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INVITED REVIEW

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Beneficial effects of cannabidiol from *Cannabis*

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Abstract

Cannabis, traditionally used for recreation due to psychoactive compounds in its leaves, flowers, and seeds, has not been thoroughly explored for potential therapeutic benefits. Δ9-*trans*-Tetrahydrocannabinol, a key cannabinoid in cannabis, causes hallucinogenic effects and delirium symptoms. In contrast, cannabidiol (CBD) does not induce hallucinations and has shown effectiveness in treating symptoms of various rare, incurable diseases. Cannabis exhibits neuroprotective, anti-inflammatory, anti-thrombotic, anti-bacterial, analgesic, and antiepileptic properties, recently attracting more attention. This review aims to summarize comprehensively the impact of cannabis on human health, focusing on endocannabinoids and their receptors. It also delves into recent CBD research advancements, highlighting the compound's potential medical applications. Overall, this paper provides valuable insights into the prospective development of medical cannabis, with a particular emphasis on CBD.

Keywords Cannabis, Cannabidiol, Endocannabinoid system, Medical industry, Δ9-*trans*-tetrahydrocannabinol

Introduction

Cannabidiol (CBD), a significant phytocannabinoid from the *Cannabis sativa* plant, has recently gained considerable attention for its wide-ranging therapeutic potential and its apparent absence of psychoactive effects [1, 2]. Unlike tetrahydrocannabinol (THC), another well-known cannabis component known for its psychoactive properties [3], CBD has become a focus of scientific research and public interest due to its potential medicinal benefits [4–6]. CBD, not inducing a "high" like THC, shows promise in treating various medical conditions [1]. This interest in CBD is due to its interaction with the endocannabinoid system, a vital regulatory system in the human body, and its potential in treating conditions such as epilepsy, chronic pain, anxiety, and inflammation [7]. As the scientific community delves deeper into the therapeutic effects of CBD, exploring and understanding its mechanisms of action, potential health benefits, and associated risks becomes imperative [6]. This research focusing on CBD aims to contribute to the growing body of knowledge surrounding this compound and its medical applications. By elucidating the biological pathways through which CBD exerts its effects and evaluating its efficacy in specific medical contexts, we can advance our understanding of its therapeutic potential and inform evidence-based practices in healthcare.

In this review, we delve into existing literature to examine the current state of knowledge on CBD. Our exploration encompasses its pharmacological properties, mechanisms of action, and the accumulating evidence supporting its use in various medical conditions. Additionally, we critically assess challenges and controversies surrounding CBD research, including regulatory considerations and potential adverse effects. Through

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this comprehensive analysis, we aim to contribute to the ongoing dialogue on CBD's therapeutic utility and its implications for clinical practice and public health.

Cannabis, an annual plant in the Cannabaceae family, has given rise to numerous varieties and cultivars. These plants bear anemophilous (wind-pollinated) flowers [8]. Notably, cannabis species exhibit dioecy, with plants being distinctly male or female rather than hermaphroditic [9]. Originating from Central Asia, cannabis's wild variant in India is classified into subspecies, differentiated by morphological features, particularly leaf shape [10]. Currently, three species of the genus *Cannabis* are distributed worldwide: *C. sativa* subsp. *sativa*, *C. sativa* subsp. *indica*, and *C. sativa* subsp. *ruderalis* [11]. Additionally, due to the anemophilous nature of their flowers, natural crossbreeding occurs frequently, resulting in the description of over 600 cannabis varieties thus far [12].

The main characteristics of the three recognized cannabis species are summarized as follows: *C. sativa* L. (*C. sativa* subsp. *sativa*), approximately 5 m tall, is indigenous to East Asia but is now globally distributed due to widespread cultivation [13]. Larger than *C. indica*, it has thin, elongated leaves, resulting in a lighter dry weight. It predominantly thrives in equatorial regions and has a higher THC and lower CBD content compared to *C. indica*. Notable for its psychoactive effects, *C. sativa* stimulates creative thinking, induces euphoria, and increases vitality [14]. *C. indica* L. (*C. sativa* subsp. *indica*) is approximately 2 m tall and is mainly produced in Central Asia and India [10]. It has dense leaves, is relatively small, and its flowering time is 15–25 days faster than that of *C. sativa* [15]. Moreover, compared with *C. sativa*, *C. indica* has lower THC levels and a higher CBD content. *C. indica* is often used in inducing deep sleep, alleviating pain, enhancing appetite, and providing relaxation [16]. Additionally, *C. indica* serves as a key ingredient in the production of hashish [3]. *C. ruderalis* Janisch (*C. sativa* subsp. *ruderalis*), typically less than 1 m in height [17], is predominantly found in Eastern Europe and Russia, where it adapts well to short and irregular sunlight exposure [13]. Owing to its low THC and CBD content, this species is primarily employed in crossbreeding with other cannabis species, aimed at developing more resilient strains [14].

Cannabis is classified not only by variety but also by its active components [18]. The psychoactive elements in cannabis vary depending on strain or species, influencing their respective applications [3]. In the US, the official English terms for cannabis are "marijuana" and "hemp." The Department of Agriculture (USDA) and the broader scientific community classify cannabis based on morphological features and THC content, which significantly impacts its psychoactive effects [19]. Cannabis with a THC concentration of 0.3% or lower is designated as "hemp," while varieties exceeding this THC threshold are termed "marijuana." Hemp, with its minimal THC levels, is utilized primarily in industrial applications. In contrast, marijuana, containing 6%-20% THC, is used predominantly for recreational and medical purposes [11].

Cannabis is reported to contain up to 545 phytocompounds, with 441 being non-cannabinoids and the remaining 104 identified as cannabinoids. The 441 non-cannabinoids primarily consist of terpenes and flavonoids [20]. Among the 104 cannabinoids, vegetable cannabinoids are a noteworthy group, predominantly found in cannabis. This group includes compounds such as THC, CBD, cannabitriol, cannabicyclol, cannabinol, cannabielsoin, and cannabichromene [14].

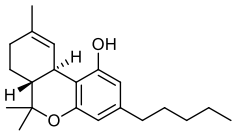
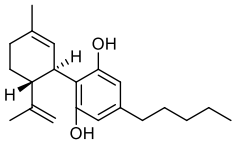
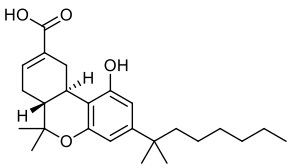
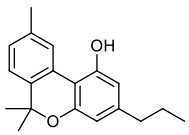
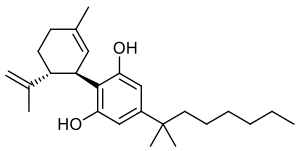
Cannabinoids

Cannabinoids, chemical components of cannabis, notably include THC and CBD. As previously mentioned, around 104 cannabinoids constitute a significant portion of cannabis's active compounds. However, cannabinoids are not exclusively found in cannabis [21]. These compounds are classified into three categories based on synthesis and origin: phytocannabinoids, synthetic cannabinoids, and endocannabinoids [22]. Phytocannabinoids originate in plants, synthetic cannabinoids are manufactured chemically, and endocannabinoids are biosynthesized in the human body [23]. Disruptions in the endocannabinoid system, which is regulated by endocannabinoids, can lead to various physiological issues, such as anxiety, abnormal sleep patterns, appetite irregularities, digestive problems, pain, and weakened immunity. Interestingly, humans produce their own cannabinoids, essential for the endocannabinoid system's functionality [24]. Key phytocannabinoids and their analogs, including THC, CBD, ajulemic acid (AJA), cannabivarin (CBV), and (−)-5'-(1,1-dimethylheptyl) cannabidiol (DMH-CBD), are listed in Table 1. Synthetic cannabinoids, further categorized into classical, non-classical, and aminoalkylindole types, encompass significant compounds such as HU-210, HU-211, WIN 55,212-2 (CID5311501), and CP55940 (CID3086156) as shown in Table 2. Additionally, the human body produces endogenous cannabinoids, including anandamide (ANA), 2-arachidonoyl glycerol ether, and 2-arachidonoyl glycerol, with ANA being the most prevalent endocannabinoid, detailed in Table 3 [25].

THC

THC (Fig. 1) is a phytocannabinoid with one of the highest proportions in cannabis. This compound acts as the principal psychotropic component of cannabis, with THC being its most prevalent isomer [26]. THC, like

Table 1 Phytocannabinoids from cannabis

Compound	Chemical structure	Pharmacological activity	References
THC		$CB_1 = CB_2$ agonist	[63–65]
CBD		No activity at CB1 or CB2 antagonism of non-CB1 or non-CB2 modulator of α1-adrenoreceptor inhibition of AEA uptake and metabolism	[66–68]
AJA		$CB_1 = CB_2$ agonist	[69]
CBV		$CB_1 = CB_2$ agonist	[70]
DMH-CBD		$CB_1 = CB_2$ agonist inhibition of AEA uptake	[68]

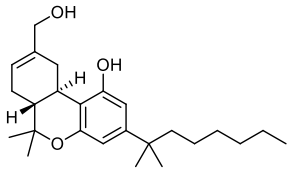
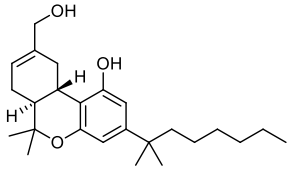
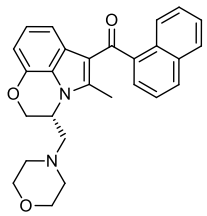
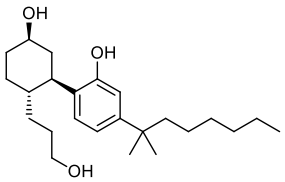
other cannabinoids, contains phenolic groups that protect neurons from oxidative stress caused by glutamate-induced excitotoxicity. Additionally, THC is poorly soluble in water but dissolves effectively in organic solvents, including hydrocarbons and ethanol [27]. It interacts with the body's cannabinoid system, leading to alterations in brain chemistry. Being lipophilic, THC can affect the brain by nonspecifically binding to fatty tissues, including brain tissue. As a psychotropic drug, THC causes changes in brain function, influencing perception, emotion, time awareness, and behavior [28]. Recreational cannabis use can enhance mental activity, rendering THC a controlled and regulated substance [29].

Nevertheless, THC provides notable medical benefits. For instance, it acts as a painkiller by interacting with cannabinoid receptors in the body, thereby regulating nerve function and reducing pain signals sent to the brain [30]. Additionally, THC alleviates symptoms associated with sleep disorders, anxiety, and insomnia and functions as an antidepressant. However, excessively high doses of THC can negatively affect thinking, concentration, perception, and mental function, potentially leading to behavioral disorders, hallucinations, delusions, and psychosis [31]. Due to these side effects and associated risks, THC remains a regulated substance [32].

CBD

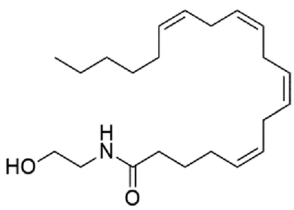
CBD (Fig. 1), one of 104 cannabinoids identified in cannabis, comprises up to 40% of plant extracts' phytocompounds [20]. Discovered in 1940, CBD was initially thought to have negligible pharmaceutical properties [24]. Subsequent studies, however, have revealed CBD's medical potential. Notably, CBD possesses four side-chain homologs: methyl, *n*-propyl, *n*-butyl, and *n*-pentyl groups [33]. Although CBD and THC exhibit significant structural similarities, CBD's distinct features include a bicyclic structure and a pentyl side chain comprising terpene and aromatic rings, differentiating it from THC [34]. In CBD's molecular structure, two aromatic rings are arranged perpendicularly, contributing to the absence of psychoactive effects, a characteristic not shared with THC [35]. CBD presents a promising alternative for patients who rely on more hazardous opioid-based analgesics for pain management. It alleviates overall discomfort associated with chronic pain and inflammation [36]. CBD has shown effectiveness in managing both invasive and neurological pain by interacting with pain

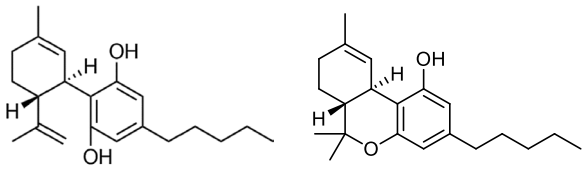
Table 2 Synthetic cannabinoids

Compound	Chemical structure	Pharmacological activity	References
Classical			
HU-210		$CB_1 = CB_2$	[63]
HU-211		No activity at CB_1 or CB_2 noncompetitive NMDA antagonist	[71]
Non-classical			
WIN 55,212–2		$CB_1 = CB_2$ agonist	[63, 64, 72]
Aminoalkylindol			
CP55940		$CB_1 = CB_2$ agonist	[33, 63, 72, 73]

transmission receptors, thereby reducing pain sensations. Consequently, CBD is beneficial in treating conditions like arthritis, endometriosis, multiple sclerosis, and fibromyalgia [37]. Additionally, CBD exhibits neuroprotective effects, preventing neuronal damage induced by chronic diseases [38]. Its potent anti-inflammatory properties contribute to the treatment of inflammation by blocking the activation of cytokines and chemokines, which are the primary proteins responsible for inflammatory responses in the body [39]. Acting as a vasodilator, CBD can alleviate pain associated with stenosis and inflammation of arteries and veins. It also reduces pain linked to poor blood circulation [40]. CBD is often chosen over THC, the most common ingredient in cannabis, due to its lack of psychoactive effects, such as hallucinations [24].

Table 3 Endogenous cannabinoids (eicosanoids)

Compound	Chemical structure	Pharmacological activity	References
ANA		$CB_1 > > CB_2$ agonist $TRPV_1$ agonist	[63, 74–76]



1 **2**

Fig. 1 Chemical structures of CBD (**1**) and THC (**2**)

Endocannabinoid system

The term "endocannabinoid" originates from "endo," meaning internal to the human body, and "cannabinoid," referring to active substances in cannabis that interact with cannabinoid receptors [41]. This system includes receptors in the brain and body that correspond to cannabinoids found in cannabis plants [42]. Cannabis compounds, such as THC and CBD, engage these receptors, eliciting a response [43]. Research in the early 1990s, focusing on THC's mechanism of action led to the discovery of the endocannabinoid system [44]. The first identified cannabinoid receptor, now known as CB1, was discovered through studies showing that orphan G protein-binding receptors from a cerebral cortex cDNA library facilitated THC's pharmacological effects [45]. Later, in 1993, a G protein-binding receptor in the human promyelocytic leukemia cell line HL60 was identified as the second cannabinoid receptor, later termed CB2 [46].

The endocannabinoid system comprises two G protein-coupled cannabinoid receptors (GPCRs), CB1 and CB2, along with enzymes that synthesize and break down endocannabinoids and their ligands [47]. Both receptor types connect to adenylyl cyclase and mitogen-activated protein kinase (MAP kinase) through a G protein [48]. CB1 receptors, predominantly located in the central nervous system, are among the most abundant GPCRs in the brain. They are involved in the neurotransmission of γ-aminobutyric acid (GABA) and glutamate [3, 49]. CB1 receptor activation leads to a decrease in cyclic adenosine monophosphate (cAMP) levels and suppresses the activity of cAMP-dependent protein kinases. Additionally, stimulating CB1 receptors enhances MAP kinase activity, affecting synaptic plasticity, cell migration, and neuronal growth. In contrast, CB2 receptors are mostly found in white blood cells and other immune cells, though some are also present in the central nervous system, including in microglial cells [50].

The distribution of receptors in the body closely aligns with the physiological effects of cannabinoids [41]. THC primarily interacts with CB1 receptors, influencing their presence [51]. These receptors are predominantly found in the brain and spinal cord, with high concentrations in areas associated with behavior changes [48]. Notably, the hypothalamus and amygdala, which regulate appetite, stress, anxiety, nausea, and the processing of memory and emotions, contain these receptors [52]. CB1 receptors, also located in nerve endings, play a role in diminishing pain sensations [53]. Conversely, CBD primarily interacts with CB2 receptors, affecting their presence and distribution [54]. CB2 receptors are mainly found in immune cells of the peripheral nervous system, notably in immune tissues and organs like the spleen, bone marrow, thymus, and tonsils. Their activation triggers an immune response that helps reduce inflammation, a key factor in managing various chronic diseases [25].

Benefits of CBD

Cannabis research history and antipsychotic properties of CBD

The history of cannabis research, particularly the investigation of CBD's antipsychotic properties, is crucial for grasping the compound's diverse benefits [55]. Although CBD's discovery dates back to the 1940s, it initially attracted scant research due to perceptions of insignificant pharmacological properties. Interest surged in the early 1970s when research indicated CBD's potential to mitigate THC's effects. This insight spurred detailed investigations, notably by Elisaldo Carlini, into CBD, THC, and other cannabinoids [56]. Carlini's experiments included synthetic extracts with THC, cannabinol, and CBD [57]. These experiments showed that taking THC and CBD together reduced anxiety and psychotic symptoms more effectively than taking THC alone [58]. This finding highlights the importance of the combination of THC and CBD in products like Sativex, a commercial cannabinoid-based drug. Sativex is significant for reducing pain and convulsions in patients with multiple sclerosis [59]. Notably, CBD exhibits anxiolytic (anxiety-reducing) properties [1]. This was demonstrated in rodent experiments using the elevated plus maze (EPM) test, a standard test for general anxiety. In this test, CBD showed an anxiolytic effect at low doses, but this effect decreased at higher doses. However, with repeated administrations, there was a reduction in anxiety in rodents, suggesting CBD's potential effectiveness against panic, post-traumatic stress disorder (PTSD), obsessive–compulsive disorder, and stress [60]. Moreover, the impact of CBD on anxiety in real-life situations was demonstrated in a double-blind trial using a simulated public speaking test (SPST). In this trial, subjects given various doses of CBD, along with ipsapirone and diazepam, showed significant reductions in anxiety. This trial provides valuable information about CBD's anxiolytic effects [61]. Crucially, the antipsychotic profile of CBD distinguishes it from traditional antipsychotic drugs [55]. Unlike haloperidol, CBD does not cause ankylosis, a

motor disorder typically linked to antipsychotic medications [62]. Instead, high doses of CBD lead to increased levels of prolactin, similar to the effect of clozapine, suggesting an atypical antipsychotic profile [63]. Additionally, CBD is effective in reducing hyperlocomotion induced by amphetamines and pre-pulse inhibition (PPI) in rats. This shows promise for treating motor disorders related to conditions like Parkinson's disease [64]. This thorough examination of CBD's historical context and antipsychotic properties enhances our understanding of its varied therapeutic benefits [1].

CBD as an adjuvant to treat schizophrenia

Schizophrenia, marked by unusual patterns in thinking, emotions, wills, and impulses, presents considerable challenges for those affected [65]. It leads to a detachment from reality and problems in social interaction [66]. Typically emerging in adolescence, the disorder appears in individuals showing introverted behaviors and nonsocial, aggressive characteristics, often driven by genetic influences [67]. Recent advances in treating schizophrenia have introduced targeted drug therapies, underlining the necessity of vigilant monitoring for early detection and intervention [68]. Schizophrenia symptoms are generally classified into two categories: positive and negative [69]. Positive symptoms include hallucinations, heightened excitement, and forgetfulness [70]. In contrast, negative symptoms are characterized by depression, emotional dullness, aphasia, a lack of warmth in emotional expression, and social withdrawal [71]. Traditional medications for schizophrenia usually function as dopamine antagonists, working to suppress dopamine activity [72]. However, CBD, derived from cannabis, represents a new approach as it does not depend on dopamine antagonism [73]. This difference makes CBD a potential candidate for investigating new treatment methods for schizophrenia. A recent study investigated the stability and effectiveness of CBD as a supplementary treatment for schizophrenia [74]. Regarding stability, CBD showed fewer side effects than the commonly used medication "Amisulpride." Additionally, CBD was effective in improving symptoms of schizophrenia that were resistant to haloperidol. Notably, CBD has minimal side effects and does not rely on dopamine D2 antagonism, distinguishing it from conventional schizophrenia treatments. Despite these encouraging results, further large-scale studies are necessary to fully evaluate the suitability and efficacy of CBD as an adjunct in treating schizophrenia [75]. This ongoing research into CBD's potential in schizophrenia treatment underscores its promise as an emerging area in psychiatric research.

CBD as an epilepsy treatment

Dravet Syndrome (DS), identified as a rare and severe epilepsy form manifesting in the first year of life, remains a focal point in epilepsy research [76]. Originally termed severe myoclonic epilepsy in infancy, DS poses a considerable challenge [77]. This is exemplified by a 5 year-old girl's case, who experienced up to 50 bilateral ankylosing epilepsy seizures monthly. Notably, a significant breakthrough occurred with CBD-rich cannabis treatment, leading to a remarkable 90% reduction in seizures for this patient. This success has sparked substantial interest in CBD as a potential epilepsy treatment. The growing demand for medical cannabis and CBD treatment, spurred by media coverage and the hopes of patients severely affected by epilepsy, has accelerated recent research into CBD's therapeutic efficacy [78]. Anecdotal reports of successful CBD treatments for severe epileptic seizures have fueled increased public and academic interest. Rigorous studies, such as placebo-controlled, randomized, and controlled trials, have consistently shown the effectiveness of pharmaceutical-grade CBD in epilepsy treatment. The significant approvals by the US Food and Drug Administration (FDA) and the European Union for pharmaceutical-grade CBD to treat DS, Lennox-Gastaut syndrome, and tuberous sclerosis complex highlight the rising acceptance of CBD in mainstream medicine [79]. Numerous studies have confirmed the effectiveness of CBD in treating epilepsy-related brain disorders, such as DS, Lennox-Gastaut syndrome, and tuberous sclerosis complex. CBD has demonstrated a substantial reduction in seizure frequency in patients with these conditions, accompanied by minimal withdrawal symptoms. Additionally, emerging evidence indicates CBD's positive effects on behavior and cognition [80]. Epilepsy, frequently resistant to conventional drugs, presents a notable challenge [81]. Cannabinoids, especially CBD, show promise for patients experiencing epileptic seizures [80]. Although the effects are largely positive, concerns remain about the potential side effects of CBD. This highlights the necessity for more studies to verify the compound's safety. Physicians face difficulties in prescribing cannabinoids because of the limited scientific research on CBD. This underscores the continued challenges in incorporating these treatments into standard medical practices fully.

Chronic pain relief effects of CBD

Numerous studies have highlighted the pain-relieving properties of CBD, presenting it as a potential alternative to mitigate the risks associated with opioid addiction and physical dependence [82]. Opioids, powerful painkillers derived from opium or synthesized equivalents, are a primary choice for managing chronic pain [83]. They work

by acting on opioid receptors in the central nervous system, effectively blocking the release of neurotransmitters that transmit pain signals [84]. Despite their effectiveness in relieving severe or acute chronic pain, especially in conditions like terminal cancer, myocardial infarction, and childbirth, their prolonged use leads to serious side effects. These include developing resistance, addiction, physical dependence, drowsiness, constipation, and, in extreme cases, fatal overdose [85]. Therefore, it is crucial to explore alternative methods to reduce the ongoing dependence on opioids [86]. In a notable study by Capano et al., 97 chronic pain patients, each with a history of opioid use for at least two years, were involved. The study found that administering CBD extracts led to a significant reduction in opioid use for 53.2% of the participants during the eight-week period. Remarkably, some patients completely stopped using opioids. In contrast, those who did not receive CBD showed no decrease in opioid consumption. The study highlighted a notable improvement in quality of life (QoL) for 94% of the participants. For patients treated with CBD, the pain index (PDI) decreased by 36.4% at week 4 and 34.1% at week 8, demonstrating CBD's effectiveness in pain management. Sleep quality, assessed by the Pittsburgh Sleep Quality Index (PSQI), improved for CBD-treated patients, with a decrease from 12.09 to 10.3 over eight weeks. This suggests that CBD, unlike opioids, may have a positive impact on sleep quality [87]. In conclusion, the study showed that replacing highly addictive opioids with CBD effectively alleviates pain, enhances sleep quality, and improves the overall QoL for individuals suffering from chronic pain [88].

Effects of CBD in cancer patients

Cannabinoids, recently approved for use in palliative care due to their pain-relieving and antiemetic properties, are now also showing potential anticancer properties. Research across multiple cancers indicates that synthetic, exogenous, endogenous, and phytocannabinoids affect cell proliferation and survival by modulating key signaling pathways. A growing number of in vitro and in vivo studies consistently demonstrate cannabinoids' ability to inhibit cancer cell proliferation, induce autophagy and apoptosis, and obstruct angiogenesis and metastasis [89, 90]. In exploring the antitumor effects of cannabinoids, researchers have closely examined an in vivo model of pancreatic cancer. A study focusing on cannabis receptors has revealed the presence of CB1 and CB2 receptors in pancreatic cancer cells, noting their markedly low or undetectable mRNA levels in normal pancreatic cells [91]. Supporting these findings, Michalski et al., among others, have confirmed the increased expression of cannabinoid receptors in pancreatic cancer tissues compared to normal pancreatic tissues [92]. More recent research has shed light on the crucial role of G protein-coupled receptor 55 (GPR55), which are regulated by the tumor suppressor p53, in the development of pancreatic cancer through mechanisms involving cell cycle regulation and the MAPK signaling pathway. Studies have verified that CBD interacts with the GPR55 receptor, inhibiting its activity [93]. This interaction results in inhibited growth, disrupted cell cycle progression, and suppressed MAPK signaling in pancreatic cancer cell lines, including ASPC1, HPAFII, BXPC3, and PANC1. Significantly, when used alongside the cytotoxic anticancer drug gemcitabine, CBD substantially reduced the growth of HPAFII and PANC1 cells. Gemcitabine targets cancer cells during DNA replication, and recent evidence suggests that inhibiting GPR55 may enhance its effectiveness against pancreatic cancer cells [92]. Furthermore, cannabinoids significantly promote apoptosis in cells experiencing DNA damage induced by gemcitabine [94]. These findings collectively highlight the diverse anticancer properties of cannabinoids, presenting promising opportunities for future therapeutic interventions in cancer treatment (Table 4).

CBD and diabetes

Diabetic cardiomyopathy, defined as left ventricular cardiomyopathy independent of arteriosclerosis or coronary artery disease, presents a complex challenge [95, 96]. The causes of heart dysfunction in diabetic patients are complex and varied. Many animal studies have explored the protective role of CBD in myocardial cells subjected to high glucose levels in diabetes, highlighting its potential in preventing and treating diabetic complications [97]. CBD has been shown to reduce myocardial oxidative stress caused by diabetes [98]. Importantly, CBD reduces the build-up of diabetes-related inducible nitric oxide synthase (iNOS), thus alleviating nitrosative stress from diabetes. Additionally, CBD is effective in reducing diabetes-induced myocardial apoptosis and inhibiting the activation of the diabetes-induced mitogen-activated protein kinase (MARK). CBD treatment also counters hemodynamic changes caused by diabetes, particularly in left ventricular diastole and systole function, typically observed at 12 weeks of diabetes. Notably, an 11-week CBD intervention within this period significantly reduces this dysfunction. CBD also inhibits oxidative/nitrogen stress, inflammation, cell death, and fibrosis pathways in diabetes. These findings highlight CBD's significant potential in treating diabetic cardiovascular disease and its complications [99]. In a different study, treatment with CBD showed notable effectiveness in reducing diabetes occurrence in non-obese diabetic (NOD) mice. The incidence decreased from 86% in untreated control mice

Table 4 Benefits of CBD

CBD benefits	Supporting research	References
Antipsychotic Properties	Numerous studies suggest that CBD possesses antipsychotic properties, offering relief from symptoms without the side effects associated with traditional antipsychotic drugs	[1, 55-62, 64]
CBD as an Adjuvant for Schizophrenia	Research supports the potential role of CBD as an adjuvant in the treatment of schizophrenia, complementing conventional medications and enhancing overall therapeutic outcomes	[73– 75]
CBD in Epilepsy Treatment	CBD has demonstrated significant promise in reducing seizures, particularly in conditions like Dravet syndrome. Its effectiveness has led to approval for use in epilepsy treatment by regulatory authorities	[78–81]
Chronic Pain Relief Effects	A multitude of studies provide compelling evidence for the efficacy of CBD in alleviating chronic pain. CBD has been shown to provide relief for conditions such as arthritis and multiple sclerosis, contributing to improved quality of life	[87–88]
Effects on Cancer Patients	Research indicates that CBD exhibits anticancer properties by regulating critical cell pathways, inhibiting proliferation, and inducing apoptosis in cancer cells. This suggests potential therapeutic benefits for cancer patients	[89–93]

to 30% in those treated with CBD. This treatment was associated with a significant drop in the plasma levels of pro-inflammatory cytokines, including IFN-γ and TNF-α. Additionally, CBD substantially lowered the production of Th1-associated cytokines in T-cells and peritoneal macrophages activated in vitro while increasing the levels of Th2-associated cytokines, such as IL-4 and IL-10, in comparison to untreated control mice. Histological analysis of the pancreatic islets in CBD-treated mice showed a significant decrease in insulitis. These results indicate that CBD may reduce the incidence of diabetes, potentially via immunomodulatory actions, by suppressing and delaying the production of inflammatory cytokines in NOD mice [100]. The comprehensive insights from these studies highlight the potential of CBD in managing various aspects of diabetes and related complications.

CBD and COVID-19

SARS-CoV-2, the virus responsible for COVID-19, has a broad host range that includes humans, birds, rodents, and various mammals. It is the largest RNA virus identified to date, with a genetic size of approximately 30 kb [101]. Initially isolated from human airway epithelial cells, severe acute respiratory syndrome-associated coronavirus-2 (SARS-CoV-2) bears resemblance to its predecessor, SARS-CoV. The virus uses the angiotensin-converting enzyme 2 (ACE2) as its cellular entry point. ACE2 is found in high concentrations in the lungs, nasal mucosa, kidneys, testicles, and the gastrointestinal tract. Regions with elevated ACE2 levels, particularly the lungs and intestinal epithelium, are more vulnerable to SARS-CoV-2 infection. Interestingly, ACE2 expression tends to increase with age, which correlates with the severity of the disease. This finding suggests that reducing ACE2 levels could be a viable approach to decrease disease susceptibility [102]. CBD, known for its impact on gene expression and inflammation, has been shown to regulate ACE2 expression in inflammation-induced 2D tissues. Additionally, given the role of transmembrane protease serine subtype 2 (TMPRSS2) in SARS-CoV-2 infection, where TMPRSS2 primes the virus spike protein for entry, inhibitors of TMPRSS2 are critical for blocking viral entry. While treatment with CBD alone does not significantly inhibit TMPRSS2, administering a cannabis extract results in decreased TMPRSS2 expression [103]. Researchers at the Global Cannabis Innovation Center, Oregon State University, have developed a mass spectrometry-based chemical screening method. This method confirms the effects of cannabis-derived compounds on SARS-CoV-2. Cannabinoids and cannabigerolic acid (CBDA) demonstrate binding to the spike protein, which SARS-CoV-2 uses for human cell penetration, inhibiting key stages of infection. Notably, CBDA binds to spike proteins, preventing their interaction with the ACE2 receptor and hindering cell entry. Combining CBD with vaccination could potentially enhance the suppression of SARS-CoV-2 infection rates [104]. These findings suggest a complex interplay between CBD and SARS-CoV-2, offering avenues for further exploration in therapeutic strategies and preventive measures (Table 4).

Industrial application of CBD

Cannabis plants, with their diverse components, including roots, stems, leaves, flower stalks, and seeds, present varied applications across multiple industries. Traditionally, stem bark has been used in the textile industry to produce thread, clothing, and ropes. The stems are employed in the manufacturing of paper, building materials, and fuel. Seeds are utilized in food and herbal medicine, while seed oil is used in fuel, cosmetics, and massage oil production. The flower stalks and leaves,

which are rich in cannabinoids, are increasingly acknowledged as potential raw materials for medicinal products [105].

In Canada, the company "Wildflower" is actively developing wellness products that incorporate CBD, such as capsules, tinctures, soap, cool sticks, and healing sticks. Epidiolex, a prescription CBD-based medication developed in the UK and approved by the FDA for treating childhood epilepsy, demonstrates the expanding therapeutic applications of CBD. The legalization of CBD for medical use has spurred ongoing research in CBD processing and product development, which is facilitating the integration of smart farm cultivation with CBD-based drug production [106].

In the US, a burgeoning trend involves the rise of cannabis cosmetics, frequently referred to as CBD cosmetics, which contain hemp extract. These products are garnering attention for their perceived benefits in alleviating muscle pain, inflammation, and skin dryness. CBD oil, a key component in the CBD skincare market, is renowned for treating acne and is particularly effective for dry and sensitive skin due to its targeted action on deficient cells. Hemp extract, rich in essential fatty acids, not only moisturizes the skin but also relieves itching from psoriasis and exhibits powerful antioxidant effects. This makes it a fundamental ingredient in various skin, body, and hair care products [107].

CBD oil, known for its analgesic properties, influences cannabinoid receptor activity, diminishes inflammation, and engages with neurotransmitters to mitigate chronic pain. It is utilized in managing pain linked to multiple sclerosis and improving life quality and sleep in individuals with rheumatoid arthritis. Moreover, CBD oil is effective in lessening anxiety and depression, interacting with serotonin and GABA receptors to foster relaxation without adverse effects. It assists in improving sleep in patients with insomnia or chronic pain, enhances appetite in cancer patients, and decreases seizure frequency in epilepsy patients, frequently outperforming the effectiveness of current medications [3].

Several cannabinoid-based medications have entered the commercial market with regulatory approval, targeting various medical conditions. Epidiolex, used for epilepsy, contains only CBD and excludes THC. It has shown effectiveness in treating DS and Lennox-Gastaut syndrome [108]. Cesamet, prescribed for multiple sclerosis, and Sativex, for appetite enhancement in AIDS patients, are other examples. Additionally, marinol is approved for controlling nausea post-chemotherapy.

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Declarations

Competing interests
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