada and Uruguay have or continue to legalize cannabis as "medical marijuana". In addition, one of its active cannabinoids, cannabidiol, is being used to treat a wide variety of clinical conditions though it has been only recently approved for only one indication, Dravet and Lennox-Gastaut syndromes, a type of epilepsy in children two years of age and older (https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm611046.htm). Thus, it is of paramount importance that addiction physicians become familiar with the adverse effects of cannabis use, clinical evidence supporting the use of cannabis or its various cannabinoid chemicals as medicine, and current laws and policies governing medical cannabis, before they recommend or prescribe cannabis or its products for the treatment of any clinical condition. Therefore, we decided to review the published literature in English on the medicinal properties of cannabis and its products, their use in clinical practice and offer observations.

Methods

To prepare this review, we used the NIH PubMed database and keywords including cannabis, marijuana, cannabinoids, delta-9-tetrahydrocannabinol, THC, cannabidiol, CBD, health terms including epilepsy, health effects, medical consequences, and identified, retrieved and reviewed the papers published in English language relevant to the medicinal value of cannabis and cannabinoids.

Cannabis as Medicine

Cannabis belongs to a species of the Cannabinaceae family, first classified by Carl Linnaeus in 1793.[3] Generally, of the many varieties of cannabis cultivated in various parts of the world, three are most commonly used: Cannabis sativa Linn, C. indica Linn, and C. ruderalis Janisch, corresponding to useful, Indian and wild cannabis plants. The chemotaxonomic analysis of Cannabis shows that there are two biotypes of Cannabis, C. sativa Linn. and four biotypes of C. indica Linn. Plants with relatively high levels of tetrahydrocannabivarin (Δ^9-THCV) and/or cannabidivarin (CBDV) were common only in C. indica Linn., thereby supporting a two-species concept of Cannabis.[4] It is a complex plant that has hundreds of chemical constituents but only a few are pharmacologically active. Of the 560 identified and characterized chemicals in cannabis,[5] 104 are classified as cannabinoids,[6] while the rest are terpenes and flavinoids. Of the 104 cannabinoids, only two—delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)—have been extensively studied for their potential therapeutic applications. The other cannabinoids such as cannabichromene (CBC), cannabidolic acid (CBDA), cannabidiol (CBD), delta-9-tetrahydrocannabivarin (Δ^9-THCV), cannabinol (CBN), delta-9-tetrahyrocannabinol (Δ^9-THC), cannabinol (CBL), delta-9-tetrahydrocannabivaric acid (Δ^9-THCAA), are the major components of C. sativa, while cannabigerolic acid (CBGA), cannabigerol (CBG) and delta-8-tetrahydrocannabinol (Δ^8-THC) are minor constituents[7] (Gul et al. 2015) and have been postulated to have some medicinal value.[8] Figure 1 below shows the biosynthetic pathway of cannabinoids in the plant.[9] In addition to phytocannabinoids, some endocannabinoids serve as neurotransmitters within the brain or its periphery and act on cannabinoid receptors in the brain,[10] (CB1) [11] or in periphery (CB2).[12] The synthetic cannabinoids are structurally similar to endocannabinoids and act by similar mechanisms. Much work has been conducted with the most prominent cannabinoid, Δ^9-THC, and then with the second most studied cannabinoid, cannabidiol (CBD), which has been postulated to have many pharmacologic mechanisms of action, including immunosuppressive, anti-inflammatory, analgesic, neuroprotective, antiepileptic, and antipsychotic effects (Figure 2).[13] Limited pre-clinical or almost non-existent clinical research has been conducted with other cannabinoids. This paper reviews the current research available on medicinal properties of cannabis and its products including cannabinoids. Furthermore. the data is discussed in the order of strength of available evidence on various cannabis products. (Figure 1 & 2)

The Chinese Emperor Shen-Nung was the first to describe the medicinal value of **cannabis** [14] in 2737 BC and since then many preparations of cannabis have been used for recreational and medicinal purposes[15,16,17]. The biological plausibility of cannabis as medicine is based on the endocannabinoid system that is believed to be involved in a wide range of bodily functions, including analgesia, vomiting, immune system regulation, appetite, cognitive processes and motor control. Cannabinoids, THC and CBD, exert their effect by interacting with CB1 and CB2 receptors in the body. The CB1 receptor is distributed widely and at high levels in the hippocampus, cerebellum, basal ganglia, and neocortex, in addition to peripheral nerve terminals. CB1 receptors have been reported to possess analgesic, anti-spasmodic, anti-tremor, anti-inflammatory, appetite stimulant, and anti-emetic properties. The CB2 receptors are found largely within the periphery of the brain, including cells of the immune system, and have been reported to possess anti-inflammatory, analgesic, anticonvulsant, anti-psychotic, antioxidant, and neuroprotective properties.[18] As a result, both THC and CBD have been tested for their therapeutic potential.[13]

The medicinal value of cannabis plant and/or its products

has been discussed in recent excellent reviews[19,20,21,22] that show that there is little doubt about the potential of cannabis or its cannabinoid constituents to treat a wide range of clinical conditions. But many investigators and medical organizations like the National Academy of Sciences[23] and American Society of Addiction Medicine (ASAM)[24] have recommended that additional research be conducted before cannabis product or an individual cannabinoid is prescribed for any clinical indication. Currently, there are no FDA-approved indications for cannabis as a medication. Below we will review the available pharmacological, pre-clinical and clinical research on cannabis, and various cannabinoids that show that a few of these do have a potential to treat a wide range of health conditions.

Currently, **cannabis** is not approved for any clinical condition. Smoked cannabis was tested in a few studies for effectiveness against nausea/vomiting but was found to be of limited success[25] and resulted in side effects including sedation.[26] For its appetite stimulant effects, in one study, smoked marijuana (one to three cigarettes with total THC content of 3.9% a day) significantly increased weight gain without increasing the viral load.[27] In only one randomized, double-blind, placebo-controlled study,[28] one marijuana cigarette containing 2% THC significantly reduced intraocular pressure (IOP), suggesting it could be developed to treat glaucoma. In a recent study,[29] 22 patients with symptoms of Parkinson's disease who were treated with smoked marijuana, showed significant improvement in their sleep and pain scores without developing any adverse effects. There are no clinical studies where smoked cannabis was tested for treating either muscular sclerosis (MS), spinal cord injuries, epilepsy, dystonia, or post-traumatic stress disorder (PTSD).

Delta-9-Tetrahydrocannabinol alone or in combination with Cannabidiol

THC is the most active psychoactive component of Cannabis sativa. Linn. Based on extensive pre-clinical and clinical studies including clinical trials, a synthetic THC, dronabinol [Marinol®, Syndros®] has been approved for the treatment of anorexia associated with weight loss in AIDS patients and chemotherapy-induced nausea and vomiting,[18] Nabilone [Cesamet®], also a synthetic cannabinoid similar to THC, has been approved for the treatment of nausea and vomiting in patients undergoing cancer treatment; and Sativex,® an oral spray containing two cannabinoids—THC and CBD—in a 1:1 ratio, has been approved in 28 countries including Canada[30] (but not the U.S.) for moderate to severe spasticity due to multiple sclerosis (MS) in patients who have not responded adequately to other treatments. Although, both nabilone and dronabinol were found to be potent anti-emetic medications as compared to non-herbal medications such as chlorpromazine, prochlorperazine, metoclopramide, and haloperidol, their use has declined due to their undesirable side effects—including drowsiness, euphoria, and sedation. THC significantly stimulated appetite and improved weight gain of in HIV-infected patients[31] and others.[32] Health Canada has approved Marinol as an appetite stimulant in the treatment of AIDS-associated anorexia and weight loss.[30]

Analgesic Effect. Oral THC in doses of 15 mg and 20 mg was found effective against pain in 10 patients, but most of those patients developed drowsiness and confusion. A lower dose of 10 mg THC was ineffective as analgesic.[33] Similarly, 10 mg and 20 mg doses of oral THC were as effective as 60 mg and 120 mg of codeine in 36 patients with cancer pain. However, the higher doses of THC frequently produced drowsiness, dizziness, and mental disorders in patients.[34] In a study of 40 women with postoperative pain, a 5 mg dose of oral THC was ineffective as an analgesic.[35] In another study of 21 patients, a single inhaled dose of 25 mg of 9.4% THC herbal cannabis three times a day for five days reduced the intensity of pain, improved sleep, and was well-tolerated by patients with neuropathic pain, whereas lower doses of THC (i.e., 2.5% and 6.0%) were ineffective.[36] On the other hand, intravenous administration of THC was ineffective as an analgesic in 10 healthy volunteers undergoing tooth extraction.[37] The analgesic effects of THC or cannabidiol were comparable with codeine or morphine. Finally, a sublingual single spray containing THC and CBD in a 1:1 ratio (2.5 mg each), given daily for four weeks, was effective as an analgesic in 34 patients with chronic pain. Reported adverse reactions included dry mouth, drowsiness, euphoria/dysphoria, and dizziness.[38]

Multiple Sclerosis. In several studies, oral THC in capsule, oral and sublingual spray containing THC and CBD were tested for the treatment of multiple sclerosis. A double-blind, randomized placebo-controlled trial of 630 patients evaluated oral THC in capsule (206 patients), and oral cannabis extract 2.5 mg THC+1.25 mg CBD, plus <5% other cannabinoids in a capsule (211 patients) and 213 subjects on placebo for 15 weeks.[39] There were no objective effects on spasticity, but subjective improvement in spasticity was observed. There was objective improvement in mobility and reduced frequency of hospitalization with oral THC. Adverse drug reactions were mild and tolerable. One-year follow-up showed positive effects on spasticity. Another study [40], involving 160 patients, evaluated oral Sativex® (THC 2.5 mg plus 2.7 mg CBD) at doses of 2.5 to 120 mg/daily for six weeks. There was a significant reduction in spasticity, better sleep quality and mobility in patients treated with Sativex compared to placebo. Adverse events were mild and well-tolerated. Another small randomized, double-blind, parallel groups, placebo-controlled study of 64 subjects reported beneficial effects of THC+CBD (1:1 ratio) on pain and sleep disturbance when given for four weeks. Adverse effects included dizziness, dry mouth, and somnolence, while cognitive effects were limited to long-term memory storage.[41]

Spinal Cord Injuries. In one study of four patients, oral

THC or C. sativa extract containing cannabidiol or a combination of the two, administered in sublingual spray, showed some improvement in spasticity, muscle spasm, pain, vesical dysfunction, and sleep quality.[42]

Gilles de la Tourette's Syndrome: In two randomized, double-blind, placebo-controlled studies of cannabinols involved 12 patients in one study[43] and 24 patients in another,[44] oral THC (up to 10 mg/d for 6 weeks) significantly reduced the frequency of tics. No drug-related serious adverse effects were reported; however, one patient dropped out because of anxiety and agitation.

Epilepsy: There are no studies of clinical significance where THC alone was tested and found effective for treating epilepsy.

Glaucoma: In one study, eye drops containing 0.01, 0.05, and 0.1% THC significantly reduced the intraocular pressure. However, study subjects experienced significant adverse effects, including tachycardia, palpitations, and postural hypotension.[45] Cannabinoids seem to have potential to treat glaucoma, but the accompanying adverse systemic effects—such as reduced blood pressure, psychotropic effects, and development of tolerance—may discourage the development of cannabis formulations for this indication.[46]

Parkinson's Disease: In two studies, one involving seven patients[47] and the other involving 19 patients with Parkinson's disease[48]—no beneficial effects of oral THC (nabilone) were found.

Dystonia: One randomized, crossover placebo-controlled study of 15 patients found no beneficial effects of oral THC (nabilone) on generalized and segmental dystonia.[49]

Post-Traumatic Stress Disorder: There are studies to show that THC was is effective in the treatment of PTSD.

Cannabidiol (CBD)

Cannabidiol (CBD), is a non-psychoactive chemical constituent of C. sativa Linn.,[50] that acts via CB2 receptors in the body. According to pharmacological profile of CBD 13 and CBD's non-addictive, anti-inflammatory, neuroprotective, and antioxidant properties, CBD alone or in combination with other cannabinoids including THC, Mannucci et al. (2017)[51] recommended that additional clinical trials would be needed to confirm its use in treating neurological conditions like Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and cerebral ischemia. In combination with THC or by itself, CBD has been tested in numerous small clinical studies and clinical trials showing that it may have potential to treat these and other conditions like anxiety, depression, and many other non-CNS conditions such as acne, heart disease, inflammation, liver disease and cancer. The available evidence is briefly reviewed below.

Neuropsychiatric disorders

Epilepsy: The use of cannabis products in the treatment of epilepsy has long been of interest to researchers and clinicians alike; however, until recently very little published data was available to support its use in the treatment of epilepsy. Excellent reviews have been published on its potential to treat several forms of epilepsy. [52,53,54,55,56,57] The antiepileptic action of CBD has been further confirmed by small clinical studies [58] and large randomized, double-blind, placebo-controlled clinical trials.[59,60;61] In a randomized, dose-ranging safety trial of CBD in Dravet syndrome, 34 patients (10, 8, and 9) were randomized to three CBD dose groups of 5, 10 and 2 mg/kg/day and 7 patients to the placebo group. Thirty-two (94%) patients completed the study.[61] The plasma levels of CBD and its metabolites were dose-related. The most common adverse effects were pyrexia, somnolence, decreased appetite, sedation, vomiting, ataxia and abnormal behavior. Although the CBD-treated patients had more side effects than placebo, it was well tolerated. CBD (Epidiolex; GW pharmaceuticals); tested in a 12-wk trial in patients with treatment resistant epilepsy, was found effective in reducing seizures.[62] CBD treatment also improved the energy level, memory, control/helplessness, cognitive function, social interaction and general global quality of life of children with epilepsy.[63] It is important to note that of the 102 clinical trials registered on CBD in www.cliniclatrials.gov, 26 trials are studying the efficacy of CBD for the treatment of one or more types of seizures. Results from well planned and designed studies clearly showed that CBD (Epidiolex) was able to reduce the frequency of convulsions (tonic-clonic, tonic, clonic and atonic) seizures in patients with Dravet and Lennox-Gastaut syndromes.[61;64] In a 2013 survey of parents of children with treatment resistant epilepsy, it was found that 84% of respondents reported reduction of seizure frequency after taking CBD.[65] On June 25, 2018, the FDA approved CBD (Epidiolex) for the treatment of rare and severe forms of epilepsy-Lenox-Gastaut syndrome and Dravet syndrome in children two years of age and older. (https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm611046.htm).

Schizophrenia: Preclinical and clinical studies show that CBD could treat schizophrenia and other mental illness related to psychosis[66] and some of the positive symptoms of schizophrenia (hallucinations, delusions) and even negative symptoms of schizophrenia such as lack of emotion, loss of social functioning.[67] This effect of CBD on schizophrenia seems to be by increasing the naturally occurring endocannabinoid, anandamide,[68] thus CBD could be as effective as prescription antipsychotics in treating psychosis, with the added benefit of causing fewer side effects. On the other hand, although CBD was well tolerated with no worsening of mood, suicidality or movement side effects, it was ineffective at a dose of 600 mg/day in treating

the cognitive impairment and other neuropsychiatric complications seen in patients with schizophrenia.[69] CBD attenuated the decrease in hippocampal neurogenesis and dendrite spines density induced by chronic stress and prevented microglia activation and the decrease in the number of parvalbumin-positive GABA neurons in a pharmacological model of schizophrenia.[70] On the other hand, Khoury et al. (2017)[71] systematically reviewed the published studies and concluded that there was no strong evidence to support CBD use in psychiatry at this time and that large well-designed clinical trials are required to assess the effects of CBD in psychiatric disorders. Osborne and his colleagues [72] also suggested that the clinical evidence for treating schizophrenia associated cognitive impairment and other neurological disorders with CBD in humans is unconvincing at this time.

The prolonged treatment of regular cannabis users with 200 mg/day of CBD over a 10-week period reduced the neuroanatomical damage in the hippocampus without causing any significant adverse side effects, suggesting the neuroprotective role CBD plays against brain structural harm conferred by chronic cannabis use.[73] Thus, CBD might be a useful adjunct in the treatment of cannabis dependence and a range of clinical disorders characterized by hippocampal pathology (e.g., schizophrenia, Alzheimer's disease, and major depressive disorder).

Alzheimer's and Parkinson's diseases: CBD prevented the development of amyloid plaques, that are biological markers of Alzheimer's disease (AD), suggesting it could treat AD.[74] Watt et al. (2017)[75] also showed in-vivo evidence that would support its use in treating AD. However, according to Mannucci et al. (2017),[51] a significant amount of clinical research and clinical trials are needed to confirm its use in treating AD and other clinical conditions. In the case of Parkinson's disease (PD), limited data are available from controlled clinical trials in which patients with PD were successfully treated with cannabinoids. In an exploratory double-blind trial[76], seven patients with PD were either treated with placebo, 75 mg/day CBD or 300 mg/day of CBD. No significant effects on motor functions or general symptoms were found, although patients reported that their quality of life improved. CBD could improve the PD-related symptoms like REM-sleep disturbances and the quality of life of PD patients. In an open-label pilot study with six patients (4 men and 2 women) with a diagnosis of psychosis for at least 3 months, CBD at 150 mg/day for 4 weeks, in addition to their usual therapy, significantly decreased the total scores of Unified Parkinson's Disease Rating Scale, with no adverse effects, suggesting that CBD may be effective, safe, and well tolerated for the treatment of the psychosis in PD.[77]

Movement disorders/Multiple Sclerosis: Recently investigators found that CBD worked well in an animal model of MS by reducing the production of pro-inflammatory cytokines, possibly by activating an important biological pathway which is blocked in MS.[78] For its anti-inflammatory and neuroprotective effects, CBD was found effective in patients with multiple sclerosis (MS) with resistant spasticity [79] and in combination with THC (Sativex [THC:CBD in a 1.1 ratio]), effective in treating MS without adversely impairing driving performance, [80] and improving the mobility in patients with MS,[81] and in a small clinical trial, patients with moderate to severe MS and who were resistant to other drugs, improved in their spasticity-related symptoms when given Sativex. [82]

Trauma/Injuries/Stroke: CBD was tested for treating spinal cord or traumatic brain injuries that can have permanent life-altering effects and for which there are no effective treatments. In rats, when CBD was applied immediately before a spinal cord injury, the animals were less likely to display problems with movement over the week following the injury, suggesting that possibly CBD minimized the extent of the damage and allowed for a better overall recovery from the injury.[83] But studies in humans are needed to confirm its support in treating spinal cord injuries. Similarly, because of its neuroprotective effects seen in animal studies,[84] where CBD protected neurons following an injury, it was suggested that it could be developed to treat traumatic brain injury in humans. In the case of stroke, animal research in rats[85] and mice [86] show that CBD protected against brain damage seen in stroke. However, there are no data from studies in humans to support its use in treating stroke in humans.

Anxiety and depressive disorders: CBD appears to be a promising drug to treat anxiety disorders including opiate use disorder, panic disorders, generalized anxiety disorder, PTSD, and social anxiety disorder.[87] Several anecdotal reports also support the benefits of CBD for treating anxiety, but more clinical research is needed to support its use in treating anxiety disorders. Pre-clinical research show that CBD acts as an antidepressant by acting on serotonin pathways in the brain.[88] CBD can specifically reduce anhedonia, a symptom of depression that makes people unable to feel joy or happiness.[89] Since CBD activates the endocannabinoid system by increasing levels of naturally-occurring cannabinoids, such as anandamide, research suggests that changes in this endocannabinoid system may be involved in depression and therefore, CBD could treat depression. Since anxiety and depression occur in bipolar disorder, it has been suggested [90;91] that CBD may be able to provide mood stabilization in bipolar disorder too. On the other hand, even though animal research suggested that CBD could protect mania-related brain damage, [92] CBD failed to improve acute manic episodes of bipolar in patients with mania.[93]

Sleep Disorders: Research in animal models shows that CBD is effective in promoting wakefulness,[94] and may be related to CBD triggering increased levels of dopamine in areas of the brain responsible for wakefulness [95] suggesting that CBD could someday play a role in promoting wakefulness in disorders causing excessive sleepiness,

such as narcolepsy. In a case report, Shannon and Opila-Lehman (2016) [96] observed that CBD improved the quality and quantity of sleep of a 10-year old young patient with PTSD, likely due to its anxiety-relieving benefits.

Inflammation and Pain (Analgesic effect)

Based on preclinical evidence, several investigators suggested that CBD could treat inflammatory diseases of the gut such as colitis, [97] inflammatory bowel disease (IBD),[98] and Crohn's disease. [99] In a randomized, placebo-controlled trial with 20 patients with Crohn's disease, Naftali et al. (2017)[99] found that CBD at 10 mg/d, po, was safe but not effective in treating Crohn's disease, possibly due to small dose of CBD, the smaller number of patients, or lack of synergism with other cannabinoids and suggested further investigation. Cannabis is commonly used as an alternative to non-steroidal pain medications to treat different forms of pain. Studies in rats and mice CBD had positive effects against incision related pain. It reduced the sensory perception and emotional effects of pain.[100] Cannabidiol was ineffective at 45 mg/day for one week in patients with chronic neuropathic pain.[19] In an excellent review of the literature, (Darkovska-Serafimovska et al. 2018) [101] suggested that CBD could treat cancer pain with mild to moderate side effects such as drowsiness, nausea, vomiting, and dry mouth, but Mucke et al. (2018)[102] concluded that the potential benefits of cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC, and THC/CBD oromucosal spray) in chronic neuropathic pain might be outweighed by their potential harms. The quality of evidence for pain relief outcomes reflects the exclusion of participants with a history of substance abuse and other significant comorbidities from the studies, together with their small sample sizes. Hauser et al. (2017)[103] concluded that there is limited evidence for a benefit of THC/CBD spray in the treatment of neuropathic pain, but there is inadequate evidence for any benefit of cannabinoids (dronabinol, nabilone, medical cannabis, or THC/CBD spay) to treat cancer pain, pain of rheumatic or GI origin, anorexia in cancer or AIDS. Treatment with cannabis-based medicines is associated with central nervous and psychiatric side effects and concluded that the public perception of the efficacy, tolerability, and safety of cannabis-based medicines in pain management and palliative medicine conflicts with the findings of systematic reviews and prospective observational studies conducted according to the standards of evidence-based medicine.

Antiemetic effect (Nausea)

The proposed use of CBD for nausea is relatively more recent. Preclinical research from animal studies showing antiemetic effects of CBD in animals suggests that CBD may stop nausea and vomiting in humans too. CBD may be particularly helpful in treating nausea in patients that are not getting relief from prescribed anti-nausea drugs.[104]

Appetite Stimulant

Although smoked cannabis has been shown to increase appetite and weight gain in patients with HIV/AIDS[27] without affecting viral load, and the oral THC also increased weight gain in patients with cachexia (extreme loss of weight),[31] there are no studies in humans where CBD was tested for appetite stimulant properties.

Treatment of Substance Use Disorders (e.g., tobacco, opiate, cannabis)

Studies have been conducted to see if CBD could be used to treat tobacco, opiate, and/or cannabis use disorders. In a 2013 study by Morgan et al. (2013),[105] 24 tobacco smokers were randomized to receive an inhaler of CBD or placebo for one week. They were instructed to use the inhaler whenever they felt a craving to smoke. Over the course of one week, those taking the CBD inhaler reduced their number of cigarettes smoked by 40% while those receiving the placebo inhaler did not decrease the number of cigarettes they smoked. In a randomized, double-blind, placebo controlled cross-over study,[106] a single dose of 800 mg oral dose of CBD, reduced the salience and pleasantness of cigarette cues, compared with placebo, after overnight cigarette abstinence in dependent smokers, but CBD did not influence tobacco craving or withdrawal or any subjectively rated side effects. When tested in chronic cannabis users to see if CBD treatment would protect against brain structural harms conferred by chronic cannabis use, CBD showed restorative effect on the subicular and CA1 subfields in current cannabis users, especially those with greater lifetime exposure to cannabis.[73] In a randomized, double blind, placebo-controlled trial, nabiximols (THC+CBD [Sativex]) combined with Motivational Enhancement Therapy and Cognitive Behavioral Therapy (MET/CBT), was well tolerated and reduced cannabis use and craving but not withdrawal symptoms in chronic cannabis users.[107] Future trials with higher doses of CBD were recommended for patients with cannabis dependence. CBD was also tested to see if it would treat psychological symptoms and cognitive function in chronic cannabis users.[108] Although, CBD was well tolerated with no reported side effects, participants retrospectively reported reduced euphoria when smoking cannabis. There were no impairment of cognition or psychological function. Importantly, participants reported significantly fewer depressive and psychotic-like symptoms at post-treatment relative to base-line, and exhibited improvements in attentional switching, verbal learning, and memory. Increased plasma CBD concentrations were associated with improvements in attentional control and beneficial changes in psychological symptoms. Greater benefits were observed in dependent than in nondependent cannabis users. It was concluded that prolonged treatment with CBD appeared to have promising therapeutic effects for improving psychological symptoms and cognition in regular cannabis users. CBD may be a useful adjunct treatment for cannabis dependence.

Miscellaneous studies

CBD has been tested for antidiabetic,[109] hemodynamic [110,111] apoptotic, cell proliferation and anticancer effects [112] and see if it would treat diabetes or glycemic control, high blood pressure, cancer or even viral hepatitis.[113] In a comprehensive review, the National Academy of Sciences[23] concluded that cannabis and cannabinoids have potential to treat a wide range of health ailments.

Thus, clinical research reviewed above and for the fact that there are approximately 100+ clinical trials registered at www.clinicaltrials.gov where CBD is being tested for treating health conditions ranging from anxiety, depression, epilepsy/seizures, Parkinson's disease, psychosis, schizophrenia, IBD, Crohn's disease, alcohol use disorder, cocaine use disorder, neuropathic pain, and others clearly suggests that CBD could be developed as a medicine.

Tetrahydro-Cannabivarin (THCV)

Since its first discovery by Merkus (1971)[114] as one of the two cannabinoids in hashish and later detected in urine of cannabis users,[115,116] THCV has been tested for its pharmacologic activity in numerous animal studies but only a few human studies. It antagonizes anandamide [117] and some of the THC effects[118] and has high affinity for CB2 receptors thereby it differs from CBD and rimonabant.[119] Since it acts on cannabinoid receptors like CBD, it may have therapeutic potential to treat a wide range of health conditions.[120]

THCV has antipsychotic, anti-inflammatory and immunomodulatory properties. Through its enhancing effects on 5-HT1A1 receptors and its anti-psychotic activity, it could treat some of the negative effects of schizophrenia.[121] Besides other cannabinoids like CBG, CBD, and CBDV, THCV has potential to treat neurodegenerative disorders like epilepsy.[122-123] In a small pilot trial, Δ^9-THCV was well tolerated at a dose of 10 mg and inhibited the THC-induced verbal recall while potentiating the memory effects of Δ^9-THC. But due to small sample size, dose selected, and lack of Δ^9-THC-induced psychotomimetic and memory-impairing effect, these findings should be interpreted with caution.[124] By activating CB2 receptors and down-regulating CB1 receptors or expression of TRP channel mRNA, it inhibited nitrite production in macrophages[125] and affected human sebocyte function and thus it could also treat dry skin conditions like acne (that is due to increased activity of sebaceous glands) and psoriasis.[126] Since it affected both the activity and the expression of transient receptor potential (TRP) channels of vanilloid type-1 or 2 (TRPV1, TRPV-2), it could treat inflammatory conditions in the GI tract.[127] It could also treat inflammatory pain in mice.[128]

THCV showed anti-nausea effects in rats.[129] In terms of metabolic activity, it showed hypophagic activity in mice[130] via both reward and aversion to food mechanisms in the midbrain, anterior cingulate cortex, putamen and caudate, suggesting its therapeutic potential in treating obesity.[131] THCV ameliorated insulin sensitivity, did not increase food intake or body weight, increased slightly the energy expenditure, and dose-dependently reduced glucose intolerance in ob/ob mice, without consistently affecting plasma lipids. THCV restored insulin signaling in insulin-resistant hepatocytes and myotubes, thereby suggesting that THCV may be a novel therapeutic agent to treat obesity-associated glucose intolerance with pharmacology different from that of CB1 inverse agonists/antagonists.[132]

In a randomized, double-blind, placebo-controlled study, THCV significantly decreased fasting plasma glucose and improved pancreatic B-cell function, adiponectin and apolipoprotein-A, suggesting that THCV could represent a new therapeutic agent in glycemic control in subjects with type2 diabetes.[109] THCV also reduced the intracellular lipid levels and adipocytes in hepatocytes, suggesting that THCV might treat obesity-and metabolic syndrome-related NAFLD/hepatosteatosis.[133]

THCV was found to be better than CBD and cannabidivarin (CBDV) in decreasing the acetylcholine-induced contractions in the mouse and human bladder and thus could treat bladder dysfunction.[134] Finally, CBD, CBDV, cannabigeral (CBG), and THCV readily penetrated the blood brain barrier despite moderate behavioral anomalies, but higher concentrations with oral administration and not intraperitoneal route. In mice, the intraperitoneal route gave higher concentrations than oral route, while in rats, oral route resulted in higher brain levels of CBD and CBDV but not THCV and CBG, and for CBG, the intraperitoneal route was more effective. These data suggested that the route of administration must be kept in mind when administering different cannabinoids.[135]

THCV also has potential to treat oxidative stress and inflammation induced conditions like cancer, pain, neurodegeneration, cardiovascular disease, obesity and metabolic syndrome, diabetes and diabetic complications, diabetic cardiovascular dysfunction, nephropathy, retinopathy, and neuropathy.[136] Finally, due to detection of THCV in oral fluids and urine of people who smoked cannabis,[115,116] it was suggested that THCV could serve as a marker of illegal use/smoking of cannabis.[137;138,139] But among those prescribed dronabinol[140] or Marinol,[116] THCV may not have the sensitivity to detect cannabis use, possibly due to variability of available cannabis strains smoked by cannabis users in community settings.[140]

Cannabidivarin (CBDV):

CBDV, first isolated from Cannabis sativa Linn.,[141] occurs in high concentrations in cannabis from northern India, C. indica, in Hashish from Pakistan, and in small concentrations in Mexican varieties of cannabis. It is found in plants that are rich

in CBD and low in THC. It is a non-psychoactive component of cannabis. Several mechanisms seem to be involved in the antiepileptic activity of CBDV.[142,52,143,144,145,146,123,147] CBDV may act via CB1 and CB2 receptors and modulate neuronal excitability and neuroinflammation, may act via TRPV1, CB1-independent mechanisms[143;144] including voltage gated potassium and sodium channels, GPR55123, desensitization of TPRV1148, GABAergic system[147], or through the expression of epilepsy-related genes (Fos, Casp3, Ccl3, Cc14, Npy, Arc, Penk, Cam2a, Bdnf, and Egr1) in the hippocampus, neocortex and prefrontal cortex.[149] These results provide the first molecular confirmation of behaviorally observed effects of CBDV, upon chemically-induced seizures and serve to underscore its suitability for clinical development.

Recently a patient with symptomatic partial epilepsy self-medicated himself with cannabis after the failure of countless pharmacological/surgical treatments. Clinical and video EEG evaluations were periodically performed, and the serum levels of CBDV, CBD, and Δ^9-THC were repeatedly measured. There was a dramatic clinical improvement in seizure frequency and cognitive function, with parallel high plasma concentrations of CBDV.[147] Several clinical studies/trials are underway to study a wide range of ailments including epilepsy that could be treated with CBDV, CBD, and other cannabinoids. Like CBC, CBDV also has anti-inflammatory activity on human sebocytes and could treat dry skin conditions like acne;[126] and it acts on human and animal bladder contractility.[134] Finally, CBDV acts as a CB1 receptor inverse agonist and could be developed to treat nausea.[129]

Cannabigerol (CBG):

Cannabigerol showed beneficial effect on neuroinflammatory and neurodegenerative processes through cell membrane cannabinoid receptor-dependent and -independent mechanisms in a chronic model of multiple sclerosis. It ameliorated the symptoms associated with TMEV infection (Theiler's Murine Encephalomyelitis Virus, a model for studying multiple sclerosis) decreased microglia reactivity and modulated the expression of genes involved in MS pathophysiology. Granja et al. (2012)[150] suggested that CBG could be developed to treat MS and perhaps other neuroinflammatory diseases. Several in-vivo studies show that it has antioxidant and anti-inflammatory properties and may treat oxidative-stress related disorders [151] and inflammatory conditions in the gut such as colitis,[97] and since it attenuated murine colitis, reduced nitric oxide production in macrophages, and reduced ROS formation in intestinal epithelial cells, it could be considered for clinical experimentation in IBD patients.[152] CBG reduced arachidonic acid-induced 'acne-like' lipogenesis,[126] and inhibited proliferation of human epidermal keratinocytes via non-CB1/CB2 mechanisms,[153] it could treat acne and psoriasis. CBG blocked progression of colon cancer in vivo and selectively inhibited the growth of colorectal cells (CRC), the investigators suggested that CBG could be developed to curing colon cancer.[154] It inhibited the growth of breast cancer cells [155] and the growth of human oral epithelioid carcinoma cells.[156]

CBG reduced the intraocular pressure (IOP) in the Brown Norway rat,[157] and in the cat [158] but not in the monkey.[159] There are no human studies where CBG was tested for treating glaucoma. CBG elicited hyperphagia by reducing latency to feed and increasing frequency of food intake without any effects on neuromotor activity in rats and thus was suggested for developing for treating conditions like cachexia and other disorders of eating and body weight regulation[160]. But in the satiated rat, CBD did not show such effects on feeding, while CBD did[161]. Like other cannabinoids CBC, THCV, and CBD, CBG also reduced the acetylcholine-induced contractions in the mouse and human bladder.[134] Both CBG and THC suppressed dose-dependently the FSH-stimulated accumulation of progesterone and estrogen biosynthesis thereby showing anti-gonadal activity in vitro;[162] and because plasma concentration of THC similar those used in this study have been reported in humans, repeated exposure of females to THC may lead to ovarian dysfunction, due in part, to the direct anti-gonadal activity to THC.

Cannabichromene (CBC)

Cannabichromene has positive effects on mouse neural stem/progenitor cells (essential for brain function) and could be used to treat neuroinflammatory conditions including seizures/epilepsy[163]. Independent of cannabinoid receptors or TRPV1 receptors[164], it selectively reduced inflammation-induced hypermotility in mice. It regulates the production of inflammatory cytokines such as MCP-2 [monocyte chemotactic protein], intraleukin-6 (IL-6), intraleukin-8 (IL-8) and tumor necrosis factor (TNF-alpha) and thus could treat allergic contact dermatitis [165] and dry skin conditions like acne due to its antifibrotic action on mouse and human skin sebocytes[126]. Finally, CBC is metabolized by cardiac CYP450 (CYP2J2 resulting in reduction in the formation of cardioprotective epoxides, the possible mechanisms of cardiac complications of cannabinoids, particularly CBC and Δ^9-THC.[166]

Cannabivarin (CBV)

Since its discovery by Merkus[114] in 1971 as one of the new cannabinoids in Hashish, no preclinical or clinical data are available on CBV.

CONCLUSION

Though cannabis has been legalized as medicine in many parts of the world, research clearly shows that at least smoked cannabis is of very limited clinical value. Its main psychoactive and addictive cannabinoid, THC, has been approved for the treatment of chemotherapy-induced nausea and vomiting, anorexia, and in combination with its non-psychoactive component, cannabidiol (Sativex)

for nausea and vomiting, appetite stimulation, and neuropathic pain in several countries except in the United States. Cannabidiol (Epidiolex) is also approved for treating a specific type of epilepsy-Dravet and Lenox-Gastaut syndromes in children two years of age and older. Further, clinical research and several clinical trials underway also suggests that there is little doubt that CBD has a great potential to treat a wide range of clinical conditions/ diseases (Figure 2) including anxiety, depression, neuropathic and other chronic pain conditions, Alzheimer's and Parkinson's diseases, MS, PTSD and inflammatory conditions. Much more systematic research including well-designed clinical trials are needed to further develop CBD as medicine and get it approved by a regulatory agency like the US Food and Drug Administration for its clinical use. With additional research, CBD may become a demonstrably effective medication to be indicated for a range of symptoms and/or medical/psychiatric disorders, with a better clinical understanding of appropriate dosing and tolerability data. Much work is also needed on other cannabinoids of the plant such as tetrahydrocannabivarin, cannabigerol and cannabidivarin before any of them is prescribed as medicine. We concur with the National Academy of Sciences,[23] ASAM,[167] and other medical organizations that have recommended that additional research be conducted before cannabis products can be prescribed for other clinical indications.

Figure 1: Cannabinoid biosynthesis, part 1-CBG, THC, CBD, and CBC (Burke, A., 2014) [9]

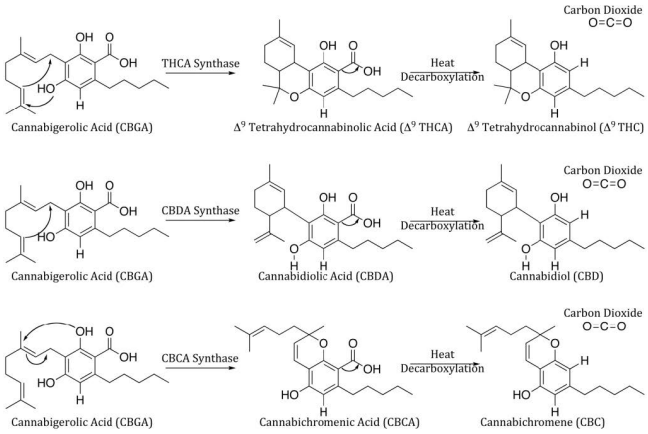
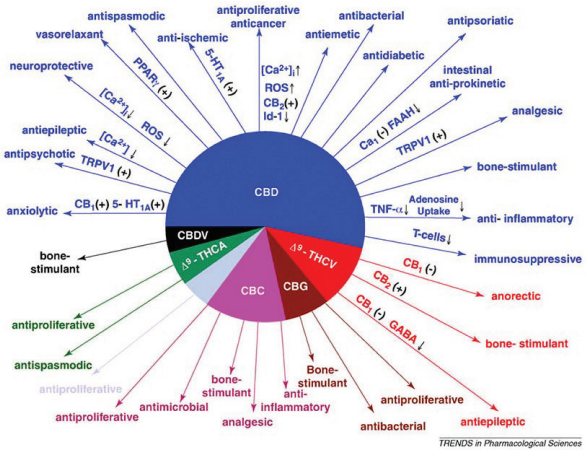


Figure 2: Pharmacologic actions of non-psychotropic cannabinoids (with the indication of possible mechanisms of action).[13] (Izzo et al. 2009)



ملخص:

يظل القنب العقار المحضورالأكثر تعاطيا في العالم في الوقت الذي يستمرفيه الجدال في الولايات المتحدة الأمريكية و غيرها من الدول حول السماح باستخدام القنب و مشتقاته كعقاقير دوائية. و رغم قلة الأدلة العلمية و السريرية التي تدعم الرأي القائل بأحقية استخدامه كدواء هناك العديد من المناطق في الولايات المتحدة الأمريكية و دول أخرى رخصت الإستخدام العلاجي للقنب. و في الوقت الحاضر وبناء على بحوث سريرية و غير سريرية فقد تم ترخيص إنتاج القنب الصناعي بمفرده، كعقار «الدرونابينول» و عقار «النابيلون» و مزجهما مع عقار «الكنابديول» (سافيتكس) واعتماده كدواء. و إضافة لذلك، تم مؤخرا اعتماد عقار «الكنابديول» كعلاج لداء الصرع عند الأطفال. و تشير البحوث كذلك أن هناك إمكانية كبيرة لتطوير عقار «الكنابديول» لعلاج كم من الحالات السريرية كأوجاع الإعتلال العصبي و داء ألزهايمر و باركنسون و داء تصلب الأنسجة و القلق و الإكتئاب والتهابات الجهاز الهضمي. إلا أن الدراسات المتوفرة في الوقت الحاضر لا تدعم استخدام القنب عن طريق التدخين كوسيلة علاجية لأي من الحالات الصحية المذكورة أعلاه. و رغم أنه تم إقامة دراسات قبل السريرية و دراسات سريرية على مشتقات القنب الأخرى كعقار «التتراهيدوكنابيفارين» و «كنابيجيرول» و غيرها إلا أن البحوث المتوفرة في الوقت الراهن تشير إلى ضرورة بذل مجهودات أوفر قبل أن يعتمد كل عقار بمفرده كدواء من قبل السلطات التنظيمية في البلد كإدارة الغذاء و الدواء في الولايات المتحدة الأمريكية على سبيل المثال.

Cannabis/cannabinoïdes comme médicament : sommes-nous là?

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Abstrait :
Le cannabis reste la drogue illicite la plus utilisée dans le monde aujourd'hui. Il y a un débat féroce en cours aux États-Unis et ailleurs si d'approuver le cannabis et ou ses produits comme un médicament. Malgré le manque de preuves scientifiques et cliniques suffisantes pour soutenir le cannabis comme médicament, de nombreuses parties des États-Unis et d'autres pays l'ont légalisée comme médicament. Actuellement, sur la base de recherches précliniques et cliniques, des produits tels que le THC synthétique seul, p. ex., dronabinol et nabilone et en combinaison avec le cannabidiol (SATIVEX) ont été approuvés comme médicament. En outre, cannabidiol a également été récemment approuvé pour le traitement de l'épilepsie chez les enfants. La recherche montre également que cannabidiol semble avoir un grand potentiel pour le développement comme médicament pour être en mesure de traiter un large éventail de conditions cliniques allant de la douleur neuropathique à l'Alzheimer et les maladies de Parkinson, la sclérose musculaire, l'anxiété, dépression aux conditions inflammatoires du système gastro-intestinal. Toutefois, les recherches actuellement disponibles ne soutiennent pas l'utilisation du cannabis fumé comme médicament pour traiter l'un des problèmes de santé mentionnés ci-dessus. D'autres cannabinoïdes tels que Cannabichromène, tétrahydro-cannabivarin, Cannabigérol et d'autres, bien que étudié dans de nombreuses études précliniques et cliniques, la recherche jusqu'à présent suggère que beaucoup de travail est encore nécessaire avant que l'un d'eux peut être individuellement approuvés comme médicament par un organisme de réglementation d'un pays comme l'administration des aliments et des médicaments des États-Unis.

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