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A systematic review of molecular mechanism and therapeutic effect of Cannabidiol (CBD)

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Abstract

Cannabidiol (CBD) is an abundant non-psychoactive phytocannabinoid in Cannabis extracts. Mechanic studies have indicated that CBD has high affinity on a series of receptors, including type 1 cannabinoid receptor (CB1), type 2 cannabinoid receptor (CB2), GPR55, transient receptor potential vanilloid (TRPV), peroxisome proliferator-activated receptor gamma (PPARγ). By modulating the activities of these receptor, CBD exhibits multiple therapeutic effects, including neuroprotective, antiepileptic, anxiolytic, antipsychotic, anti-inflammatory, analgesic and anti-cancer properties. Recently, according to some initial studies, CBD's anti-inflammatory properties could be applied for treat or prevent COVID-19. CBD has gained increased attention in recent years because of its great potential to treat various human diseases. This review provides a current overview of CBD's applications in human diseases, from mechanism of action to clinical trials.

Introduction

The herbal use of *Cannabis sativa* plant extract (also known as cannabis, hemp or marijuana) can be tracked back to ancient China, around 2900 BC. Cannabis was used in variety of ways by the ancient Chinese people to treat ailments, including joint pain, muscle spasms, gout and malaria(Ethan B. Russo, 2007). Around 1000 B.C., cannabis was used as an analgesic, hypnotic, tranquilizer and anti-inflammatory agent in India(Touw, 1981). The therapeutic use of cannabis was explored in the early 19^{th} century in Western medicine. Due to the psychoactive properties, research and uses of cannabis has been hindered by decede-long debates over its legality. Despite restrictive legislation, interest in the recreational use of cannabis intensified in the 1960s and 1970s, and scientists were able to isolate its psychoactive and therapeutic constituents. The psychoactive property of cannabis was generated from one of its extracts, delta-9-tetrahydrocannabinol (delta-9-THC). As research progressed, global policies have increased access to medical cannabis or cannabinoid-based treatments. Canada officially legalized cannabis for recreational and medical use in 2018 and Mexico legalized the recreational use of cannabis in early 2021. In 2018, the US Agriculture Improvement Act of 2018 was approved in the United States (US). Hemp (defined in US as cannabis with less than 0.3% of delta-9-THC) and hemp products are no longer considered controlled substances by the US Drug Enforcement Administration. As of August 2021, medical cannabis use is legal in 37 states and the District of Columbia (D.C.), and non-medical cannabis use is legal in 18 states in the United States("State Medical Marijuana/Cannabis Program Laws," 2021).

Cannabidiol (CBD) is one of the most abundant extracts from *Cannabis sativa* ; it has multiple bioactivities and wide health benefits without psychoactive properties. Studies suggest that the molecular mechanism of CBD largely relates to the human endocannabinoid system(Mouslech & Valla, 2009). The human en-

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docannabinoid system was discovered soon after the identification of cannabinoid receptor 1 (CB1). This system includes two main cannabinoid receptors (CB1 and CB2)(Pertwee, 2008) and endogenous ligands called endocannabinoids. There are two endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG); both of them derive from arachidonic acid(Fagundo et al., 2013). Both endogenous endocannabinoids, anandamide (AEA, also known as N-arachidonoylethanolamide and arachidonoylethanolamide) and 2-arachidonoylglycerol (2-AG) are derivatives of arachidonic acid and modulate CB1 and CB2 activities(Tsuboi, Uyama, Okamoto, & Ueda, 2018). The concentration of endocannabinoids is regulated by the enzymes fatty acid amide hydrolase (FAAH, also known as oleamide hydrolase, anandamide amidohydrolase and EC 3.5.1.99) and monoacylglycerol lipase (MAGL), which act by degrading AEA and 2-AG, respectively(Luchicchi & Pistis, 2012). The CB1 receptor is highly expressed in central nervous system (CNS) and is particularly abundant in brain areas associated with motor control, emotional responses, motivated behavior and energy homeostasis.

CB1 is also expressed in the heart, liver, pancreas, muscles, adipose tissue, and reproduction system. The CB2 receptor is mainly expressed in cells related to the immune system, such as leukocytes, but it is also found in the spleen, thymus, bone marrow, and other tissues related to immune functions.

CBD (Epidiolex®) was approved by the US Food and Drug Administration (FDA) in 2018 and European Medicines Agency (EMA) in 2019, as an add-on treatment for two rare epilepsies: Dravet Syndrome (DS) and Lennox-Gastaut Syndrome (LGS) in patients 1 year of age and older("FDA Approves New Indication for Drug Containing an Active Ingredient Derived from Cannabis to Treat Seizures in Rare Genetic Disease,"). Epidiolex® oral solution was also approved for tuberous sclerosis complex (TSC) by the FDA in 2020 and by the EMA in 2021("Epidiolex,"). Sativex®, an oral spray containing CBD and delta-9 THC in a 1 :1 ratio, is approved in several countries including, United Kingdom (UK), European Union (EU) and Canada for the treatment of multiple sclerosis associated spasticity("Sativex®,"). CBD has also exhibited tremendous treatment potential toward multiple disease states, including psychotic disorder, anxiety, diabetes and pain.

The therapeutic benefits of CBD are mainly generated from CBD's role in the endocannabinoid system. However, CBD does not bind to the orthostatic binding site of the CB1 and CB2 receptors(McPartland, Glass, & Pertwee, 2007; Tham et al., 2019; Thomas et al., 2007). An allosteric binding activity of CBD on these two receptors has been reported("Allosteric Modulators of the CB1 Cannabinoid Receptor: A Structural Update Review," 2016; Laprairie, Bagher, Kelly, & Denovan-Wright, 2015; Martínez-Pinilla et al., 2017). CBD was shown to influence endocannabinoid balance via binding to fatty acid-binding proteins(Elmes et al., 2015). Except for the endocannabinoids receptor, many other potential molecular targets have been investigated, including GPR55(Ryberg et al., 2007; Whyte et al., 2009), TRPVs(Luciano De Petrocellis et al., 2011; L. De Petrocellis et al., 2012), 5-HT receptors(Rock et al., 2012; Ethan B. Russo, Burnett, Hall, & Parker, 2005; Yang et al., 2010), $GABA_A$ receptors(Bakas et al., 2017), TRPM8 receptor(Luciano De Petrocellis et al., 2008), PPARγ nuclear receptors(Esposito et al., 2011; Granja et al., 2012; O'Sullivan, Sun, Bennett, Randall, & Kendall, 2009; Caterina Scuderi, Steardo, & Esposito, 2014), and glycine receptors(Ahrens et al., 2009; Xiong et al., 2012) (Fig. 1). In Table 1, the affinity and action of the CBD related receptors are summarized. However, the underlying mechanisms for the effects of CBD remain largely elusive(Morales, Reggio, & Jagerovic, 2017).

Previously there were some excellent reviews on CBD, such as pain management(Kevin P. Hill, 2017; Mlost, Bryk, & Starowicz, 2020; Urits et al., 2020), CNS disorders(C. Scuderi et al., 2009), anti-cancer(Paola Massi, Solinas, Cinquina, & Parolaro, 2013; Seltzer, Watters, MacKenzie, Granat, & Zhang, 2020), pharmacology and pharmacokinetics(Millar, Stone, Yates, & O'Sullivan, 2018; Pertwee, 2008), and clinical trials(Kevin P. Hill, 2017; Sholler, Schoene, & Spindle, 2020; White, 2019). This review will discuss the molecular mechanisms of action of the therapeutic effects of CBD within different disease contexts. We focus on disease in which there is human experiments or clinical studies with CBD (Table 2).

Psychotic disorder

Schizophrenia is a psychotic disorder characterized by distortions of reality, disturbances of thought and

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language, and withdrawal from social contact. Its heterogeneous symptoms can be grouped into three main categories: (1) positive symptoms (delusions, thought disorder and hallucinations), (2) negative symptoms (anhedonia, blunted affect and social withdrawal), and (3) cognitive impairment (sensory information processing attention, working memory and executive functions)(Freedman, 2003).

First-line antipsychotic drugs for schizophrenia act by blocking the central dopamine D2 receptors via receptor antagonism(Miyamoto, Duncan, Marx, & Lieberman, 2005). However, up to one-third of patients are unresponsive to these drugs. This may be attributed to the fact that some schizophrenia symptoms are not driven by elevated dopamine function. Exploring compounds with alternative molecular mechanisms might be a way to meet the unmet need for improved schizophrenia therapies. Research in both animals and humans indicates that CBD binds to various molecular targets to exerts its antipsychotic properties. CBD may bind to FAAH and FLAT (FAAH-like anandamide transporter) to inhibit anandamide degradation and uptake(F. M. Leweke et al., 2012; Schuelert & McDougall, 2011), facilitate 5-HT_{1A} receptor mediated serotonergic neurotransmission(Long et al., 2012; Ethan B. Russo et al., 2005), and activate transient receptor potential vanilloid type 1 (Bisogno et al., 2001) (Fig. 2).

An clinical study conducted in 1995 by Zuardi et al. demonstrated that daily administration of up to 1500 mg/day of CBD over 4 weeks resulted an overall improvement of psychotic symptoms(A. W. Zuardi, Morais, Guimarães, & Mechoulam, 1995) (Table 2). However, a study investigated the effects of CBD on selective attention of schizophrenic patients discovered that single and acute administration of CBD (300 mg or 600 mg) seems to have no beneficial effects on the performance of schizophrenic patients in the Stroop Color Word Test(Hallak et al., 2010) (Table 2). The first controlled, randomized, double blind clinical trial was conducted in 2012(F. M. Leweke et al., 2012) (Table 2); schizophrenic patients were treated with 600-800 mg/day of CBD, resulting in a significant clinical improvement. Moreover, a significant increase in serum anandamide levels was associated with clinical improvement following CBD treatment. Furthermore, a phase 2 trial demonstrated that schizophrenia patients who received 1000 mg/day of CBD (n = 43) for 6 weeks can clinically benefit compared to those who received the placebo (n = 45). The CBD group had lower levels of positive psychotic symptoms and tolerated the high dose of CBD(Philip McGuire et al., 2018) (Table 2). These preliminary evidence supports that CBD may be effective in the treatment of psychotic disorders. However, CBD failed to demonstrate efficacy in cognitive impairments associated with schizophrenia (CIAS) as an add-on treatment in a randomized placebo—controlled trial in chronically ill patients(Boggs et al., 2018) (Table 2). In a explorative clinical trial, CBD demonstrated efficacy in improving neurocognitive functioning in young and acutely ill schizophrenia patients(F. Markus Leweke et al., 2021) (Table 2).

Currently, there are only five clinical records on CBD treatment for schizophrenics available from Clinical Trial website("ClinicalTrials. gov,") (Table 2). Large-scale controlled and randomized clinical trials are still needed to evaluate the long-term efficacy and safety of this putative new antipsychotic agent.

Anxiety

Anxiety disorders have the highest lifetime prevalence of any mental illness worldwide, leading to high social and economic burden(Bandelow & Michaelis, 2015). Anxiety is an emotional disorder characterized by feelings of tension, worried thoughts and changes such as increased blood pressure and heart rate. People with anxiety disorders usually have intrusive thoughts or concerns(Tovote, Fadok, & Lüthi, 2015). Results from neuroimaging and biochemical studies(Freitas-Ferrari et al., 2010; Martin, Ressler, Binder, & Nemeroff, 2009; Michelle G. Craske et al., 2011) suggest that the pathophysiology of anxiety-related disorders is largely related to key neurotransmitters, including dopamine(DA)(Dunlop & Nemeroff, 2007), norepinephrine (NE)(Goddard et al., 2010), γ-aminobutyric acid (GABA)(Nemeroff, 2003), and serotonin (5-HT)(Ressler & Nemeroff, 2000). Multiple mechanisms may account for the anti-depressive and anxiolytic activities of CBD. The proposed anti-anxiety activity may result from CBD inhibiting the inactivation of anandamide, a neurotransmitter(Blessing, Steenkamp, Manzanares, & Marmar, 2015; Murrough, Yaqubi, Sayed, & Charney, 2015) and/or CBD interacting with 5-HT_{1A} receptors (Campos, Ferreira, & Guimarães, 2012; Patel, Hill, Cheer, Wotjak, & Holmes, 2017).

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Although the mechanism by which CBD decreases anxiety remains unclear, prior clinical experience has preliminarily demonstrated the anxiolytic effects of CBD (Table 2). One double-blind, cross-over study investigated the neural effects of CBD on human pathological anxiety by treating 10 men with generalized social anxiety disorder (SAD) were given an oral dose of CBD (400 mg) or placebo(Crippa et al., 2011) (Table 2). Subjective states were evaluated using the Visual Analogue Mood Scale (VAMS) and the Regional Cerebral Blood Flow (RCBF) at rest was measured twice using Single Photon Emission Computed Tomography (SPECT) neuroimaging with a Technetium-99m-ethyl cysteinate diethylester (^{99m}Tc-ECD) tracer. Subjective anxiety was significantly reduced with CBD treatment compared to placebo. SPECT results revealed that CBD significantly reduced ECD uptake in the left para-hippocampal gyrus, hippocampus, and inferior temporal gyrus, and increased ECD uptake in the right posterior cingulate gyrus. Thus, the anxiolytic effects of CBD are exerted via the modulation of the limbic and paralimbic brain areas(Crippa et al., 2011).

Further, a double-blind, placebo-controlled study was conducted to compare the effects of ipsapirone and CBD on healthy volunteers submitted to a stressful simulated public speaking (SPS) test. The results revealed that CBD treatment (300 mg) can decrease anxiety after SPS test(A. W. Zuardi, Cosme, Graeff, & Guimaraes, 1993) (Table 2). A similar study aimed to compare the treatment of CBD on healthy control patients and treatment-naïve social anxiety disorder (SAD) in SPS test. The results showed that pretreatment with CBD (600 mg) can significantly reduce anxiety, cognitive impairment and discomfort in their speech performance(Bergamaschi et al., 2011) (Table 2).

Additionally, CBD induced anxiolytic effects show an inverted U-shaped curve dose response in healthy volunteers who underwent a public speaking test. In this study, anxiety was significantly reduced in the 300 mg CBD cohort compared to the 100 mg or 900 mg CBD cohort(Antonio W. Zuardi et al., 2017). A subsequent double-blind study, 57 healthy males were allocated to receive oral CBD at doses of 150 mg, 300 mg or 600 mg; only the cohort receiving the 300 mg CBD dose had significantly reduced anxiety during the SPS test(I. M. Linares et al., 2019).

A large retrospective case series analysis revealed that within the clinical context, CBD adjuvant therapy (25 mg/day to 175 mg/day) may also benefit the outpatient psychiatric population suffering from anxiety-related disorders(S. Shannon, Lewis, Lee, & Hughes, 2019). The sample size consisted of 72 psychiatric patients presenting with primary concern of anxiety (n = 47) and anxiety levels were monitored monthly over the course of 3 months using the validated anxiety instrument the Hamilton Anxiety Rating Scale (HARS); anxiety scores decreased within the first month in 57 patients (79.2%) and remained decreased throughout the 3-month study duration(S. Shannon et al., 2019).

Overall, current clinical studies support CBD as a promising therapy for the anxiety treatment. However, there were some conflicting study results(I. M. Linares et al., 2019; Antonio W. Zuardi et al., 2017), so further research is necessary to evaluate the efficacy of CBD in treating other anxiety disorders through placebo-controlled clinical trial and determine both the appropriate dose of CBD for the anxiety treatment and the long-term safety of CBD use.

Epilepsy/seizures

Epilepsy is a central neurological system disorder associated with abnormal electrical activity in the brain. According to reported data, more than 50 million people suffer from epilepsy worldwide. The main symptom of epilepsy is recurrent seizures, but other symptoms include periods of unusual behavior, sensations, and sometimes loss of awareness("Epilepsy "). A seizure is an uncontrolled abnormal excessive or synchronous neuronal activity in the brain that causes temporary abnormalities in muscle tone or movements, behaviors, sensations or states of awareness(Fisher et al., 2014). There are three main types of seizures recognized by the International League Against Epilepsy, namely, focal, generalized and unknown seizures. For epilepsy patients, being able to control seizure determines quality of life(Fisher et al., 2017; E. L. Johnson, 2019).

Throughout the long history of cannabis's use, CBD has exhibited the ability to reduce seizures(von Wrede, Helmstaedter, & Surges, 2021). In recent years, several studies revealed that CBD has a high affinity for some receptors and channels related to epilepsy, including Transient Receptor Potential Vanilloid (TRPV)(Vilela et

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al., 2017), T-Type Ca^{2+} channels(Catterall, 2017), serotonin receptors (5-HT1A and 5-HT2A)(Gharedaghi, Seyedabadi, Ghia, Dehpour, & Rahimian, 2014), Opioid receptors(Chu Sin Chung & Kieffer, 2013) and GPR55(Kaplan, Stella, Catterall, & Westenbroek, 2017). TRPV1, an ion channel, has been implicated in the modulation of seizures and epilepsy by influencing the release of glutamate and modulating Ca^{2+} concentrations resulting in changes in neuronal activity(Mustafa, 2015). *In vitro* studies show that CBD reduced epileptiform activity and promoted desensitization of TRPV1 channels with consequent normalization of intracellular Ca^{2+}(Vilela et al., 2017). The low-voltage T-Type Ca^{2+} channels are also linked to the pathogenesis of absence epilepsy(Shin, 2006). In response to small depolarizations of the plasma membrane, T-Type Ca^{2+} channels transiently regulate neuronal Ca^{2+} entry leading to further membrane depolarization and increased neuronal excitability(Perez-Reyes, 2003). CBD may exert antiepileptic action by interacting with and blocking the T-type Ca^{2+} channels(Ross, Napier, & Connor, 2008). CBD also shows a high affinity towards serotonin receptors (5-HT_{1A} and 5-HT_{2A})(Martinez-Aguirre et al., 2020; Ethan B. Russo et al., 2005). These receptors may be involved in epilepsy even though their role is still not entirely clear(Gharedaghi et al., 2014).

In the past few decades, several clinical studies have been conducted to evaluate the safety, tolerability and efficacy of CBD in the treatment of epilepsy(Silvestro, Mammana, Cavalli, Bramanti, & Mazzon, 2019). An open-label expanded-access trial has evaluated the preliminary efficacy and safety of CBD as adjuvant antiepileptic therapy at varying doses (2-5mg/kg/day titrated up to a maximum dose of 25 or 50 mg/kg/day) in 214 patients with treatment-resistant epilepsy. Clinically meaningful reductions in seizure frequency observed in the study population(Devinsky et al., 2016) (Table 2). Additionally, CBD was demonstrated to be safe and effective as an adjuvant antiepileptic therapy for the treatment of drop seizures in patients with the Lennox-Gastaut syndrome (n = 225) in a double-blind, placebo-controlled trial(Devinsky et al., 2018) (Table 2). Patients who received an oral CBD dose of 10 or 20 mg/kg/day for 14 weeks experienced a reduction in the frequency of drop seizures compared to the placebo group(Devinsky et al., 2018). CBD is also an effective adjuvant antiepileptic therapy for the treatment of drug-resistant seizures in patients with the Dravet syndrome (n = 120). The double-blind, placebo-controlled, randomized trial showed that compared to placebo, oral CBD up to a maximum dose of 20 mg/kg/day for 14-weeks was effective at reducing the frequency of convulsive-seizures Dravet syndrome patients(Devinsky et al., 2017). Oral CBD is also indicated for the treatment of drug-resistant seizures in Tuberous Sclerosis Complex (TSC). Recently, CBD doses of 25 mg/kg/day or 50 mg/kg/day was shown to be effective at reducing TSC-associated seizures in a double-blind, placebo controlled randomized clinical trial (n = 224 patients)(Thiele et al., 2021) (Table 2). However, as has been previously documented(Devinsky et al., 2017; Devinsky et al., 2016; Devinsky et al., 2018; Silvestro et al., 2019), CBD use as an adjuvant antiepileptic therapy within the TSC context is associated with a higher frequency of adverse events such as diarrhea and elevated liver transaminase levels compared to placebo(Thiele et al., 2021).

The pharmacokinetics (PK) and tolerability of discontinuous oral CBD (single dosing at 5, 10, or 20 mg/kg and multiple dosing at 10 mg/kg/day, 20 mg/kg/day or 40 mg/kg/day, respectively) was investigated in a phase1/2 dose-escalation, open-label study for treatment-resistant epilepsy (n = 61 patients aged from 1 to 17 years)(Wheless et al., 2019) (Table 2). The PK data indicated variable inter-individual CBD exposure with single-dose administration; this variability was reduced with multiple dose administration(Wheless et al., 2019). Short-term administration was generally safe and well tolerated although a higher frequency of diarrhea, increased weight, somnolence, and psychomotor hyperactivity were observed with increased CBD dose(Wheless et al., 2019).

Sleep/Insomnia

Insomnia is a common sleep disorder that can present in either isolation or comorbid to other medical or psychiatric conditions(Suraev et al., 2020). There has been extensive interest in the use of cannabis as a therapy for the treatment of insomnia(Kesner & Lovinger, 2020). The endocannabinoids (2-AG and AEA) produce neuro-modulatory actions mainly through the actions on the CB1 receptor(Tsuboi et al., 2018). 2-AG and AEA are found in brain and throughout the body and can be produced by almost all types of

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cells in the body(C. J. Hillard, 2015; Cecilia J. Hillard, 2018). The interaction between cannabis and endocannabinoids with CB1 seems to be important in sleep stablity(Pava, Makriyannis, & Lovinger, 2016). CBD has been shown to increase concentrations of the major endogenous cannabinoid, AEA, by inhibiting the enzyme degrading it, fatty acid amid hydrolase (FAAH)(Bisogno et al., 2001). Increasing endogenous anandamide via FAAH inhibition normalized deficits in stage N3 sleep in cannabis-dependent men experiencing withdrawal(D'Souza et al., 2019). This is consistent with preclinical data showing that anandamide promotes slow wave sleep, possibly through correlated increase of extracellular adenosine(Murillo-Rodriguez, Blanco-Centurion, Sanchez, Daniele, & Shiromani, 2003). Furthermore, CBD is a promiscuous molecule that exhibits activity on a wide array of molecular targets beyond CB1 and CB2 receptors such as inhibitory $GABA_A$receptors(Bakas et al., 2017), which may also influence sleep(Gottesmann, 2002).

To date, well-designed randomized controlled trials employing objective measures to assess the effects of cannabis on sleep duration and quality is lacking in the clinical insomnia population. Previous studies(Ethan B. Russo, Guy, & Robson, 2007) have shown potential benefits in the therapeutic use of Sativex$^{(r)}$, a spray containing equal parts THC and CBD, in the relief of pain and other chronic symptoms including improved sleep, with the latter only being assessed as a secondary outcome using subjective rating scales. One case study showed that 25 mg CBD daily reduced anxiety symptoms and improved sleep disturbances in a young child with post-traumatic stress disorder(Scott Shannon & Opila-Lehman, 2016) (Table 2). Indeed, preclinical evidence(Hsiao, Yi, Li, & Chang, 2012) has demonstrated that the anxiolytic effects of CBD likely dependent on CB1 and 5-HT_{1A} receptor action, with early human experimental evidence supporting preclinical findings. Previously, 72 psychiatric adult patients were given oral doses of CBD at 25 mg/day and sleep quality was measured using by The Pittsburg Sleep Quality Index, which is a self-report measure that assesses the quality of sleep during a 1-month period. Sleep scores improved within the first month in 48 patients (66.7%) but fluctuated over time(S. Shannon et al., 2019). Although these results demonstrated that the beneficial effect of CBD on sleep, research on the impacts of CBD on sleep is still lacking. One study revealed that acute administration of CBD (300 mg) doesn't seem to alter the sleep cycle of healthy volunteers(I. M. P. Linares et al., 2018) (Table 2).

Cannabis is commonly believed to be a useful sleep aid(Vigil et al., 2018). However, there are no published studies to-date assessing its effects on sleep in people with physician-confirmed chronic insomnia disorder. Given the increased consumer interest and expansion of legal prescription for cannabis globally, it is important to better understand how cannabis-based medicines affect sleep and next-day function prior to becoming a routine clinical intervention.

Cardiovascular System/Blood pressure/vasorelaxant

The complex mechanism of action of CBD makes it possible to have multidirectional influence on the cardiovascular system(Kicman & Toczek, 2020). A number of preclinical studies have shown beneficial effects of CBD on the cardiovascular system(Stanley, Hind, & O'Sullivan, 2013). Mechanistic studies showed that CBD affects cardiovascular function by interacting with a variety of receptors, including CB1(Mukhopadhyay, Mohanraj, Batkai, & Pacher, 2008), CB2(Steffens & Pacher, 2012), TRPV1(Peng & Li, 2010), PPARs("PPARs and the Cardiovascular System," 2009) and 5-HT_{1A}(Kaumann & Levy, 2006).

A few clinical trials have assessed the effects of CBD on the cardiovascular system. A randomized crossover trial assessed the influence of a single 600 mg CBD dose on cardiovascular parameters, including blood pressure in healthy male volunteers (n = 9)(Jadoon, Tan, & O'Sullivan, 2017) (Table 2). The acute administration of CBD was shown to reduce resting systolic blood pressure and stroke volume, while increasing the heart rate and maintaining cardiac output. Furthermore, cardiovascular parameters in response to various stress stimuli was modified following CBD administration(Jadoon et al., 2017). Further studies are required to see whether CBD can play a role in the treatment of cardiovascular disorders.

However, studies carried out in animals and humans largely indicate little to no effects on resting blood pressure or heart rate following CBD administration. Still, CBD treatment was shown to reduce the cardiovascular response to various types of stress. Taken together, the cardiovascular system may benefit from

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CBD treatment, but targets sites for CBD remain to be elucidated.

Diabetes

Type 1 diabetes mellitus is an autoimmune disease resulting in destruction of pancreatic beta cells, a process assumed to be mediated mainly by CD4 Th1 and CD8 T lymphocytes(MANDRUP-POULSEN, 2003). CBD is a potent anti-inflammatory agent(Nichols & Kaplan, 2020). It is effective in suppressing IFN-γ and TNF-α production and progression of autoimmune Th1-mediated rheumatoid arthritis by inhibition of T cell proliferation(Malfait et al., 2000). Studies have shown that CBD significantly inhibited insulitis in Non-Obese Diabetic (NOD) mice(L. Weiss et al., 2006; Lola Weiss et al., 2008). CBD has multiple desirable effects in the context of hyperglycemia, mainly through its anti-inflammatory(Burstein, 2015) and antioxidant properties(Hammell et al., 2016). Interestingly, a chronic overactivation of the endocannabinoid system has been identified in obesity and type 2 diabetes, (Di Marzo, 2008) suggesting a potential therapeutic use for CBD in treating type 2 diabetes also.

The safety and effectiveness of CBD and Δ(9)-tetrahydrocannabivarin (THCV, a naturally occurring analog of THC) in insulin naïve patients with type 2 diabetes (n=62) was investigated in a randomized, double-blind, placebo-controlled, parallel group pilot study five treatment arms were assessed: CBD (100 mg twice daily), THCV (5 mg twice daily), 1:1 ratio of CBD and THCV (5 mg/5 mg, twice daily), 20:1 ratio of CBD and THCV (100 mg/5 mg, twice daily), or matched placebo for 13 weeks(Jadoon et al., 2016) (Table 2). The trial failed to meet the primary efficacy endpoint which was a change in HDL cholesterol concentrations from baseline. While both agents were well tolerated, a majority of patients experienced adverse events. Interestingly, THCV significantly decreased fasting plasma glucose and improved pancreatic beta-cell function while CBD decreased resistin and increased glucose-dependent insulin tropic peptide(Jadoon et al., 2016).

Pain management

Pain has long been characterized as a subjective experience encompassing sensory-physiological, motivational-affective and cognitive-evaluative components(Melzack & Wall, 1965). Nociceptive pain is caused by damage to body tissues and is usually described as sharp, aching, or throbbing pain. Neuropathic pain is caused by damage to sensory or spinal nerves, which send inaccurate pain messages to higher centers.(Kremer, Salvat, Muller, Yalcin, & Barrot, 2016) Inflammatory pain is caused by noxious stimuli that occur during the inflammatory or immune response(Vasko, 2009). Chronic pain is defined as recurrent or constant pain that lasts or recurs for longer than three months and can result in disability, suffering, and a physical disturbance(Cathy M. Russo & William G. Brose, 1998). Chronic pain affects 20% of the population, with musculoskeletal disorders being the most common cause(Mills, Nicolson, & Smith, 2019). The International Classification of Diseases 11 (ICD-11) has developed a systematic classification of chronic pain into seven different categories: chronic primary pain, chronic cancer-related pain, chronic postsurgical or posttraumatic pain, chronic neuropathic pain, chronic secondary headache or orofacial pain, chronic secondary visceral pain, and chronic secondary musculoskeletal pain(Treede et al., 2015).

CBD can be therapeutically beneficial in managing chronic pain. As presented before, CBD has low affinity to the orthosteric binding site of the CB_1 and CB_2 receptors(McPartland et al., 2007), and has allosteric activity on both $CB_1$and CB_2 receptors(Laprairie et al., 2015; Martínez-Pinilla et al., 2017). The CB_1 receptor is mainly expressed in the CNS, particularly in the regions of the midbrain and spinal cord that are both responsible for pain perception(Manzanares, Julian, & Carrascosa, 2006). The antagonistic effects of CBD on CB2 play an important role in the anti-inflammatory response of suppression of mast cell degranulation and neutrophil propagation in the vicinity of pain centers(Pertwee, 2008). Another putative CBD target is GPR2, which is expressed in the brain and spinal cord and is involved in pain reception(Ruiz-Medina, Ledent, & Valverde, 2011). CBD may also relieve pain by regulating the serotonin 5-HT_{1A} receptor(Ethan B. Russo et al., 2005) and TRPV1(Di Marzo, Bifulco, & De Petrocellis, 2004).

The therapeutic analgesic potential of a sublingual CBD spray for uncontrolled neuropathic pain was investigated previously in 34 patients (Table 2). The patients were given 2.5 mg CBD, 2.5 mg THC, 2.5 mg THC with 2.5 mg CBD mixture (THC:CBD) or placebo in 1-week intervals following an open-label 2-week THC :

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CBD run-in period. Pain assessments were made using a visual analog scale (VAS). During the run-in period, 16 of 34 patients had a greater than 50% decrease in VAS for either one of their two main symptoms sites. Furthermore, 10 of 16 patients reported greater than 50% reduction in VAS for both symptoms(Notcutt et al., 2004).

In another prospective cohort study, the impact of CBD on opioid use was investigated in 97 patients with a diagnosis of chronic pain and on stable opioids use for at least 1 year(Capano, Weaver, & Burkman, 2020) (Table 2). Ninety-four patients were able to tolerate twice-daily, hemp derived CBD-rich soft gels, which contained 15.7 mg CBD, 0.5 mg THC, 0.3 mg cannabidivarin, 0.9 mg cannabidiolic acid, 0.8 mg cannabichromene, and >1% botanical terpene blend. The improvement was evaluated by Pain Disability Index (PDI-4), Pittsburgh Sleep Quality Index (PSQI), Pain Intensity and Interference (PEG) and Patient Health Questionnaire (PHQ-4). Fifty of the 94 patients using the CBD extract were successfully able to reduce their dependence on opioids for pain control and 94% of CBD users reported improvements of life quality(Capano et al., 2020). There is also moderate evidence from a meta-analysis to support the analgesic use of cannabinoids in treating chronic, non-cancer pain defined as as fibromyalgia, rheumatoid arthritis, neuropathic pain, or mixed pain (Table 2). The mean treatment duration was 2.8 weeks.(Johal et al., 2020)

Cancer pain is a common problem, and 70% to 90% of patients with advanced cancer experience significant pain(Quigley, 2005). Opioids remain the keystone for the treatment of moderate to severe cancer pain(Kalso, Edwards, Moore, & McQuay, 2004). Evidence for pain control with CBD in the cancer setting comes from a Phase 2 study that recruited 177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosing(J. R. Johnson et al., 2010) (Table 2). In this study, patients received either THC:CBD extract (n = 60), THC extract (n = 58), or placebo (n = 59) for 2-weeks as an oromucosal spray. With regards to pain, 43% of patients taking the THC:CBD extract achieved a 30% or greater improvement in their pain score. Furthermore, the THC:CBD combination showed a more promising efficacy compared to THC alone(J. R. Johnson et al., 2010).

Treatment of cancer

It has been hypothesized that CBD has robust anti-proliferative and pro-apoptotic effects. In addition, it may inhibit cancer cell migration, invasion, and metastasis.(Moreno, Cavic, Krivokuca, Casadó, & Canela, 2019; Piomelli, 2003)

The anti-tumor effects of CBD may primarily be mediated through the TRPV channels(Bujak, Kosmala, Szopa, Majchrzak, & Bednarczyk, 2019). These channels play an important role in regulating the cytoplasmic calcium concentration from the extracellular sources as well as the calcium stored within the endoplastic reticulum. Disruption of cellular calcium homeostasis can lead to increased production of reactive oxygen species (ROS), ER stress, and cell death.(Haustrate, Prevarskaya, & Lehen'kyi, 2020) (Fig. 3). For a more in-depth understanding of the mechanism of the CBD in the treatment of cancer, we refer you to other excellent reviews on the topic(Paola Massi et al., 2013; Seltzer et al., 2020). Multiple cancer-related studies demonstrated that CBD exhibits pro-apoptotic and anti-proliferative actions(McAllister et al., 2011) in different types of tumors, and may also exert anti-migratory, anti-invasive(Ramer & Hinz, 2008; Ramer, Merkord, Rohde, & Hinz, 2010), anti-metastatic and perhaps anti-angiogenic properties. CBD potently inhibited the growth of different tumors, including those of breast cancer(McAllister, Christian, Horowitz, Garcia, & Desprez, 2007), lung cancer(Ramer, Rohde, Merkord, Rohde, & Hinz, 2010), colon cancer(Aviello et al., 2012), prostate cancer(Luciano De Petrocellis et al., 2013), colorectal cancer(Jeong et al., 2019; Ligresti et al., 2003; SREEVALSAN, JOSEPH, JUTOORU, CHADALAPAKA, & SAFE, 2011), glioma(Jacobsson, Rongård, Stridh, Tiger, & Fowler, 2000; P. Massi et al., 2006; Paola Massi et al., 2004), leukemia/lymphoma(Gallily et al., 2003; McKallip et al., 2006) and endocrine cancer(Lee et al., 2008; Wu et al., 2008). Interestingly, the anticancer effect of this compound seems to be selective for cancer cells, at least *in vitro* , since it did not affect normal cell lines.

Currently, there are no large efficacy clinical studies on exploring CBD treatment for cancer. Clinical evidence supporting CBD's anticancer activity comes from a case analysis study of 119 solid tumor patients

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enrolled under the Pharmaceutical Specials scheme; of the 119 patients, 28 received CBD oil as the only treatment(Kenyon, Liu, & Dalgleish, 2018) (Table 2). CBD was administered on a three days on and three days off basis, which clinically was found to be more effective than giving it as a continuous dose. The average dose was 10 mg twice daily and in some cases the dose was increased up to 30 mg twice daily. Anti-tumor effect was observed when the CBD treatment duration was at least 6 months. In the case of a five-year-old male patient with an anaplastic ependymoma who had failed all standard treatments with no further treatment options, CBD was applied as the only treatment and tumor volume had decreased by around 60% after 10 months of treatment. Other patients with prostate cancer, breast cancer, esophageal cancer, and lymphoma also saw a reduction in circulating tumor cells and tumor size. No side effects of any kind were observed when using CBD. These results strongly support the development of CBD-based products for cancer patients who have exhausted all standard treatments.(Kenyon et al., 2018)

Other than directly being used to treat cancer, CBD has also used to reduce the adverse effects associated with cancer treatment. Chemotherapy-induced nausea and vomiting (CINV) remain major adverse effects of cancer chemotherapy(Rao & Faso, 2012). The lack of adequate CINV control may be partly attributed to the fact that antiemetic treatment regimens are guided by risk factors, including level of emetogenicity of chemotherapeutic agents(Yokoe et al., 2019). CINV adversely impacts patients' quality of life. Patients rated nausea as their first most feared symptom and vomiting as their third(Bloechl-Daum, Deuson, Mavros, Hansen, & Herrstedt, 2006). A phase 2 clinical trial designed to evaluate the efficacy of cannabis-based medicine containing 2.7 mg of THC and 2.5 mg of CBD, taken in conjunction with standard anti-emetic treatment in the control of CINV was conducted in 16 patients; a higher proportion of patients in the cannabis group experienced a complete response during the overall observation period(Duran et al., 2010) (Table 2). Similarly, a phase 2 study with 78 cancer patients showed that the addition of oral cannabis extract (THC 2.5 mg/CBD 2.5 mg) to standard antimetric treatment during chemotherapy was associated with an increased proportion of patients achieving complete responses, and a lower incidence of nausea and vomiting(Grimison et al., 2020) (Table 2).

Summary and future research directions

In this review, we summarized the molecular mechanisms and clinical experience in support of CBD as a potential therapeutic compound for various diseases. Among them, CBD has been approved for the treatment of seizures associated with Lennox-Gastaut and Dravet syndromes, as well as tuberous sclerosis complex in the USA and EU. Further clinical and mechanistic studies are necessary to fully explore the therapeutic potential of CBD in various diseases. Although CBD exhibited promising therapeutic benefits for some diseases in initial clinical trials, a large percentage of clinical data comes from case studies or open-label trials, which must be interpreted cautiously due to the absence of placebo control, leading to possible biased effects associated with CBD treatment. Therefore, more well-designed, randomized, placebo-controlled, double-blind clinical trials with diverse populations are needed to evaluate and support the therapeutic efficacy and utility of CBD for multiple disease states.

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Author contributions

Jiangling Peng wrote the paper. Minjie Fan and Chelsea An edited the paper. Feng Ni, Wendong Huang and Jiankang Luo conceived the review topic and edited the paper.

Conflicts of interest

The authors declare no conflicts of interest.

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Figures

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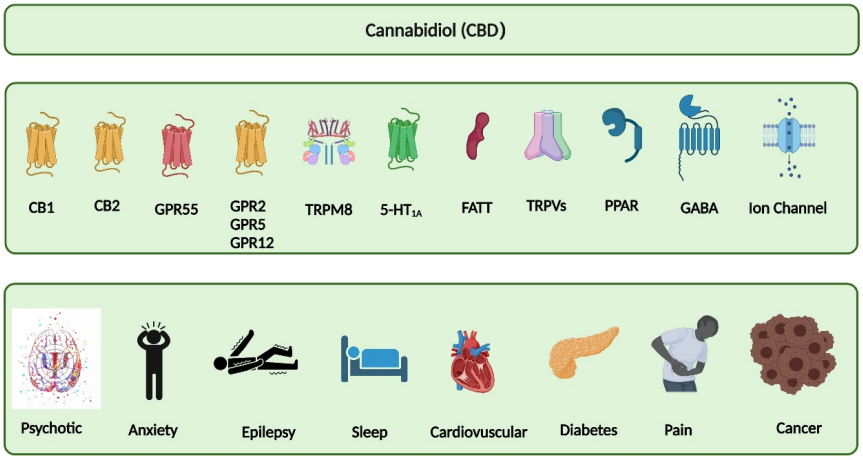

Figure 1. CBD related receptors and potential therapeutic benefits. CBD acts as agonist of the receptors TRPV1, PPARγ, and 5-HT_{1A}, and as antagonist of the receptor GPR55. CBD is an inverse agonist of the receptors GPR3, GPR5, and GPR12. Moreover, CBD antagonizes the action of CB1 and CB2 receptors agonists, and is suggested to act as an inverse agonist and a negative allosteric modulator of these receptors. CBD also inhibits FAAH, which results in increased anandamide levels. Anandamide activates CB1, CB2, and TRPV1 receptors. Clinical studies revealed that CBD has potential therapeutic benefits for psychotic disorders, anxiety, epilepsy, sleep, cardiovascular related diseases, diabetes, pain management and cancer treatment. 5-HT_{1A}, serotonin receptor 1A; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; FAAH, fatty acid amide hydrolase; GPR3, G-protein-coupled receptor 3; GPR6, G-protein-coupled receptor 6; GPR12, G-protein-coupled receptor 12; GPR55, G-protein-coupled receptor 55; PPARγ, peroxisome proliferator-activated receptor gamma; TRPV1, transient receptor potential vanilloid type 1.

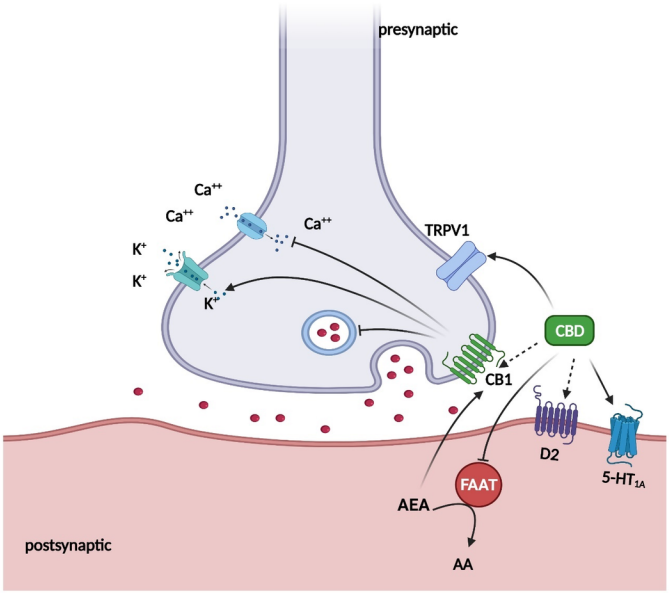

Figure 2. The proposed mechanism of CBD's effects on psychotic disorder . CBD inhibits FAAH, which results in increased anandamide levels. Anandamide activates CB1, CB2, and TRPV1 receptors. CBD

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can activate TRPV1 receptors directly. Partial agonism at D2 dopamine receptors might account for the effects of CBD on emotional memory processing by the ventral hippocampus.

AEA, anandamide; 5-HT_{1A}, 5-hydroxytryptamine 1A receptor; TRPV1, transient receptor potential vanilloid 1; D2, dopamine receptor 2; CB1, cannabinoid receptor1; FAAH, fatty acid amide hydrolase.

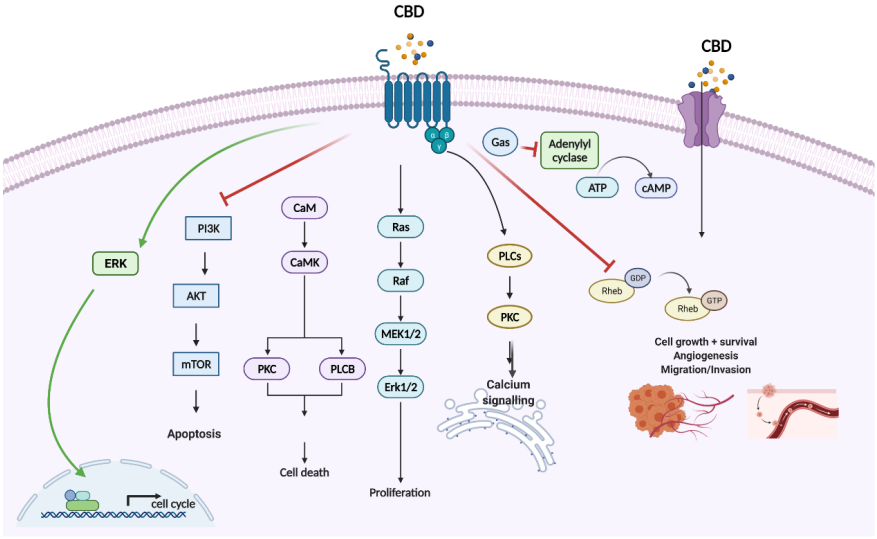

Figure 3. The pathway of CBDs' antitumor effects. The figure depicts the main signaling cascades elicited downstream of CB receptor activation by endocannabinoids and cannabinoids, which affect all the hallmarks of cancer: inhibition of cell proliferation; cell-cycle arrest; induction of cell death (apoptosis and autophagy); prevention of tumor progression (cancer cell vascular adhesiveness, invasiveness, and metastasis formation); inhibition of angiogenesis in tumor environment; and inhibition of the epithelial–mesenchymal transition.

Table 1. Pharmacodynamic properties of CBD at related receptors.

Receptor	Affinity (nM)	Function	Reference
CB1	Ki = 3.3˜4.9 microM	Inverse agonist/antagonist	(Tham et al., 2019; Thomas et al., 2007)
	IC50 = 0.27-0.96 microM	Negative allosteric modulators	(Laprairie et al., 2015)
CB2	Ki = 4.3 μM	Antagonist	(Martínez-Pinilla et al., 2017)
	EC_{50} = 503 nM	Inverse agonist	(Thomas et al., 2007)

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Receptor	Affinity (nM)	Function	Reference
	IC_{50} = 3 nM	Negative allosteric modulators	(Martínez-Pinilla et al., 2017)
GPR55	IC_{50} = 445 nM	Antagonist	(Ryberg et al., 2007)
TPPA1	EC_{50} = 110 nM	Agonist	(Luciano De Petrocellis et al., 2011)
TRPV1	EC_{50} = 1000 nM	Agonist	(Bisogno et al., 2001; Luciano De Petrocellis et al., 2011)
TRPV2	EC_{50} = 1250 nM	Agonist	(Luciano De Petrocellis et al., 2011)
TRPV3	EC_{50} = 3700 nM	Agonist	(L. De Petrocellis et al., 2012)
TRPV4	EC_{50} = 800 nM	Agonist	(L. De Petrocellis et al., 2012)
TRPM8	IC_{50} = 160 nM	Antagonist	(Luciano De Petrocellis et al., 2008)
5-HT_{1A}	N.D	Indirect agonist	(Ethan B. Russo et al., 2005)
PPARγ	EC_{50} = 2010 nM	Agonist	(Granja et al., 2012)
FAAH	27.5 μM	Inhibitor	(Bisogno et al., 2001; Elmes et al., 2015)
D2	Ki= 11 nM at $D2_{High}$ Ki = 2800 nm at $D2_{Low}$	Partial agonist	(Ryberg et al., 2007)

5-HT_{1A}, serotonin receptor 1A; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; FAAH, fatty acid amide hydrolase; FLAT: FAAH-like anandamide transporter protein; GPR3, G-protein-coupled receptor 3; GPR6, G-protein-coupled receptor 6; GPR12, G-protein-coupled receptor 12; GPR55, G-protein-coupled receptor 55; PPARγ, peroxisome proliferator-activated receptor gamma; TRPV1, transient receptor potential vanilloid type 1; TRPV2, transient receptor potential vanilloid type 2. TRPV3, transient receptor potential vanilloid type 3; TRPV4, transient receptor potential vanilloid type 4; $GABA_A$, γ-Aminobutyric acid type A (GABAA) receptors; T-Type Ca^{2+} receptors; D2, dopamine receptor 2; TRPM8, Transient receptor potential cation channel 8.

Table 2. Summary of CBD's clinical studies.

Disease	Study design	Study sample	Treatment schedule	Primary findings	Ref.
Psychotic	Psychotic Double-blind, placebo, controlled study	Psychotic Subjects with schizophrenia N = 28	Psychotic CBD or placebo 300 mg, 600 mg/day	Psychotic No improvements on selective attention were observed with either dose of CBD	Psychotic (Hallak et al., 2010)

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Disease	Study design	Study sample	Treatment schedule	Primary findings	Ref.
	Randomized, placebo-controlled, parallel group, fixed-dose study	Subjects with chronic schizophrenia N = 41	CBD or placebo 600 mg/day in addition to regular anti-psychotic treatment	Patient augmented with CBD showed no improvement in positive, negative and cognitive symptoms of schizophrenia	(Boggs et al., 2018)
	Double-blind, randomized, parallel-group, controlled study	Subjects with schizophrenia and schizophreni-form psychosis N = 42	CBD 800 mg/day or 800 mg Amisulpride/day	CBD was as effective as the amisulpride in treating the symptoms of psychosis. CBD had no effect on negative symptoms	(F. M. Leweke et al., 2012)
	Randomized, double-blind, placebo-controlled parallel group study	Subjects with schizophrenia N = 88	CBD or placebo 1000 mg/day in addition to regular anti-psychotic treatment, administered orally for 6 weeks.	Patients augmented with CBD showed improvement in positive and no improvements in negative and cognitive symptoms of schizophrenia	(Philip McGuire et al., 2018)
	Explorative, double-blind, active-controlled, randomized, parallel-groups trial	Subjects with schizophrenia or schizophreni-form psychosis N = 42	CBD 800 mg/day	CBD improves neurocognitive functioning with comparable efficacy in younger and acutely ill schizophrenia patients	(F. Markus Leweke et al., 2021)
Anxiety	Anxiety Randomized, double-blind, placebo controlled, cross-over study	Anxiety Subjects with SAD N = 10	Anxiety CBD or placebo 400 mg	Anxiety Decreases in state anxiety in the CBD group	Anxiety (Crippa et al., 2011)

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Disease	Study design	Study sample	Treatment schedule	Primary findings	Ref.
	Double-blind, placebo-controlled study	Healthy volunteers N = 10	CBD 300 mg or placebo	CBD decreases anxiety after SPS test	(A. W. Zuardi et al., 1993)
	Randomized, double-blind, placebo-controlled trial	Never-treated patients with SAD N = 24, Health control N = 12	CBD 600 mg or placebo	CBD reduces anxiety in SPS test	(Bergamaschi et al., 2011)
	Randomized, double-blind, placebo-controlled trial	Healthy subjects N = 60	CBD (100, 300 and 900 mg)	Anxiety was reduced with CBD 300 mg, but not with CBD 100 and 900 mg, in the post-speech phase	(Antonio W. Zuardi et al., 2017)
	Randomized, double-blind, placebo controlled	Healthy subjects N = 57	CBD (150, 300 and 600 mg)	Pretreatment with 300 mg of CBD significantly reduced anxiety during the speech	(I. M. Linares et al., 2019)
	A large Retrospective case series	Primary concerns of anxiety (n = 47) or poor sleep (n = 25), total 72	CBD 25-75 mg/day	Symptoms of anxiety decreased	(S. Shannon et al., 2019)
Epilepsy/ seizures	Epilepsy/ seizures	Epilepsy/ seizures	Epilepsy/ seizures	Epilepsy/ seizures	Epilepsy/ seizures
	Open-label interventional trial	Subjects with severe intractable, childhood-onset treatment-resistant epilepsy N = 214	CBD from 2 to 50 mg/kg/day	CBD might reduce seizure frequency and might have an adequate safety profile in children and young adults with highly treatment-resistant epilepsy	(Devinsky et al., 2016)
	Randomized, double-blind, placebo-controlled study	Subjects with the Lennox-Gastaut syndrome N = 225	CBD from 10 mg to 20 mg/kg/day	CBD resulted in reductions in frequency of drop seizures	(Devinsky et al., 2018)

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Disease	Study design	Study sample	Treatment schedule	Primary findings	Ref.
	Double-blind, placebo-controlled trial	Subjects with Dravet syndrome and medication resistant seizures N = 120	CBD up to 20 mg/kg/day	CBD reduced convulsive-seizure frequency	(Devinsky et al., 2017)
	Randomized, placebo-controlled trial	Subjects with drug resistant seizures in tuberous sclerosis complex N = 225	CBD 25 mg/kg/day or 50 mg/kg/day	CBD significantly reduced TSC-associated seizures.	(Thiele et al., 2021)
	Open-label, multiple-ascending dose, phase I/II study	Subjects with treatment-resistant epilepsy N = 61	CBD from 5 mg/kg to 20 mg/kg	The pharma-cokinetics (PK) results were obtained.	(Wheless et al., 2019)
Sleep/Insomnia	Sleep/Insomnia A large Retrospective case series	Sleep/Insomnia Primary concerns of anxiety (n = 47) or poor sleep (n = 25), total 72	Sleep/Insomnia CBD 25-75 mg/day	Sleep/Insomnia Sleep scores improved with the first month in 66.7% patients	Sleep/Insomnia (S. Shannon et al., 2019)
	Case report	A ten-year-old girl with PTSD	CBD 25 mg	Steady improvement in the quality and quantity of sleep	(Scott Shannon & Opila-Lehman, 2016)
	Double-blind, placebo-controlled, crossover study.	Healthy subjects N = 27	CBD 300 mg	CBD does not seem to interfere with the sleep cycle of healthy volunteers.	(I. M. P. Linares et al., 2018)
Blood pressure/vasorelaxant	Blood pressure/vasorelaxant	Blood pressure/vasorelaxant	Blood pressure/vasorelaxant	Blood pressure/vasorelaxant	Blood pressure/vasorelaxant
	Randomized crossover study	Healthy subjects N = 9	CBD 600 mg	CBD reduces resting BP and the BP increase to stress in humans	(Jadoon et al., 2017)
Diabetes	Diabetes	Diabetes	Diabetes	Diabetes	Diabetes

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Disease	Study design	Study sample	Treatment schedule	Primary findings	Ref.
	Randomized, double-blind, placebo-controlled, parallel group pilot study	Subjects with non-insulin-treated type 2 diabetes N = 62	CBD 100 mg twice daily	CBD decreased resistin and increased glucose-dependent insulinotropic peptide	(Jadoon et al., 2016)
Pain relieves	Pain relieves Randomized, double-blind, placebo-controlled, crossover study	Pain relieves Subjects with chronic, stable pain, poorly responsive to other modalities of control N = 34	Pain relieves Sublingual spray with2.5 mg of THC, 2.5 mg CBD, or 2.5 mg THC + 2.5 mg CBD or matching placebo.	Pain relieves Extracts with THC proved most effective in symptom control	Pain relieves (Notcutt et al., 2004)
	Prospective, single-arm cohort study	Subjects between 30 to 65 years old with chronic pain who have been on opioids for at least 1 year. N = 131	CBD-rich soft gels, 15.7 mg CBD each. Two gels daily	CBD could significantly reduce opioid use and improve chronic pain and sleep quality of patients	(Capano et al., 2020)
	Multicenter, double-blind, randomized, placebo-controlled, parallel-group trial	Patinets with cancer pain experienced inadequate analgesia despite chronic opioid dosing N = 177	22-32 mg/day THC and 20-30 mg/day CBD.	CBD combine with THC showed a statistically significantly reduction of pain NRS score	(J. R. Johnson et al., 2010)
Cancer	Cancer Report of objective clinical responses	Cancer 119 cancer patients	Cancer CBD 5 mg to 15 mg/day	Cancer Clinical responses were seen in 92% of the 119 cases	Cancer (Kenyon et al., 2018)
	Pilot, randomized, double-blind, placebo-controlled phase II trial	Subjects suffering from CINV N= 16	CBD 2.5 mg and THC 2.7 mg or placebo	A higher proportion of patients in the cannabis group experienced a complete response	(Duran et al., 2010)

Disease	Study design	Study sample	Treatment schedule	Primary findings	Ref.
	Randomized, placebo-controlled, phase 2 crossover trial	Subjects experienced CINV N = 78	CBD 2.5 mg and THC 2.5 mg or placebo	THC:CBD was active and tolerable in preventing CINV	(Grimison et al., 2020)

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