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Review: Cannabinoids as Medicinals

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Abstract

Purpose of review There have been many debates, discussions, and published writings about the therapeutic value of cannabis plant and the hundreds of cannabinoids it contains. Many states and countries have attempted, are attempting, or have already passed bills to allow legal use of cannabinoids, especially cannabidiol (CBD), as medicines to treat a wide range of clinical conditions without having been approved by a regulatory body. Therefore, by using PubMed and Google Scholar databases, we have reviewed published papers during the past 30 years on cannabinoids as medicines and comment on whether there is sufficient clinical evidence from well-designed clinical studies and trials to support the use of CBD or any other cannabinoids as medicines.

Recent findings Current research shows that CBD and other cannabinoids currently are not ready for formal indications as medicines to treat a wide range of clinical conditions as promoted except for several exceptions including limited use of CBD for treating two rare forms of epilepsy in young children and CBD in combination with THC for treating multiple-sclerosis-associated spasticity.

Summary Research indicates that CBD and several other cannabinoids have *potential* to treat multiple clinical conditions, but more preclinical, and clinical studies and clinical trials, which follow regulatory guidelines, are needed to formally recommend CBD and other cannabinoids as medicines.

Keywords Cannabis · Cannabinoids · Delta-9-tetrahydrocannabinol · THC · Cannabidiol · CBD · Substance-related disorders

Introduction

Cannabis sativa, Linn., is a complex plant that has 567 chemicals of which 125 have been identified and characterized as cannabinoids, and the remaining chemicals are terpenes, flavonoids, and alkaloids. Most recently, Radwan et al. [1•] have identified several additional cannabinoid-like chemicals in *C. sativa* varieties grown in different regions of the USA. Several cannabinoids including cannabidiol (CBD), cannabichromene (CBC), cannabidiolic acid (CBDA), delta-9-tetrahydrocannabivarin (Δ^9-THCV), cannabinol (CBN), delta-9-tetrahydrocannabivaric acid (Δ^9-THCAA), cannabigerolic acid (CBGA), cannabigerol (CBG), and delta-8-tetrahydrocannabinol (Δ^8-THC) have been postulated to exhibit some medicinal value [2]. Based on the pharmacology of cannabinoids [3•], only two cannabinoids—Δ^9-THC, the most psychoactive component of the plant, and CBD, a non-psychoactive component, have been extensively studied for their potential therapeutic applications. Both CBC and CBL (cannabicyclol) have no psychoactive properties [4]. While much work has been conducted with the most prominent cannabinoids, Δ^9-THC and CBD, limited preclinical and almost non-existent clinical research exists on other cannabinoids. During the last decade, numerous investigators have published excellent systematic reviews of the published preclinical and clinical research suggesting that cannabinoids have potential to treat a wide range of clinical conditions [5, 6•, 7–11]. However, the research reviewed has been limited to only two cannabinoids, THC and CBD. Furthermore, many researchers have concluded that there is a lack of sufficient clinical research to support the use of any cannabinoid as medicine at this time and have recommended additional research.

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In this narrative review, based on review of the published research, retrieved from PubMed and Google Scholar, and without duplicating what has already been published, we wish to report on the currently available clinical evidence on not only THC and CBD, but also on other discovered cannabinoids of C. *sativa* plant as medicinals and comment on whether the evidence is sufficient to support their use as medicines.

Cannabinoids

Delta-9-tetrahydrocannabinol (Δ^9-THC)

Delta-9-tetrahydrocannabinol, the most psychoactive component of C. *sativa* plant, has been studied in numerous preclinical and clinical studies and clinical trials for its therapeutic value in treating a wide range of clinical conditions including nausea/vomiting [12], anorexia, appetite stimulation, sleep apnea [13], dystonia, Parkinson's disease (PD), Alzheimer's disease (AD), agitation associated with AD [14] to post-traumatic-stress-disorder (PTSD) and others with limited success.

In a small study of seven patients, treatment with THC (nabilone) was linked to improved motor scores on the Unified Huntington's Disease Rating Scale (UHDRS) for chorea and dystonia. There was clinical improvement of gait, fine motor skills, and weight gain. There was less irritability, apathy, and less hypersalivation in some cases [15].

In a 14-week randomized, double-blind, crossover trial, Herrmann and colleagues [16] examined safety and efficacy of nabilone at doses of 1–2 mg in 39 patients (mean age of 87 years) with moderate-to-severe AD with agitation/aggression. They found that nabilone may be an effective treatment for agitation but suggested that sedation and cognition should be closely monitored. It is important to note that in the nabilone treatment group, there were a total of 51 adverse events including treatment-related sedation relative to 14 in the placebo group. In addition, one death occurred during the placebo washout phase (sudden death) following 6 weeks of the placebo phase, and one participant died on the last day of nabilone treatment (suspected stroke), after being titrated down to 0.5 mg.

Nabilone has been suggested as a treatment for PTSD [17], but according to Hindocha and colleagues [18], 'most studies to date are small and of low quality, with significant limitations to the study designs precluding any clinical recommendations about its use in routine clinical practice.' According to the investigators, the evidence is weak and additional well-designed, randomized, double-blind clinical trials are needed to support the use of cannabinoids in treating PTSD and associated symptoms like sleep disturbances and nightmares.

In a placebo-controlled, randomized trial, dronabinol at doses of 2.5 mg or 10.0 mg dose-dependently improved sleep apnea, self-reported sleepiness, and overall treatment satisfaction [13]. In the case of dystonia, in one randomized, double-blind, crossover placebo-controlled study of 15 patients, oral nabilone did not show any beneficial effects on generalized and segmental dystonia [19].

Both dronabinol and nabilone have been associated with adverse effects. Based on a survey of 10,010 subjects in a database in Germany, it was found that the use of dronabinol (65%), nabilone (0.3%) or Sativex (13%), for spasticity or anorexia/wasting was associated with adverse effects like tiredness, dizziness, dry mouth, and nausea. The potentially serious adverse effects of depression, suicidal ideation, delusions, hallucinations, dissociation, and misperceptions were each reported with frequencies higher than 0.1% [20].

Nabilone, as compared to placebo, failed to reduce cannabis use in 10 patients with cannabis use disorder [21]. Nevertheless, based on results from several preclinical and clinical studies and trials, synthetic THC (dronabinol, Marinol) [22–24] has been approved for the treatment of anorexia associated with weight loss in AIDS patients and chemotherapy-induced nausea and vomiting [25].

Nabilone [Cesamet®] is a synthetic cannabinoid like THC. Nabilone has been approved for the treatment of nausea and vomiting in patients undergoing cancer treatment [26]. THC in combination with CBD in a 1:1 ratio (nabiximols, Sativex®, an oral spray) is approved in 28 countries including Canada for treatment of moderate to severe spasticity due to multiple sclerosis (MS) in patients who have not responded adequately to other treatments. However, it has not yet been approved in the USA.

Whether THC alone will be further developed to treat other clinical conditions remains to be seen. However, due to its strong psychoactive properties and possible psychotogenic effects, it appears unlikely that THC alone will be further developed and approved as medicine for treating other clinical indication in near future. However, a non-psychoactive component of cannabis, CBD, has shown significant potential to treat several clinical indications, and these are further discussed in more detail below.

Cannabidiol (CBD)

CBD, one of the 125 cannabinoids present in Cannabis *sativa*, Linn., is a non-psychoactive chemical constituent [27] that acts via CB2 receptors in the body and other molecular targets discussed by Izzo and colleagues [28]. CBD is relatively safe. However, interactions between CBD and THC occur [29]. In a randomized, placebo-controlled trial, CBD alone, THC alone and CBD plus THC were tested for safety in a group of 36 (31 male) participants. Doses tested were placebo, CBD alone at 400 mg, THC alone at a dose

of 8 mg or THC plus 4 mg or 400 mg CBD. The low doses of CBD significantly ($p < 0.0001$) enhanced, while the high doses of CBD reduced the intoxication effects of THC. The enhancement of intoxication by low-dose CBD was particularly prominent in people with infrequent cannabis use and was consistent across objective and subjective measures. The investigators suggested that 'these findings should be considered when recommending proportions of THC and CBD in cannabis plant matter whether used medicinally or recreationally by people without or people with less cannabis histories' [30]. Furthermore, the use of CBD at oral dose of 200 mg daily for 10 weeks was also safe without any adverse psychological and cognitive effects in 20 individuals with frequent cannabis use [31].

CBD, given its non-addictive, anti-inflammatory, neuroprotective, and antioxidant properties, alone or in combination with other cannabinoids including THC, could potentially produce beneficial effects in PD, AD, MS, Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and cerebral ischemia [32]. However, additional clinical trials are needed to confirm its safety and efficacy in each of these neurological conditions. CBD in combination with THC or by itself 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.

Epilepsy: The use of cannabis products in the treatment of epilepsy has long been of interest. CBD interacts with human 5-HT_{1A} receptors of the hippocampus and temporal neocortex. At concentrations of 1 μM to 10 μM, the effect of CBD upon $G_{i/o}$ protein activation is limited. However, at a concentration of 100 μM, CBD acts as an inverse agonist of 5-HT_{1A} receptors and thus could modify neuronal excitation and epileptic seizures in patients with drug-resistant mesial temporal lobe epilepsy (DR-MTLE; [33]). CBD, given its antiepileptic potential, could treat several forms of seizures [34–38].

Small clinical studies [39] and large randomized, double-blind, placebo-controlled clinical trials [40•, 41] have further confirmed antiepileptic effects of CBD. For an example, 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 20 mg/kg/day and 7 patients to the placebo group. Thirty-two (94%) patients completed the study. There were dose-related changes in plasma levels of CBD and its metabolites. The most common adverse effects were pyrexia, somnolence, decreased appetite, sedation, vomiting, ataxia, and abnormal behavior. Although the CBD-treated patients had more adverse effects than placebo, CBD was well tolerated [41]. CBD tested in a 12-week trial in patients with treatment-resistant epilepsy, was efficacious in reducing seizures [42]. CBD treatment was also linked to improved energy level, memory, control/helplessness, cognitive function, social interaction, and general global quality of life in children with epilepsy [43]. Results from these studies provide support for CBD in reducing the frequency of convulsions (tonic–clonic, tonic, clonic and atonic) seizures in patients with Dravet and Lennox-Gastaut syndromes [41].

CBD (Epidiolex) is approved for treating only two rare conditions of seizures—a rare form of epilepsy, known as Lenox-Gastaut and Dravet syndromes in patients two years of age and older [44], and a rare genetic condition known as tuberous sclerosis, where people suffer from seizures from benign tumors in the brain. Incidentally, it is important to note that as of February 8, 2022, of the 245 clinical trials registered on CBD [45], 31 trials are studying the efficacy of CBD for the treatment of one or more types of seizures [45].

Autism: Autism-spectrum disorder (ASD) is a neurodevelopmental disorder characterized by core deficits in social communication and restricted, repetitive patterns of behavior for which there are only two FDA-approved medications, risperidone, and aripiprazole, for ASD-associated irritability. Data from several small clinical studies suggest that cannabis and cannabinoids, including CBD and CBDV, although not approved by the FDA, may have potential in treating not only the core symptoms of ASD but also irritability and behavioral problems in ASD [46].

CBD-rich medical cannabis appears to be safe, efficacious, and tolerable for treating many ASD-associated symptoms [47]. For example, treatment with CBD (containing < 3%THC) at an average daily dose of 0.7 mg/kg/d for 6.5 months was associated with improved behavioral problems, cognition, expressive language, and social interaction in 33 (27 males and 6 females; mean age of 7.7 ± 5.5 years) individuals with ASD [48]. In an observational study, CBD-enriched cannabis extract also was associated with improved ASD symptoms in 15 of the 18 ASD patients [49]. In a retrospective study of 60 children (mean age of $11.8 + 3.5$, range 5.0 to 17.5 years) with ASD and severe behavioral problems, CBD-rich cannabis treatment was also safe and reduced the behavioral problems in 61% of patients, suggesting that it is feasible to conduct clinical trials to determine if CBD can be used to treat children with ASD [50]. Furthermore, Pretzsch and colleagues showed that CBD affects the brain function in patients with ASD. In an fMRI study of men with ASD, they showed that, compared to placebo, a dose of 600 mg CBD significantly increased the amplitude of low-frequency fluctuations in the cerebellar vermis and the right fusiform gyrus, the areas important for movement, language, and social processing [51].

Schizophrenia: Preclinical and clinical research show that CBD may have efficacy in treating schizophrenia and other psychotic disorders [52]. CBD may help improve positive symptoms of schizophrenia (hallucinations, delusions) and

negative symptoms of schizophrenia such as lack of emotion, loss of social functioning [53], possibly by increasing the naturally occurring endocannabinoid, anandamide [54].

According to Boggs et al., CBD could be as effective as prescription antipsychotics in treating psychosis, with the added benefit of generating fewer adverse effects. However, in a randomized, placebo-controlled trial, although CBD at an oral dose of 600 mg/d was well tolerated without worsening of mood, suicidality, or movement adverse effects, it was not efficacious in treating the cognitive impairment and other neuropsychiatric complications seen in patients with schizophrenia [55]. Taken together, the current evidence is unconvincing for supporting CBD use in psychotic disorders, and large well-designed clinical trials are required to assess the effects of CBD in psychotic and other psychiatric disorders [56•, 57].

Anxiety Disorders and Depression: Given CBD effects on serotonergic, GABAergic and other neurotransmitter systems, it may hold promise for treating disorders of generalized anxiety, social anxiety, panic, and post-traumatic stress [58]. Preclinical research shows that CBD may exert antidepressant effects by impacting serotonin pathways in the brain [59], and CBD may reduce anxiety through 5-HT_{1A} receptor activation in rats [60]. Thus, CBD may act as an antidepressant [61], and via its effects on specific $GABA_A$ receptor subtypes, as an anxiolytic agent [62]. When CBD was tested at an oral dose of 30 mg/kg orally in two 'depressive-like' genetic models of rats, Wistar Kyoto and Flinders Sensitive Line, the results showed that CBD also decreased immobility of rats in the forced swim test in males of both strains and in female of Wistar Kyoto strain, suggesting a role of CBD in treating mental disorders with prominent symptoms of helplessness and anhedonia (diminished feeling of joy or happiness) [63, 64].

Since CBD also increases the levels of naturally occurring endocannabinoids, such as anandamide, CBD may also hold promise for treating depression [59]. Since anxiety and depression occur in bipolar disorder, it has been suggested [65, 66] that CBD may stabilize mood in bipolar disorder too. However, CBD failed to improve acute manic episodes of bipolar in patients with mania [67], even though animal research suggested that CBD may mitigate potential mania-related brain damage [68].

Alzheimer's and Parkinson's diseases: CBD may prevent the development of amyloid plaques, a biological marker of AD, suggesting it could help treat AD [69, 70]. In vivo evidence where CBD coated by nano-chitosan showed good potential for reducing plaques, increasing brain CB1 and levels CB2, and improving learning and memory in Alzheimer's rats [71] also suggests the possible utility of CBD in treating AD [72], but additional clinical research is needed to confirm its clinical potential in treating AD [32].

Limited data from controlled clinical trials also suggest efficacy of treating PD with CBD. In an exploratory double-blind trial [73], seven patients with PD were either treated with placebo, 75 mg/day of CBD or 300 mg/day of CBD. Neither motor functions nor general symptoms improved, although the quality of life of patients improved. CBD may potentially reduce PD-related symptoms like REM-sleep disturbances and improve the quality of life of PD patients [74].

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. These findings raise the possibility that CBD may be effective, safe, and well tolerated for the treatment of the psychosis in PD [75].

Movement disorders/Multiple Sclerosis: In an animal (C57/BL6 mice) model of multiple sclerosis, CBD promoted neuronal survival by inhibiting JNK and p38 MAP kinases, suggesting that the regulation of an important biological pathway, PI3K/Akt/mTOR, by CBD administration, could be a potential therapeutic target for MS [76]. With its anti-inflammatory and neuroprotective effects [77, 78], CBD was found to be efficacious in patients with MS with resistant spasticity [79]. CBD treatment also was associated with improved mobility in patients with MS [80], 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 (CBD-THC in 1:1 ratio; [81]).

Cannabinoids have been reported to be efficacious in treating dystonia symptoms in seven patients with Huntington's disease [15]. Nevertheless, based on data from clinical trials, Sativex was found efficacious in treating MS-related neuropathic pain without adversely impairing driving performance [82] and has been approved in 28 countries including Canada. However, it has not yet been approved in the USA.

Trauma/Injuries/Stroke: Although there are no data from clinical studies to show that CBD would be effective in treating stroke and/or spinal cord injuries in humans, data from preclinical studies suggest that CBD could be tested for treating trauma, injuries, and/or stroke in humans. When CBD was applied to rats immediately before spinal cord injury, the rats displayed fewer problems with movement over the week following the injury, and there was less extensive damage in their spinal cords. These findings suggest that CBD possibly minimized the extent of the damage and allowed for a better overall recovery from the injury [83]. Similarly, in the case of stroke, CBD protected against brain damage in rats [84] and in mice [85].

Sleep Disorders: There is limited preclinical or clinical evidence for supporting the use of cannabinoids for treating sleep disorders. CBD promoted wakefulness in rats [86],

possibly via increasing levels of dopamine in brain regions responsible for wakefulness [87], suggesting that CBD could be further developed for treating narcolepsy. In a case report, CBD administration was linked to improved quality and quantity of sleep of a 10-year-old patient with PTSD, perhaps due to CBD's anxiolytic effects [88].

Inflammation/pain: Preclinical research suggests that CBD, given its anti-inflammatory effects, could potentially treat gastrointestinal GI diseases such as colitis [89], inflammatory bowel disease (IBD) [90]), and Crohn's disease [91]. In a randomized, placebo-controlled trial with 20 patients with Crohn's disease, CBD at 10 mg/d, po, was well tolerated but not efficacious in treating Crohn's disease, possibly due to small dose of CBD, the smaller number of patients, or lack of synergism with other cannabinoids, or other possibilities [91].

CBD has also shown analgesic effects against incision-related pain in rats by reducing the sensory perception and emotional effects of pain [92]. CBD could be effective in treating chronic pain, arthritic pain, or cancer-related pain. Research suggests that CBD may be most effective in treating chronic and neuropathic pain, while it has limited use in treating short-term pain. Although Darkovska-Serafimovska et al. [93] suggest that CBD could treat cancer pain with mild to moderate adverse effects such as drowsiness, nausea, vomiting, and dry mouth, Mucke and colleagues [94] concluded that 'the potential benefits of cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC, THC/CBD oromucosal spray) in chronic neuropathic pain may be outweighed by their potential harms.' Hauser et al. [95] conducted a systematic review of the publications between 2009 and 2017 and concluded that 'there is limited evidence for a benefit of THC/CBD spray in the treatment of neuropathic pain, and 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, or anorexia in cancer or AIDS.'

Treatment with cannabis-based medicines has been associated with central nervous and psychiatric adverse effects. However, 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. On the other hand, when Whiting and colleagues [45] conducted a systematic review of 79 clinical trials where dronabinol, nabilone, CBD, nabiximols, or cannabis was tested for the treatment of chronic pain or spasticity, they found moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. According to them, there is low-quality evidence for supporting the use of cannabinoids for treating or improving chemotherapy-associated nausea and vomiting, weight gain in HIV infection, sleep disorders, and Tourette syndrome. In addition, cannabinoids have been associated with short-term adverse effects including dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucinations.

Nausea/Appetite Stimulation: The proposed use of CBD for nausea is relatively more recent. Preclinical research [96] suggests that CBD may stop nausea and vomiting in humans. CBD may be particularly helpful in treating nausea in patients who are not getting relief from prescribed anti-nausea drugs [97]. However, more clinical research is needed to support its use for treating nausea/vomiting in humans.

In terms of appetite-stimulating effects, there are no studies in humans where CBD stimulated appetite. On the other hand, smoked cannabis did increase appetite and weight gain in patients with HIV/AIDS [98] without affecting viral load, and the oral THC also resulted in weight gain in patients with cachexia (extreme loss of weight) [25]. More research is needed to study the effects of CBD and other cannabinoids on appetite.

Substance Use Disorders: Limited research suggests that CBD may have potential in treating substance use disorders including those involving tobacco, cannabis, and opiates. In a 2013 study [99], a group of 24 individuals with tobacco smoking 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 crossover study of people with tobacco use disorder, 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. However, CBD did not influence tobacco craving or withdrawal or any subjectively rated adverse effects [100].

In the case of cannabis use disorder (CUD), Beale and colleagues [101] treated individuals with regular cannabis use with 200 mg/day of CBD over a 10-week period. CBD treatment appeared to reduce neuroanatomical damage in the hippocampus without generating any significant adverse effects, thereby suggesting a neuroprotective role of CBD against possible brain structural harm conferred by chronic cannabis use. Beale et al. [101] further suggested that CBD might be a useful adjunct in the treatment of CUD and a range of clinical disorders characterized by hippocampal pathology (e.g., schizophrenia, Alzheimer's disease, and major depressive disorder). Adaptive Bayesian trials provide a platform for sequential learning. They assume the 'a priori' knowledge of probability models, in such a way that

it is possible to build more precise models of phenomena starting from experimental data and then use the models to make predictions. In a phase 2a, double-blind, placebo-controlled, randomized, adaptive Bayesian trial, Freeman and colleagues [102•] showed that synthetic CBD at doses of 400 mg (2 capsules of 100 mg each twice daily) or 800 mg (2 capsules of 200 mg each twice daily) for 4 weeks, compared to placebo, was safe and efficacious in reducing cannabis use in patients with CUD. The dose of 200 mg was not efficacious.

In another randomized, double blind, placebo-controlled trial, nabiximols 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 people with chronic cannabis use [103•]. Future trials with higher doses of CBD were recommended for patients with severe CUD.

In a study of 128 cannabis dependent patients with CUD (98 men and 30 women), treatment with placebo or nabiximols (47.5 mg THC + 44 mg CBD; Sativex), combined with psychosocial interventions appeared efficacious. Thus, they may represent a safe approach for reducing cannabis use among treatment-seeking individuals with CUD [104]. In a subsequent study, Lintzeris and colleagues [105] also reported that the benefits of treatment incorporating nabiximols with psychosocial interventions in reducing cannabis use appears to persist for up to 3 months after the cessation of treatment, leading the authors to propose a stepped care model of treatment. In yet another double-blind randomized clinical inpatient trial with a 28-day follow-up study [106], a group of 51 treatment-seeking individuals with DSM-IV-TR cannabis dependence received a 6-day regimen of nabiximols (maximum daily dose, 86.4 mg of Δ9-THC and 80 mg of CBD) or placebo with standardized psychosocial interventions during a 9-day admission. Nabiximols attenuated cannabis withdrawal symptoms and improved patient retention in treatment. However, placebo was as effective as nabiximols in promoting long-term reductions in cannabis use following medication cessation. Nevertheless, the data support further evaluation of nabiximols for management of CUD and withdrawal in treatment-seeking populations.

Other studies also suggest a positive profile of CBD in treating CUD. Solowij and colleagues [31] reported that CBD was well tolerated by people with chronic cannabis use without affecting their cognitive or psychological function. The participants reported reduced euphoria when smoking cannabis, experienced significantly fewer depressive and psychotic-like symptoms at post-treatment relative to baseline, 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 people with more severe relative to less severe cannabis use. The investigators concluded that prolonged treatment with CBD appeared to have promising therapeutic effects for improving psychological symptoms and cognition in people with regular cannabis use and that CBD might be a useful adjunct treatment for CUD.

In a case report, CBD also helped symptoms of cannabis withdrawal in a 19-year-old woman with CUD [107]. Shannon and Opilla-Lehman [108] reported a case where CBD oil decreased the addictive use of marijuana and provided anxiolytic and sleep benefits. 'The patient was a 27-year-old male who presented with a long-standing diagnosis of bipolar disorder and a daily use of marijuana. In the described intervention, the only change made to the patient's treatment was the addition of CBD oil with the dosage gradually decreasing from 24 to 18 mg. With use of the CBD oil, the patient reported being less anxious, as well as settling into a regular pattern of sleep. He also indicated that he had not used any marijuana since starting the CBD oil. With the decrease in the dosage to 18 mg, the patient was able to maintain his abstinence of marijuana' [108]. Whether they would respond to treatment with another cannabinoid remains unknown. Furthermore, research also shows that dronabinol, nabilone, or nabiximols, either alone or in combination with other drugs, may have promise in reducing cannabis withdrawal symptoms, possibly in a dose-dependent manner [109]. Finally, in the case of opioid use disorder (OUD), Hurd and colleagues [110•] reported that CBD reduced cue-induced craving and anxiety in people with OUD but suggested that larger clinical trials are needed to confirm the efficacy of CBD in treating the condition. The National Academy of Sciences [111] also suggests that CBD has a potential to treat a wide range of health ailments but more clinical research is needed before it is used for treating conditions for which it is not yet approved.

Miscellaneous Effects: CBD has been tested for treating diabetes [112], hemodynamic conditions [113, 114], ischemic stroke [115], apoptotic cell proliferation and anticancer effects [116], and viral hepatitis [117]. In addition, based on the anti-inflammatory, cardioprotective, and anti-angiogenesis effects of CBD [118], protection of endothelial function [119] shown in preclinical research, and by blocking 'cytokine storm' effects, it may warrant further evaluation in treating patients with multiple complications of corona virus disease-19 (COVID-19). However, the investigators cautioned that only highly pure forms of CBD showed significant effects on COVID-19 complications [120]. More clinical research is needed to investigate CBD's potential for treating these indications. Although cannabis and its cannabinoids have been proposed as therapies for cancer [5, 121–126], more studies are needed before any cannabinoid(s) can be recommended for treating cancer.

Cannabichromene (CBC)

Cannabichromene is a major, non-psychotropic, anti-inflammatory and biologically active phytocannabinoid component of C. *sativa* plant [127, 128]. CBC selectively reduces inflammation-induced gastric hypermotility in mice [4]. CBC acts as an analgesic by interacting with several target proteins involved in nociceptive control, suggesting that CBC may be a useful therapeutic agent for treating pain. CBC seems to work via CB1 and TRPA1 (transient receptor potential-ankyrin type 1) receptors [129]. CBC may also exert antidepressant-like actions and thus may contribute to the overall mood-elevating properties of cannabis [130]. In addition, CBD may induce apoptosis and inhibit the growth of several cancer cell lines including breast cancer cells, suggesting that CBC could be further developed for treating cancer [131].CBC has positive effects on mouse neural stem/progenitor cells (essential for brain function) and could possibly be investigated to treat neuroinflammatory conditions including seizures/epilepsy [132]. Based on its action on inflammatory cytokines like MCP-2 [monocyte chemotactic protein], intraleukin-6 (IL-6), intraleukin-8 (IL-8) and tumor necrosis factor (TNF-alpha), it could be developed for treating allergic contact dermatitis [133]. Given its antifibrotic action on mouse and human skin sebocytes, CBC could be investigated to treat acne [134]. Long-term safety, preclinical, and clinical studies and clinical trials are needed to investigate CBC's potential as a medicine.

Cannabidivarin (CBDV)

CBDV, synthesized from cannabigerolic acid (CBGA) in the presence of CBD synthase, is non-psychoactive and seems to have similar applications in medicine as CBD to treat seizures and epilepsy [34, 135–139]. CBDV may act via CB1 and CB2 receptors and modulate neuronal excitability and neuroinflammation via several mechanisms including the expression of epilepsy-related genes (Fos, Casp3, Ccl3, Cc14, Npy, Arc, Penk, Cam2a, Bdnf, and Egr1) in the hippocampus, neocortex, and prefrontal cortex [140]. Based on data from animal models of seizures [139], CBDV could be developed for treating different forms of epilepsy. Several clinical studies/trials are underway to determine if CBDV could be used to treat epilepsy [135]. Given its anti-inflammatory activity on human sebocytes, it may have potential for treating acne [134]. Since it also acts as a CB1 receptor inverse agonist, it may have potential for treating nausea [141].

Given effects of CBD on brain excitatory-inhibitory systems in ASD [51, 142], CBDV may similarly have potential for treating ASD [50, 143–145]. In a double-blind, randomized-order, crossover design study using magnetic resonance spectroscopy (MRS), Pretzsch and colleagues [142] compared glutamate (Glx = glutamate + glutamine) and GABA + (GABA + macromolecules) levels following placebo (baseline) and 600 mg CBDV in 17 healthy men with ASD and 17 healthy men without ASD. They found that CBDV significantly modulated the glutamate-GABA system in the basal ganglia but not in frontal regions.

Finally, the investigators [146] prospectively collected data from 188 ASD patients treated with cannabis oil containing 30% CBDV and 1.5% THC for 6 months and found that 30%, 53.7%, 6.4% reported a significant, moderate, and slight improvement, respectively. While eight (8.6%) patients had no change in their condition, 23 patients (25.2%) experienced at least one adverse effect; the most common was restlessness (6.6%). CBDV was well tolerated by ASD patients suggesting that CBDV appears to be a safe and effective option to relieve symptoms associated with ASD [146].

Tetrahydrocannabivarin (THCV)

Tetrahydrocannabivarin is a non-psychoactive component of the cannabis plant. Based on its numerous pharmacologic effects including anti-psychotic, anti-inflammatory, immunomodulatory properties, effects on 5-HT1A, CB1 and CB2 receptors, and on metabolism, it has been suggested that THCV has the potential to treat a wide range of clinical conditions including schizophrenia, epilepsy, nausea, obesity, and some skin conditions [134]. 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 [147].

Regarding anti-inflammation, Batkai and colleagues [148] showed that Δ(8) -THCV activated CB2 receptors in vitro and decreased tissue injury and inflammation in vivo. The model involved ischemia-perfusion hepatic injury, and the effect was observed partly via CB2 receptor activation.

In a placebo-controlled, double-blind, crossover pilot trial of 10 cannabis-using men (< 25 occasional uses), THCV at an oral dose of 10 mg protected against THC-induced delayed verbal recall and increased heart rate. However, THCV potentiated the THC effects of memory intrusions [149]. Together, more extensive well-designed clinical studies and trials are needed to investigate THCV's potential [150].

Cannabigerol (CBG)

Cannabigerol, a minor component of the cannabis plant, is the parent molecule from which other cannabinoids are synthesized. CBG has shown positive effects on neuroinflammatory and neurodegenerative processes through cell membrane cannabinoid receptor-dependent and -independent mechanisms, and modulation of the expression of genes

involved in MS pathophysiology. Thus, CBG could be investigated as a potential treatment for MS and possibly other neuroinflammatory diseases [151]. Given CBG's antioxidant and anti-inflammatory effects seen in in vivo studies, it could also be investigated as a potential treatment for inflammatory conditions like colitis [89], IBD [123], 'acne-like condition,' dry skin syndrome [134], and psoriasis [152]. Given its inhibitory effects on growth of colorectal cells, it could also be developed for the prevention and treatment of colorectal and other cancers including breast cancer [123, 153].

Cannabivarin (CBV)

Cannabivarin (CBV) was discovered in 1971 as one of the cannabinoids in hashish [154]. However, to date, no data are available from any preclinical or clinical studies.

Safety of cannabinoids, drug-drug interactions among cannabinoids and other medications, and role of genetics of cannabis variants

Cannabinoids are associated with short-term adverse events including dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, hallucinations, sedation [45], and possibly death [16]. In addition, cannabinoids may also interact with other drugs used in clinical practice via several drug-metabolizing cytochrome-p-450 (CYP450) isoforms including CYP1A2, CYP2B6, CYP2C9, and CYP2D6 by THC; CYP3A4, CYP2B6, CYP2C9, CYP2D6, and CYP2E1 by CBD; and CYP2B6, CYP2C9, and CYP2E1 by cannabinol [155].

For example, the CYP2C9-mediated metabolism was inhibited by several cannabinoids with estimated K_i values of 0.2–3.2 μM. Of the cannabinoids like CBD, CBG, CBDV, CBN, THC, THCA, and THCV tested, most inhibited CYP2C19, whereas CYP2D6, CYP3A4, and CYP2B6 were either not affected or only partially inhibited by the cannabinoids [156]. THC and CBD may inhibit several CYP450 enzymes in vitro, whereas smoke from cannabis may induce one specific CYP450 enzyme. In the case of dronabinol, it is primarily metabolized by CYP2C9, which is responsible for the formation of the major active metabolite (11-hydroxy-delta-9-THC). Individuals with less CYP2C9 activity ('CYP2C9 poor metabolizers') have two–threefold increased exposure to dronabinol from similar doses and thus appear at an increased risk of adverse effects including sedation, physical weakness, facial flushing, and palpitations. Further, the FDA-approved drug label for dronabinol recommends monitoring for the increased adverse reactions that could potentially occur in individuals with genetic variants associated with diminished CYP2C9 function [157]. Along with a lack of robust clinical studies, inconsistencies in chemical compositions and methods of ingestion of various cannabis products make it challenging to clinically assess for and predict interactions between cannabis and other medications.

In addition to potential pharmacokinetic interactions relating to differences in drug metabolism, potential pharmacodynamic interactions (e.g., adverse effects secondary to the use of cannabis with other psychoactive drugs) are also important to consider [158]. Further, the high frequency and increasing use of cannabis also invites the need for clinicians to familiarize themselves with potential drug-drug interactions in people receiving select psychotropic agents, and additionally consuming medical and/or recreational marijuana [8, 159].

Despite being a controversial crop, *Cannabis sativa* L. has a long history of cultivation throughout the world. As mentioned, following recent legalization in Canada, *Cannabis* is emerging as an important plant for both medicinal and recreational purposes. It is important to recognize that recent progress in genome sequencing of both cannabis and hemp varieties allow for systematic analysis of genes coding for enzymes involved in the cannabinoid biosynthesis pathway [160]. Single-nucleotide polymorphisms in the coding regions of cannabinoid synthases play an important role in determining plant chemotype [161].

In addition, recent genomic research shows that the NIDA-supplied cannabis varieties, used in basic and clinical research, are divergent from the private legal commercial varieties in terms of cannabinoids profile. The NIDA-supplied cannabis varieties lack diversity in the single-copy portion of the genome, the maternally inherited genomes, the cannabinoid genes, and in the repetitive content of the genome. Therefore, investigators [162] have suggested that results based on NIDA's varieties may not generalize regarding the effects of cannabis after consumption.

A better understanding of how cannabis variants may influence enzyme activity and accumulation of cannabinoids will allow for breeding of novel cultivars with desirable cannabinoid profiles. For future study and development of pure compounds, comprehension of system biological approaches is required to accomplish further development of cannabis as an FDA-approved medication for distinct diseases. In addition, since synthetic CBD is now available and both natural, plant-extracted CBD are pharmacologically similar [163], it remains to be seen whether synthetic CBD will become the standard chemical in research and/or clinical practice.

Finally, it is important to note that in its 92-year history, the US FDA has approved only two botanical drugs as medicines (whole plant-products—such as sinecatechins, Veregen® for treating genital and perianal warts and crofelemer, Mytesi™ for AIDS-associated diarrhea), mainly because of immense technical/chemical and other problems in obtaining well-characterized products from chemically

complex plant. Therefore, it seems highly unlikely that the FDA will approve cannabis plant per se as a medicine, since its purified individual chemical components like THC, CBD or other cannabinoids may be readily obtained and used in research as well as in treatment.

Discussion

In general, of the hundreds of chemical constituents found in a plant, there is one main pharmacologically active chemical constituent like nicotine (Tobacco plant), cocaine (Erythroxylon coca), morphine (Papaver *somniferum*), and so on. But research shows that Cannabis *sativa*, Linn., has been an important plant used in folk medicine [164] for centuries for its uniqueness in the plant kingdom such that it contains not one but several pharmacologically active chemical constituents with therapeutic potential. As discussed above, of the 125 cannabinoids, although only two (THC and CBD) have been more extensively studied for their pharmacological effects and therapeutic effects, other cannabinoids discussed above also show pharmacological activity and possible therapeutic value. There are several cannabis-related or cannabis-like pharmacologically active products that seem to act via either CB1 and/or CB2 receptors, but only four products have been approved as therapeutics. Other products have been either withdrawn by the manufacturer for failed efficacy or due to observed serious adverse reactions (Table 1) [Table 1 goes here].

Synthetic THC in the form of Marinol and Nabilone have approved as medicines for the treatment of chemotherapy-associated nausea and vomiting, and as an appetite stimulant in patients with AIDS. Further, in combination with CBD (as Sativex) THC is also approved as medicine for the treatment of MS-associated spasticity in several countries, although not in the USA. However, due to its addictive properties and adverse effect profile, THC may not be an ideal candidate for further development as a medicine. Of the many cannabinoids, arguably the most studied is CBD. Several clinical studies and trials resulted in its approval as medicine for treating two rare forms of epilepsy: Lennox-Gastaut and Dravet syndromes in young children and seizures from rare tumors in the brain. However, CBD is not approved as a medicine for treating any other clinical indication even though, in an estimated annual 20 billion market, it is often being promoted, sometimes like a 'wonder drug' for treating multiple clinical indications. On the other hand, research clearly suggests that it has potential for further development. Nevertheless, there is a need for conducting clinical studies and clinical trials specific for each separate clinical indication as evident from several clinical trials currently underway (https://clinicaltrials.gov).

Similarly, in the case of the other cannabinoids reviewed above, each needs further testing. For example, given its neuroinflammatory effects, cannabichromene (CBC) could be investigated for treating seizures; given its effects on inflammatory cytokines, it could be developed to treat allergic dermatitis, and given its antifibrotic effects, could be developed for treating acne. For its neuroinflammatory effects, cannabidivarin (CBDV) also could be investigated for treating seizures, and for its anti-inflammatory effects on human sebocytes, developed for treating acne. Like CBD, tetrahydrocannabivarin (THCV) has antipsychotic, anti-inflammatory, and immunomodulation effects and thus could be investigated for treating a wide range of clinical conditions including schizophrenia, epilepsy, obesity, nausea, neuropathy, retinopathy nephropathy, pain, and dermal conditions like dermatitis and acne [147]. Given its antioxidant, anti-inflammatory, and modulation of genetic expression effects, cannabigerol (CBG) could be investigated for treating dermal conditions like dermatitis, acne, colorectal cancer, and colitis. Thus, the cannabinoids discussed above have potential to treat a wide range of clinical conditions, for which several clinical trials are in various stages of progress as registered at: https://clinicaltrials.gov and that we briefly summarize in Table 2.

(Table 2 goes here).

Finally, we should be cognizant of significant variability in the CBD content and unknown level of adulteration with newly discovered cannabinoids, many of which are CBD-like or THC-like [165]. These may impact on safety and efficacy of CBD and other cannabinoids sold as medicines. It is also important to utilize an evidence-based approach, including when considering substances considered illegal under US federal law. Clinicians, especially addiction physicians, should weigh risks and benefits of the use of cannabinoids or medical marijuana in their patients and should ensure that patients asking for prescription for unapproved cannabinoids have tried other treatment modalities with higher levels of evidence for use when available and appropriate [166]. We believe that researchers and clinicians may want to engage in the systematic investigation of cannabinoids including CBD as a therapeutic, instead of promoting, recommending, or marketing any of these cannabinoids without these having gone through FDA-recommended systematic drug development guidelines. These include conducting studies of pharmacological effects, mechanisms of drug action, pharmacokinetic/pharmacodynamic and drug-drug interactions, and long-term safety studies, and in compliance with the good manufacturing practice (GMP), good laboratory practice (GLP), and good clinical practice (GCP) guidelines for conducting Phase I, Phase II, and pivotal Phase III clinical trials for each specific clinical indication. In view of the substantial cost of conducting clinical research and FDA-required clinical trials, it remains to be seen whether pharmaceutical companies will venture to develop CBD or any other cannabinoid as therapeutics for treating a wide range of clinical indications.

Table 1 FDA-approved and non-approved Cannabis-based Pharmaceuticals (Pharmaceutical Drugs Based on Cannabis—Medical Marijuana—ProCon.org; accessed 07,232,022) (FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD) | FDA; accessed 07,232,022)

Product	Manufacturer	Cannabis-related properties	Potential/approved indication	Current approval status
Dronabinol/Marinol	Solvay pharmaceuticals	Synthetic THC	Chemotherapy-related nausea/vomiting; appetite stimulation in AIDS patients	Approved
Nabilone/ Cesamet	Valeant Pharmaceuticals International	Synthetic cannabinoid like THC	Chemotherapy-related nausea/vomiting	Approved
CBD/ Epidiolex	GW pharmaceuticals	CBD	Epilepsy/LG-Dravet syndrome	Approved
Nabiximols/Sativex	GW pharmaceuticals	CBD + THC in 1:1 ratio, oral mouth spray	MS-associated Neuropathic pain and spasticity	Approved in 28 countries but not in the US
Dexanabinol	Solvay pharmaceuticals	Synthetic non-psychotic cannabinoid that blocks NMDA receptors and COX-2 cytokines and chemokines	Neuroprotective for use after cardiac surgery, regain memory and brain function following traumatic brain injury, possible anti-cancer	NOT approved due to failed efficacy
CT-3 (ajulemic acid)	Indevus pharmaceuticals	Synthetic, potent analog of THC metabolite, THC-11-oic acid	MS-associated spasticity; anti-inflammatory for arthritic pain	NOT approved
Cannabinor (PRS-211,275)	Pharmos	Synthetic cannabinoid that binds to CB2 receptors	Anti-inflammatory for chronic neuropathic pain, bladder control	NOT approved
HU-308	Pharmos	Synthetic cannabinoid that binds to CB2 receptors	Anti-inflammatory; hypertension	NOT approved
HU-331	Cayman chemicals	Synthetic cannabinoid that binds to CB1 and CB2 receptors	Memory, weight loss, appetite stimulant, neurogeneration, tumor surveillance, analgesia, inflammation	NOT approved
Rimonabant/Acomplia	Sanofi/Aventis	Synthetic chemical blocks endocannabinoids	Anti-obesity (appetite suppression)	NOT approved; Sanofi withdrew due to adverse effects of suicidal ideations
Taranabant/MK-0364	Merck	Synthetic chemical targets appetite controlling receptors; acts via CB1R receptors	Anti-obesity	NOT approved; Merck stopped further development due to ADRs like anxiety and depression

ADRs = adverse drug reactions

Table 2 Therapeutic Potential of Cannabinoids Based on Research Reviewed

Cannabinoid	Pharmacologic activity	Potential Indication
Cannabidiol	Anti-inflammatory, neuroprotective, antioxidant, cardioprotective, anti-angiogenesis	Anxiety (94*), Alzheimer's, autism, depression (61*), epilepsy/seizures (44*), inflammation, multiple sclerosis (7*), pain (64*), Parkinson's disease (4*), trauma, colitis, skin disorders, substance use disorders (15*)
Cannabichromene	Anti-inflammatory, neuroprotective	Epilepsy, skin disorders
Cannabidivarin	Anti-inflammatory, neuroprotective	Autism, epilepsy, skin disorders,
Tetrahydrocannabivarin	Anti-inflammatory, neuromodulatory, antioxidant, cardioprotective	Cancer, cardiovascular dysfunction, diabetes, neuropathy, nephropathy, pain, retinopathy
Cannabigerol	Anti-inflammatory, neuroprotective, anti-proliferative	Inflammation, pain, multiple sclerosis, colitis, skin disorders, cancer

The clinical conditions summarized above are where individual cannabinoids have shown some clinical evidence supporting further development as a therapeutic; * = number of clinical trials investigating clinical conditions registered at: https://clinicaltrials.gov

Conclusion

Based on preliminary preclinical and clinical research, cannabinoids could be further investigated for their potential in treating a wide range of clinical conditions. For their effects on neuroinflammation, inflammatory cytokines, psychosis, fibrosis, and immunomodulation, many of these cannabinoids may be further investigated for treating clinical indications ranging from seizures/epilepsy in adults, schizophrenia, obesity, nausea, neuropathy, retinopathy nephropathy, pain, and dermal conditions like dermatitis and acne [147]. Finally, it is less likely that THC, given its strong psychoactive properties and other potential adverse effects, would be further developed as a medicine. However, CBD has potential to treat a wide range of clinical conditions/diseases. Currently, CBD seems most indicated for treating two rare forms of epilepsy in young children and in combination with THC as Sativex as these indications have been approved in several other countries except in the USA. Many investigators and medical organizations like the National Academy of Sciences [111] and the American Psychiatric Association [167] recommend that additional basic and clinical research is needed before CBD, or any other cannabinoids are approved by a regulatory agency like the US Food and Drug Administration for clinical use. None of the other cannabinoids discussed above should be currently considered formally as medicines to treat unapproved clinical indications at this time as further investigations are needed.

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