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MINI REVIEW

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A narrative 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 which 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) and peroxisome proliferator-activated receptor gamma (PPARγ). By modulating the activities of these receptors, CBD exhibits multiple therapeutic effects, including neuroprotective, antiepileptic, anxiolytic, antipsychotic, anti-inflammatory, analgesic and anticancer properties. CBD could also be applied to treat or prevent COVID-19 and its complications. Here, we provide a narrative review of CBD's applications in human diseases: from mechanism of action to clinical trials.

KEYWORDS

cannabidiol, cannabinoid receptor, clinical trial, endocannabinoid system

1 | 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.[1] Around 1000 BC, cannabis was used as an analgesic, hypnotic, tranquilliser and anti-inflammatory agent in India.[2] The therapeutic use of cannabis was explored in the early 19th century in Western medicine. Due to the psychoactive properties, research and uses of cannabis has been hindered by decade-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. Hemp (defined in the United States 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.[3]

Cannabidiol (CBD) (Figure 1) is one of the most abundant extracts from *C. 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.[4] The human endocannabinoid system was discovered soon after the identification of cannabinoid receptor 1 (CB1). This system includes two main cannabinoid receptors (CB1 and CB2)[5] and endogenous ligands called endocannabinoids. There are two endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG); both of them derive from arachidonic acid.[6] Both endogenous endocannabinoids AEA (also known as *N*-arachidonoylethanolamide and arachidonoylethanolamide) and 2-AG are derivatives of arachidonic acid and modulate CB1 and CB2 activities.[7] The concentration of endocannabinoids is regulated by the enzymes fatty acid amide hydrolase (FAAH, also known as oleamide hydrolase, AEA amidohydrolase and EC 3.5.1.99) and monoacylglycerol lipase (MAGL), which act by degrading AEA and 2-AG, respectively.[8] The CB1 receptor is highly expressed in the central nervous system (CNS) and is particularly abundant in brain areas associated with motor control, emotional responses, motivated behaviour 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.[9] Epidiolex® oral solution was also approved for tuberous sclerosis complex (TSC) by the FDA in 2020 and by the EMA in 2021.[10] Sativex®, an oral spray containing CBD and delta-9 THC in a 1: 1 ratio, is approved in several countries including United Kingdom, European Union (EU) and Canada for the treatment of multiple sclerosis-associated spasticity.[11] CBD has also exhibited tremendous treatment potential towards 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.[12–14] An allosteric binding activity of CBD on these two receptors has been reported.[15–17] For example, CBD binds to CB1 as an inverse agonist/antagonist with Ki from 3.3 to 4.8 nM, but binds to CB2 as an antagonist with Ki = 4.3 nM (Table 1). In the ECS, CBD was shown to influence endocannabinoid balance via binding to fatty acid-binding proteins (producing an EC50 of 27.5 μM; Table 1).[18] The TRPVs are the molecular targets for CBD with a highly potent (EC50 of TRPV1 = 1 μM, EC50 of TRPV2 = 1.25 μM, EC50 of TRPV3 = 3.7 μM and EC50 of TRPV4 = 0.8 μM; Table 1).[19–21] Moreover, CBD binds to PPARγ at EC_{50} of 2 μM (Table 2).[22] Many other potential molecular targets have been investigated, including GPR55 (EC50 value of 445 nM; Table 1),[23] 5-HT receptors,[24–26] $GABA_A$ receptors and[27] TRPM8 receptor.[28] 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.[29]

Among these receptors, FAAH, 5-HT_{1A} and TRPV1 receptors were found to play a role in CBD's antipsychotic properties. The anti-depressive and anxiolytic activities of CBD may be ascribed for the inhibition ability of CBD on inactivation of AEA and the interaction between CBD and 5- HT_{1A}. CBD has been revealed that has high affinity to receptors and channels related to

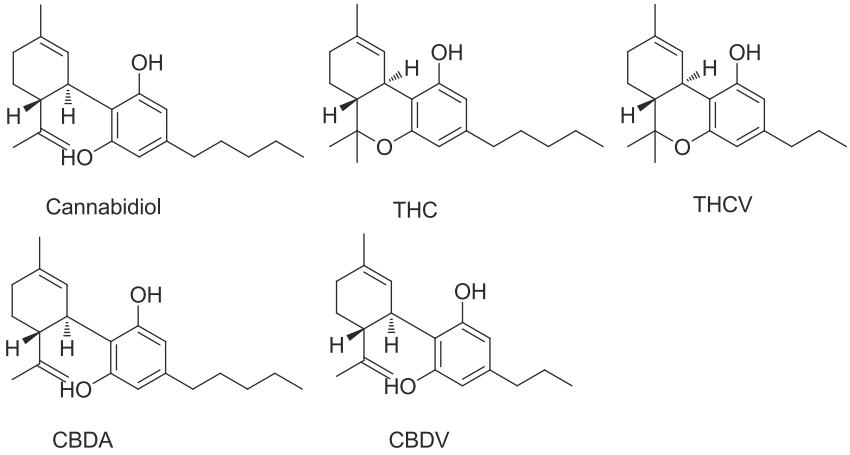


FIGURE 1 Chemical structures of CBD, THC, THCV, CBDA and CBDV

TABLE 1 Pharmacodynamic properties of CBD at related receptors

Receptor	Affinity (nM)	Function	Reference
CB1	Ki = 3.3 ~ 4.9mM	Inverse agonist/antagonist	13,14
	IC50 = 0.27–0.96mM	Negative allosteric modulators	15
CB2	Ki = 4.3 μM	Antagonist	17
	EC_{50} = 503 nM	Inverse agonist	13
	IC_{50} = 3 nM	Negative allosteric modulators	17
GPR55	IC_{50} = 445 nM	Antagonist	23
TPPA1	EC_{50} = 110 nM	Agonist	19
TRPV1	EC_{50} = 1000 nM	Agonist	19,21
TRPV2	EC_{50} = 1250 nM	Agonist	19
TRPV3	EC_{50} = 3700 nM	Agonist	20
TRPV4	EC_{50} = 800 nM	Agonist	20
TRPM8	IC_{50} = 160 nM	Antagonist	28
5-HT_{1A}	N.D.	Indirect agonist	24
PPARγ	EC_{50} = 2010 nM	Agonist	22
FAAH	27.5 μM	Inhibitor	18,21
D2	Ki = 11 nM at $D2_{High}$ Ki = 2800 nm at $D2_{Low}$	Partial agonist	23

Abbreviations: 5-HT_{1A}, serotonin receptor 1A; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; D2, dopamine receptor 2; FAAH, fatty acid amide hydrolase; FLAT, FAAH-like anandamide transporter protein; $GABA_A$, γ-aminobutyric acid type A (GABAA) receptors; GPR12, G-protein-coupled receptor 12; GPR3, G-protein-coupled receptor 3; GPR55, G-protein-coupled receptor 55; GPR6, G-protein-coupled receptor 6; PPARγ, peroxisome proliferator-activated receptor gamma; TRPM8, transient receptor potential cation channel 8; 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.

epilepsy, including TRPV receptors, T-type Ca^{2+} channels, serotine receptors and GPR55. CBD has also been found be involved in the interaction with the Ca^{2+} channels, which are linked to the pathogenesis of epilepsy. CBD has been shown to influence sleep by inhibition of FAAH, which is related to the concentration of AEA. CBD also inhibits GABA receptors, which may influence sleep. Studies have been shown that CBD affects cardiovascular system by interacting with CB1, TRPV1, PPARs and 5-HT_{1A}. The effects of CBD on diabetes may be ascribed from its suppression of IFN-γ and TNF-α production and inhibition of T-cell proliferation. CB1, CB2 and GPR2 are the putative targets for CBD's pain relief. The antitumour effects of CBD may mainly work through the TRPV channels. Clinical studies reveal that CBD has potential therapeutic benefits for psychotic disorders, anxiety, epilepsy, sleep, cardiovascular diseases, diabetes, pain management and cancer treatment (Figure 2).

Previously, there were some excellent reviews on CBD, such as pain management,[30–32] CNS disorders,[33] anticancer,[34,35] pharmacology and pharmacokinetics (PK)[5,36] and clinical trials.[32,37,38] This review will discuss the molecular mechanisms of action of the therapeutic effects of CBD within different disease contexts. We focus on diseases in which there are human experiments or clinical studies with CBD (Table 2).

2 | PSYCHOTIC DISORDER

Schizophrenia is a psychotic disorder characterized by distortions of reality, disturbances of thought and 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).[39]

First-line antipsychotic drugs for schizophrenia act by blocking the central dopamine (DA) D2 receptors via receptor antagonism.[40] 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 DA 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

TABLE 2 Summary of CBD's clinical studies

Disease	Study design	Study sample	Treatment schedule	Primary findings	Ref.
Psychotic					
	Double-blind, placebo, controlled study	Subjects with schizophrenia $N = 28$	CBD or placebo 300 mg, 600 mg/day	No improvements on selective attention were observed with either dose of CBD	45
	Randomized, placebo-controlled, parallel group, fixed-dose study	Subjects with chronic schizophrenia $N = 41$	CBD or placebo 600 mg/day in addition to regular antipsychotic treatment	Patient augmented with CBD showed no improvement in positive, negative and cognitive symptoms of schizophrenia	47
	Double-blind, randomized, parallel-group, controlled study	Subjects with schizophrenia and schizophreniform 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	41
	Randomized, double-blind, placebo-controlled parallel group study	Subjects with schizophrenia $N = 88$	CBD or placebo 1000 mg/day in addition to regular antipsychotic treatment, administered orally for 6 weeks	Patients augmented with CBD showed improvement in positive and no improvements in negative and cognitive symptoms of schizophrenia	46
	Explorative, double-blind, active-controlled, randomized, parallel-group trial	Subjects with schizophrenia or schizophreniform psychosis $N = 42$	CBD 800 mg/day	CBD improves neurocognitive functioning with comparable efficacy in younger and acutely ill schizophrenia patients	48
Anxiety					
	Randomized, double-blind, placebo controlled, crossover study	Subjects with SAD $N = 10$	CBD or placebo 400 mg	Decreases in state anxiety in the CBD group	63
	Double-blind, placebo-controlled study	Healthy volunteers N = 10	CBD 300 mg or placebo	CBD decreases anxiety after SPS test	64
	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	65
	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	66
	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	67

(Continues)

TABLE 2 (Continued)

Disease	Study design	Study sample	Treatment schedule	Primary findings	Ref.
	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	68
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	85
	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	86
	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	87
	Randomized, placebo-controlled trial	Subjects with drug-resistant seizures in tuberous sclerosis complex $N = 225$	CBD 25 or 50 mg/kg/day	CBD significantly reduced TSC-associated seizures	88
	Open-label, multiple-ascending dose, Phase 1/2 study	Subjects with treatment-resistant epilepsy $N = 61$	CBD from 5 to 20 mg/kg	The pharmacokinetics (PK) results were obtained	89
Sleep/insomnia					
	A large retrospective case series	Primary concerns of anxiety ($n = 47$) or poor sleep ($n = 25$), total 72	CBD 25–75 mg/day	Sleep scores improved with the first month in 66.7% patients	68
	Case report	A 10-year-old girl with PTSD	CBD 25 mg	Steady improvement in the quality and quantity of sleep	99
	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	101
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	110
Diabetes					
	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	119

(Continues)

TABLE 2 (Continued)

Disease	Study design	Study sample	Treatment schedule	Primary findings	Ref.
Pain relieves					
	Randomized, double-blind, placebo-controlled, crossover study	Subjects with chronic, stable pain, poorly responsive to other modalities of control $N = 34$	Sublingual spray with2.5 mg of THC, 2.5 mg CBD, or 2.5 mg THC + 2.5 mg CBD or matching placebo	Extracts with THC proved most effective in symptom control	129
	Prospective, single-arm cohort study	Subjects between 30 and 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	130
	Multicentre, double-blind, randomized, placebo-controlled, parallel-group trial	Patients 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	134
Cancer					
	Report of objective clinical responses	119 cancer patients	CBD 5 mg to 15 mg/day	Clinical responses were seen in 92% of the 119 cases	155
	Pilot, randomized, double-blind, placebo-controlled Phase 2 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	159
	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	160

indicates that CBD binds to various molecular targets to exert its antipsychotic properties. CBD may bind to FAAH and FLAT (FAAH-like AEA transporter) to inhibit AEA degradation and uptake,[41,42] facilitate 5-HT_{1A} receptor-mediated serotonergic neurotransmission[24,43] and activate transient receptor potential vanilloid type 1[21] (Figure 3).

A 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[44] (Table 2). However, a study investigating the effects of CBD on selective attention of schizophrenic patients discovered that single and acute administration of CBD (300 or 600 mg) seems to have no beneficial effects on the performance of schizophrenic patients in the Stroop Colour Word Test[45] (Table 2). The first controlled, randomized, double-blind clinical trial was conducted in 2012[41] (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 AEA 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[46] (Table 2). This 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[47] (Table 2). In an explorative clinical trial, CBD demonstrated efficacy in improving neurocognitive functioning in young and acutely ill schizophrenia patients[48] (Table 2).

Currently, there are only five clinical records on CBD treatment for schizophrenics available from the Clinical Trial website[49] (Table 2). Large-scale controlled and

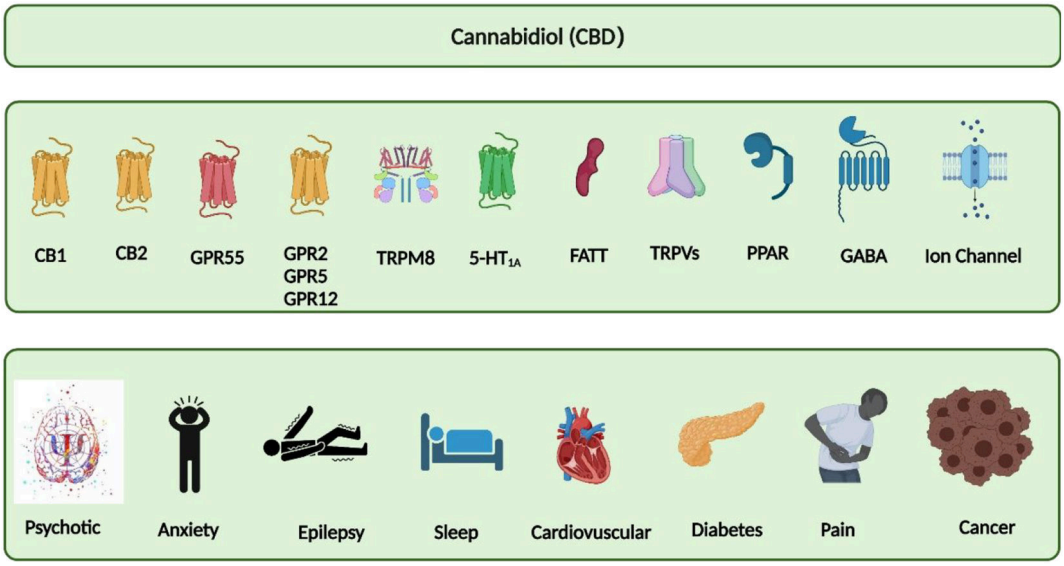
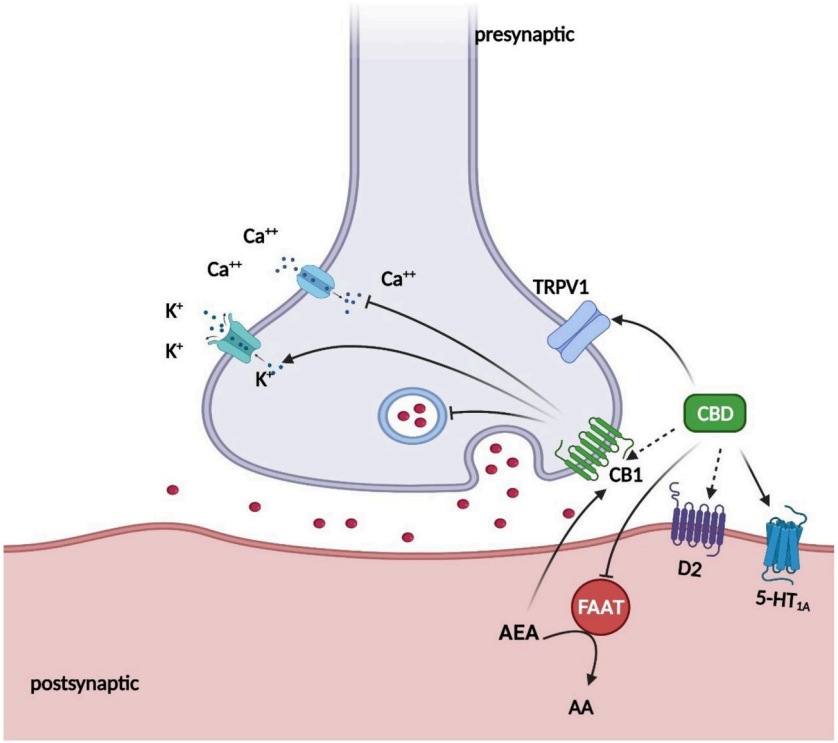


FIGURE 2 CBD-related receptors and potential therapeutic benefits. CBD acts as the agonist of the receptors TRPV1, PPARγ and 5-HT_{1A} and as antagonist of the receptor GPR55. CBD is an inverse agonist of the receptors GPR3, GPR5 and GPR12. Moreover, CBD antagonizes the action of CB1 and CB2 receptors' 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; GPR12, G-protein-coupled receptor 12; GPR3, G-protein-coupled receptor 3; GPR55, G-protein-coupled receptor 55; GPR6, G-protein-coupled receptor 6; PPARγ, peroxisome proliferator-activated receptor gamma; TRPV1, transient receptor potential vanilloid type 1

FIGURE 3 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 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. 5-HT_{1A}, 5-hydroxytryptamine 1A receptor; AEA, anandamide; CB1, cannabinoid receptor1; D2, dopamine receptor 2; FAAH, fatty acid amide hydrolase.TRPV1, transient receptor potential vanilloid 1



randomized clinical trials are still needed to evaluate the long-term efficacy and safety of this putative new antipsychotic agent.

3 | ANXIETY

Anxiety disorders have the highest lifetime prevalence of any mental illness worldwide, leading to high social and economic burden.[50] 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.[51] Results from neuroimaging and biochemical studies[52–54] suggest that the pathophysiology of anxiety-related disorders is largely related to key neurotransmitters, including DA,[55] norepinephrine (NE),[56] γ-aminobutyric acid (GABA),[57] and serotonin (5-HT).[58] Multiple mechanisms may account for the antidepressive and anxiolytic activities of CBD. The proposed anti-anxiety activity may result from CBD inhibiting the inactivation of AEA, a neurotransmitter[59,60] and/or CBD interacting with 5-HT_{1A} receptors.[61,62]

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 and crossover study investigated the neural effects of CBD on human pathological anxiety. In this study, 10 men with generalized social anxiety disorder (SAD) were given an oral dose of CBD (400 mg) or placebo[63] (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 parahippocampal 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.[63]

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. In this study, four independent groups were set to receive placebo, CBD (300 mg), diazepam (10 mg) and ipsapirone (5 mg). The results revealed that CBD treatment (300 mg) can decrease anxiety after SPS test[64] (Table 2). A similar study aimed to compare the treatment of CBD on healthy control patients and treatment-naïve 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[65] (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.[66] In a subsequent double-blind study, 57 healthy males were allocated to receive oral CBD at doses of 150, 300 or 600 mg; only the cohort receiving the 300-mg CBD dose had significantly reduced anxiety during the SPS test, while no significant differences were observed between groups receiving CBD 150 mg or 600 mg and placebo.[67]

A large retrospective case series analysis revealed that within the clinical context, CBD adjuvant therapy (25–175 mg/day) may also benefit the outpatient psychiatric population suffering from anxiety-related disorders.[68] 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.[68]

Overall, current clinical studies support CBD as a promising therapy for treatment of anxiety. There were some positive results on the effective dosing of CBD,[66,67] 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.

4 | 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 worldwide suffer from epilepsy. The main symptom of epilepsy is recurrent seizures, but other symptoms include periods of unusual behaviour, sensations and sometimes loss of awareness.[69] A seizure is an uncontrolled abnormal excessive or synchronous neuronal activity in the brain that causes temporary abnormalities in muscle tone or movements, behaviours, sensations or states of awareness.[70] 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.[71,72]

Throughout the long history of cannabis use, CBD has exhibited the ability to reduce seizures.[73] 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),[74] T-Type Ca^{2+} channels,[75] serotonin receptors (5-HT_{1A} and 5-HT_{2A}),[76] opioid receptors[77] and GPR55.[78] 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.[79] In vitro studies show that CBD reduced epileptiform activity and promoted desensitization of TRPV1 channels with consequent normalization of intracellular Ca^{2+} concentration.[74] The low-voltage T-Type Ca^{2+} channels are also linked to the pathogenesis of absence epilepsy.[80] 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.[81] CBD may exert anti-epileptic action by interacting with and blocking the T-type Ca^{2+} channels.[82] CBD also shows a high affinity towards serotonin receptors (5-HT_{1A} and 5-HT_{2A}).[24,83] These receptors may be involved in epilepsy even though their role is still not entirely clear.[76]

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.[84] An open-label expanded-access trial has evaluated the preliminary efficacy and safety of CBD as adjuvant anti-epileptic therapy at varying doses (2–5 mg/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 were observed in the study population[85] (Table 2). Additionally, CBD was demonstrated to be safe and effective as an adjuvant anti-epileptic therapy for the treatment of drop seizures in patients with the LGS ($n = 225$) in a double-blind, placebo-controlled trial[86] (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.[86] CBD is also an effective adjuvant anti-epileptic therapy for the treatment of drug-resistant seizures in patients with the DS ($n = 120$). 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 in reducing the frequency of convulsive seizures in DS patients.[87] Oral CBD is also indicated for the treatment of drug-resistant seizures in TSC. Recently, CBD doses of 25 or 50 mg/kg/day was shown to be effective in reducing TSC-associated seizures in a double-blind, placebo-controlled, randomized clinical trial ($n = 224$ patients)[88] (Table 2). However, as has been previously documented,[84–87] CBD use as an adjuvant anti-epileptic therapy within the TSC context is associated with a higher frequency of adverse events such as diarrhoea and elevated liver transaminase levels compared to placebo.[88]

The PK and tolerability of discontinuous oral CBD (single dosing at 5, 10 or 20 mg/kg and multiple dosing at 10, 20 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)[89] (Table 2). The PK data indicated variable inter-individual CBD exposure with single-dose administration; this variability was reduced with multiple dose administration.[89] Short-term administration was generally safe and well tolerated although a higher frequency of diarrhoea, increased weight, somnolence and psychomotor hyperactivity were observed with increased CBD dose.[89]

5 | SLEEP/INSOMNIA

Insomnia is a common sleep disorder that occurs in either isolation or comorbid to other medical or psychiatric conditions.[90] There has been extensive interest in the use of cannabis as a therapy for the treatment of insomnia.[91] The endocannabinoids (2-AG and AEA) produce neuromodulatory actions mainly through the actions on the CB1 receptor.[7] 2-AG and AEA are found in brain and throughout the body and can be produced by almost all types of cells in the body.[92,93] The interaction between cannabis and endocannabinoids with CB1 seems to be important in sleep stability.[94] CBD has been shown to increase concentrations of the major endogenous cannabinoid, AEA, by inhibiting the enzyme degrading it, FAAH.[21] Increasing endogenous AEA via FAAH inhibition normalized deficits in stage N3 sleep in cannabis-dependent men experiencing withdrawal.[95] This is consistent with preclinical data showing that AEA promotes slow wave sleep, possibly through correlated increase of extracellular adenosine.[96] 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,[27] which may also influence sleep.[97]

To date, well-designed randomized controlled trials employing objective measures to assess the effects of cannabis on sleep duration and quality are lacking in the clinical insomnia population. Previous studies[98] have shown potential benefits in the therapeutic use of Sativex®, 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[99] (Table 2). Indeed, preclinical evidence[100] has demonstrated that the anxiolytic effects of CBD likely is 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 Pittsburgh Sleep Quality Index (PSQI), 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.[68] 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) does not seem to alter the sleep cycle of healthy volunteers[101] (Table 2).

Cannabis is commonly believed to be a useful sleep aid.[102] 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.

6 | CARDIOVASCULAR SYSTEM/ BLOOD PRESSURE/ VASORELAXANT

The complex mechanism of action of CBD makes it possible to have multidirectional influence on the cardiovascular system.[103] A number of preclinical studies have shown beneficial effects of CBD on the cardiovascular system.[104] Mechanistic studies showed that CBD affects cardiovascular function by interacting with a variety of receptors, including CB1,[105] CB2,[106] TRPV1,[107] PPARs[108] and 5-HT_{1A}.[109]

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 ($n = 9$)[110] (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.[110] 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 CBD treatment, but target sites for CBD remain to be elucidated.

7 | 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.[111] CBD is a potent anti-inflammatory agent.[112] 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.[113] Studies have shown that CBD significantly inhibited insulitis in non-obese diabetic (NOD) mice.[114,115] CBD has multiple desirable effects in the context of hyperglycaemia, mainly through its anti-inflammatory[116] and antioxidant properties.[117] Interestingly, a chronic overactivation of the endocannabinoid system has been identified in obesity and Type 2 diabetes,[118] 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 analogue of THC) in insulin-naïve patients with Type 2 diabetes ($n = 62$) were investigated in a randomized, double-blind, placebo-controlled and parallel group pilot study. In this 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[119] (Table 2). The trial failed to meet the primary efficacy endpoint which was a change in HDL cholesterol concentrations from baseline. Interestingly, THCV significantly decreased fasting plasma glucose and improved pancreatic beta-cell function, while CBD decreased resistin and increased glucose-dependent insulin tropic peptide.[119]

8 | PAIN MANAGEMENT

Pain has long been characterized as a subjective experience encompassing sensory-physiological, motivational-

affective and cognitive-evaluative components.[120] 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 centres.[121] Inflammatory pain is caused by noxious stimuli that occur during the inflammatory or immune response.[122] Chronic pain is defined as recurrent or constant pain that lasts or recurs for longer than 3 months and can result in disability, suffering and a physical disturbance.[123] Chronic pain affects 20% of the population, with musculoskeletal disorders being the most common cause.[124] 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.[125]

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[12] and has allosteric activity on both CB_1 and CB_2 receptors.[15,17] 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.[126] 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 centres.[5] Another putative CBD target is GPR2, which is expressed in the brain and spinal cord and is involved in pain reception.[127] CBD may also relieve pain by regulating the serotonin 5-HT_{1A} receptor[24] and TRPV1.[128]

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: CBD run-in period. Pain assessments were made using a Visual Analogue 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.[129]

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 opioid use for at least 1 year[130] (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), 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.[130] There is also moderate evidence from a meta-analysis to support the analgesic use of cannabinoids in treating chronic, non-cancer pain defined as fibromyalgia, rheumatoid arthritis, neuropathic pain or mixed pain (Table 2). The mean treatment duration was 2.8 weeks.[131]

Cancer pain is a common problem, and 70%–90% of patients with advanced cancer experience significant pain.[132] Opioids remain the keystone for the treatment of moderate to severe cancer pain.[133] 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[134] (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 regard 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.[134]

9 | 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.[135,136]

The antitumour effects of CBD may primarily be mediated through the TRPV channels.[137] These channels play an important role in regulating the cytoplasmic calcium concentration from the extracellular sources as well as the calcium stored within the endoplasmic reticulum (ER). Disruption of cellular calcium homeostasis can lead to increased production of reactive oxygen species (ROS), ER stress and cell death.[138] (Figure 4). 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.[34,35] Multiple cancer-related studies demonstrated that CBD exhibits pro-apoptotic and anti-proliferative actions[139] in different types of tumours and may also exert anti-migratory, anti-invasive,[140,141] anti-metastatic and perhaps anti-angiogenic properties. CBD potently inhibited the growth of different tumours,

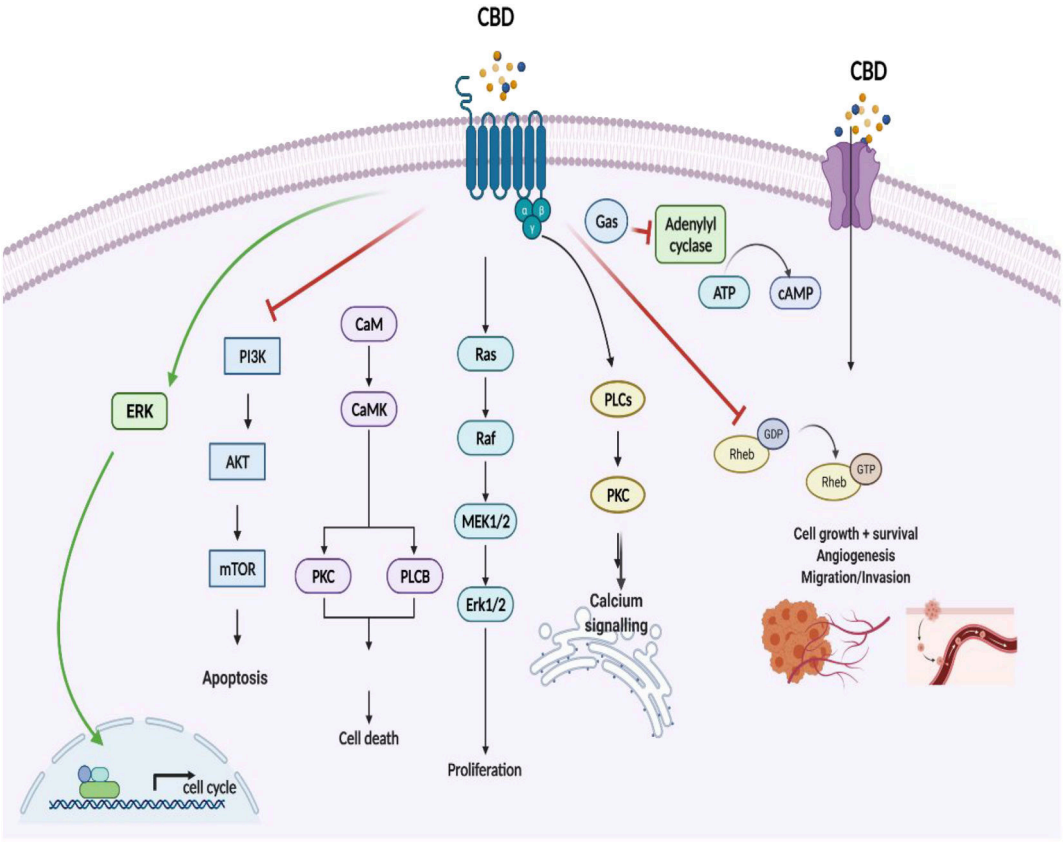


FIGURE 4 The pathway of CBDs' anti-tumour effects.[168] The figure depicts the main signalling cascades elicited downstream of CB receptor activation by endocannabinoids and cannabinoids, which affect all the hallmarks of cancer: inhibition of cell proliferation; cell-cycle arrest; induction of cell death (apoptosis and autophagy); prevention of tumour progression (cancer cell vascular adhesiveness, invasiveness and metastasis formation); inhibition of angiogenesis in tumour environment; and inhibition of the epithelial–mesenchymal transition

including those of breast cancer,[142] lung cancer,[143] colon cancer,[144] prostate cancer,[145] colorectal cancer,[146–148] glioma,[149–151] leukaemia/lymphoma[152,153] and endocrine cancer.[154,155] 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 tumour patients enrolled under the Pharmaceutical Specials scheme; of the 119 patients, 28 received CBD oil as the only treatment[156] (Table 2). CBD was administered on a 3 days on and 3 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. Antitumour effect was observed when the CBD treatment duration was at least 6 months. In the case of a 5-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 tumour volume had decreased by around 60% after 10 months of treatment. Other patients with prostate cancer, breast cancer, oesophageal cancer and lymphoma also saw a reduction in circulating tumour cells and tumour 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.[156]

Other than directly being used to treat cancer, CBD has also been used to reduce the adverse effects associated with cancer treatment. Chemotherapy-induced nausea and vomiting (CINV) remain major adverse effects of cancer chemotherapy.[157] The lack of adequate CINV control may be partly attributed to the fact that anti-emetic treatment regimens are guided by risk factors, including level of emetogenicity of chemotherapeutic agents.[158] CINV adversely impacts patients' quality of life. Patients

rated nausea as their first most feared symptom and vomiting as their third.[159] 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[160] (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 anti-emetic treatment during chemotherapy was associated with an increased proportion of patients achieving complete responses and a lower incidence of nausea and vomiting[161] (Table 2).

10 | THERAPEUTICAL POTENTIAL IN THE COVID-19

The COVID-19 pandemic has resulted in unprecedented loss of life and economic, social and health consequences.[162] An estimated 45% of adults in the United States reported that their mental health had been negatively impacted due to stress over the virus.[163] There were some results from clinical trials to support CBD for treating anxiety, depression and other neurological complications.[164,165] The anti-anxiety or anti-depression therapeutic properties of CBD could be applied to treat COVID-19-associated mental health conditions. But there are limited data from well-designed clinical trials to support the use of CBD for treating mental health issue associated with COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for COVID-19. There was one study reporting that CBD inhibited SARS-CoV-2 infection. CBD and its metabolite, 7-OH-CBD, have potential therapeutical benefit for SARS-CoV-2 at early stages of infection.[166] Currently, nine active clinical trials on CBD for the treatment of COVID-19 and related diseases are listed on FDA clinical trial website. Based on the encouraging results, CBD may be a promising candidate drug for treating COVID-19 and related disease. In an open-label, single-site, randomized clinical trial, the safety and efficacy of CBD therapy for the reduction of emotional exhaustion and burnout symptoms among frontline healthcare professionals working with patients with COVID-19 was investigated. The results indicated that CBD therapy reduced the symptoms of burnout and emotional exhaustion.[167] However, further double-blind, placebo-controlled clinical trials are needed to confirm those results.

11 | 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 LGS and DS, as well as TSC in the United States 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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CONFLICT OF INTEREST

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