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REVIEW ARTICLE

Cannabidiol as an immune modulator: A comprehensive review

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Abstract
Cannabidiol (CBD), a non-psychoactive phytocannabinoid derived from *Cannabis sativa*, has emerged as a promising therapeutic agent due to its diverse pharmacological properties, including potent anti-inflammatory, neuroprotective, and immunomodulatory effects. CBD modulates immune responses, including the regulation of T cell activity, induction of macrophage apoptosis, suppression of pro-inflammatory cytokines, and modulation of signaling pathways involved in inflammation and immune homeostasis. A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science databases to identify relevant preclinical and clinical studies on CBD's immunomodulatory effects. Preclinical and clinical studies demonstrate its efficacy in treating autoimmune diseases such as Type 1 diabetes, multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease, along with its potential in neuropathic pain and cancer therapy. Recent advancements in nanotechnology-based delivery systems have further enhanced CBD's therapeutic potential by improving its solubility, bioavailability, and targeted delivery, enabling innovative approaches for wound healing, inflammation management, and cancer treatment. However, challenges such as variability in immune responses, limited long-term safety data, and potential drug-drug interactions persist. This review comprehensively examines CBD's pharmacokinetics, pharmacodynamics, and immunomodulatory mechanisms, highlighting its clinical potential, existing limitations, and future directions in advancing its integration into precision medicine and immune regulation.

Keywords Cannabidiol · Pharmacokinetics · Pharmacodynamics · Immune cells · Immune modulation · Autoimmune diseases

1 Introduction

Cannabinoids are a class of structurally similar chemicals, primarily found in plant-derived cannabis, commonly known as marijuana. Among these, tetrahydrocannabinol (THC) is the primary psychoactive constituent. While *Cannabis* contains 538 identified chemical compounds, only about 100 of them are naturally occurring cannabinoids known as phytocannabinoids (El Oihabi et al. 2024). These phytocannabinoids are categorized into 11 major subclasses: cannabinol (CBN), cannabigerol (CBG), delta 9-tetrahydrocannabinol (THC), cannabielsoin, D8THC, cannabicyclol, cannabichromene (CBC), cannabitriol, cannabidiol (CBD), cannabinodiol, and miscellaneous (Berman et al. 2018). Among these, CBD and delta-9-THC have drawn the greatest scientific attention. CBD was first isolated from Mexican marijuana by Adams and colleagues in the late 1930s (Adams et al. 1940) while in the 1963, Mechoulam and Shvo were the first to study THC synthesis and isolate other cannabinoids. They also confirmed the stereochemical structures of THC and CBD, laying the groundwork for future cannabinoid research (Mechoulam and Shvo 1963; Hively et al. 1966).

CBD is non-psychoactive and differs from THC, the compound in cannabis responsible for the 'high' sensation

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and potential dependence (Legare et al. 2022). The use of CBD-based products has expanded significantly, driven by its purported therapeutic benefits. While Epidiolex® remains the only FDA-approved CBD product, unregulated CBD formulations are widely available for self-medication in regions with lenient cannabis regulations (Britch et al. 2021). Despite increasing popularity, clinical trials remain limited, and the pharmacological mechanisms of CBD, including its pharmacokinetics and pharmacodynamics, are not yet fully understood.

CBD exerts diverse pharmacological effects through its interaction with molecular targets such as cannabinoid receptors, serotonin receptors, ion channels, and nuclear receptors (Martini et al. 2023). These interactions underpin its potential to modulate inflammatory pathways, immune responses, and oxidative stress, making it a promising therapeutic candidate for conditions such as inflammation, autoimmune diseases, neuropathic pain, and cancer. Preclinical and clinical studies have demonstrated that CBD modulates immune cells, including macrophages, neutrophils, mast cells, and T cells, by influencing cytokine production and other inflammatory processes (Nichols and Kaplan 2020). However, the effects of CBD on immune function remain inconsistent, with studies reporting both anti-inflammatory and pro-inflammatory outcomes under different conditions.

Given the multifaceted pharmacological properties of CBD, it holds significant promise as a therapeutic agent. Yet, the translation of preclinical findings into clinical applications faces challenges, including limited understanding of its mechanisms, variability in pharmacokinetics across formulations and species, and potential drug-drug interactions. This review aims to comprehensively summarize the current knowledge on CBD's pharmacokinetics, pharmacodynamics, immunomodulatory effects while exploring its applications in autoimmune diseases, safety data and drug-drug interactions. By integrating available evidence, this work seeks to address existing gaps and pave the way for the clinical development of CBD-based therapies.

2 Pharmacokinetics (PK) of CBD

2.1 Pre-Clinical PK

The pharmacokinetic profile of CBD is influenced by various factors, including the route of administration, formulation type, dosing schedule (single or multiple doses), and the specific formulation system used (Polidoro et al. 2022a, b; Limsuwan et al. 2024). CBD absorption in the gastrointestinal tract is assumed to be low, with oral bioavailability reported at only 19% in dogs (Samara et al. 1988). The formulation type plays a critical role in oral absorption, as demonstrated in this study assessing plasma CBD kinetics in 32 dogs after a single oral dose of four formulations (oil-based, nanoemulsion, water-soluble, semi-solid treat) in a 1-period, 4-treatment parallel design, showing that the nanoemulsion had the fastest absorption (T_{max} ~ 3 h) and highest C_{max} (314 µg/L), the water-soluble form had a similar plasma profile to the oil-based form, and the semi-solid treat resulted in the lowest CBD levels (Limsuwan et al. 2024). Similarly, a study in cats evaluated the pharmacokinetics of a CBD-rich hemp paste, showing a CBD C_{max} of 282.0 ± 149.4 ng/mL with a half-life of ~ 2.1 ± 1.1 h, and higher cannabinoid retention after 1 week of twice-daily dosing. Compared to oil-based formulations, this paste demonstrated better CBD absorption with no adverse effects or significant biochemical alterations, indicating short-term safety (Wang et al. 2022). CBD undergoes extensive hepatic metabolism, as evidenced by the detection of metabolites in the urine of dogs (Samara et al. 1990), prompting the exploration of alternative administration routes. For example, a study assessed CBD pharmacokinetics in six Beagle dogs (3–8 years) after intranasal (IN, 20 mg), intrarectal (IR, 100 mg), and oral (PO, 100 mg) administration, showing that IR CBD was undetectable, while IN had a faster T_{max} (0.5 h) but lower AUC (61 ng/mLh) and C_{max} (28 ng/mL) than PO (T_{max} 3.5 h, AUC 1,376 ng/mLh, C_{max} 217 ng/mL). Despite faster absorption with IN, PO was the most effective and practical route, while IR was unsuitable for clinical use (Polidoro et al. 2022a, b). Pharmacokinetic parameters such as half-life, C_{max}, mean residence time (MRT), and area under the curve (AUC) frequently vary following oral administration of CBD oily solutions, even at standardized doses. Factors such as age, breed, and sex can contribute to these variations due to anatomical and physiological differences, including reduced renal and hepatic function or variations in water-to-adipose tissue ratio (Di Salvo et al. 2023).

2.2 Clinical PK

The clinical pharmacokinetics of CBD have garnered increasing interest due to its therapeutic potential, yet its absorption, distribution, metabolism, and excretion remain complex and influenced by various factors. CBD is a highly lipophilic compound with poor oral bioavailability, estimated at as low as 6%, largely due to extensive first-pass metabolism (Agurell et al. 1981). Strategies to improve its bioavailability have led to the development of advanced formulations, such as oil-based products, self-emulsifying drug delivery systems (SEDDS), and gelatin pellets, which enhance its therapeutic potential (Zgair et al. 2016; Knaub et al. 2019). Alternative administration routes influence absorption, as shown by a systematic review of 24 studies reporting pharmacokinetic parameters in humans. The CBD half-life was 1.4–10.9 h (oromucosal), 2–5 days (chronic oral), 24 h (IV), and 31 h (smoking). Bioavailability was 31% for smoking,

but absolute bioavailability for other routes remains unreported. AUC and C_{max} increased dose-dependently, with a faster T_{max} (0–4 h) for smoking/inhalation compared to oral/oromucosal routes, while C_{max} was higher in fed states and lipid formulations (Millar et al. 2018). Once absorbed, CBD is distributed extensively throughout the body, accumulating in lipophilic tissues such as adipose tissue and perfused organs, including the brain, spleen, heart, lungs, and liver. This distribution pattern leads to a gradual redistribution to less perfused tissues, contributing to declining plasma concentrations over time (Bardhi et al. 2022). CBD metabolism occurs predominantly in the liver, involving cytochrome P450 enzymes such as CYP3A4 and CYP2C19, with minor contributions from CYP2D6, CYP2C9, CYP1A2, and CYP1A1 (Nasrin et al. 2021). Despite the identification of several metabolites, the pharmacological effects of these metabolites in humans remain poorly characterized. CBD exhibits a prolonged terminal elimination half-life, as demonstrated in healthy volunteers, where twice-daily dosing over seven days resulted in a half-life of 56–61 h (Taylor et al. 2018). The compound is excreted primarily in feces, with a smaller fraction eliminated in urine as CBD and its glucuronide conjugates (Ujváry and Hanuš 2016). The availability of diverse formulations, including oils, tablets, sublingual sprays, capsules, creams, and nasal sprays, provides flexibility in CBD administration and expands its therapeutic applications (Schlag et al. 2021). The data derived from preclinical and clinical studies on the pharmacokinetics of CBD are summarized in Table 1.

3 Drug-drug interactions and safety considerations

CBD and its active metabolite, 7-hydroxy-CBD (7-OH-CBD), are primarily metabolized by CYP3A4 and CYP2C19, with additional involvement of CYP2C9, 1A2, 2C8, 2B6, and 2E1 (Nasrin et al. 2021). CBD acts as both a substrate and an inhibitor of various CYP450 enzymes, notably inhibiting CYP2C8, 2C9, 2D6, and 2C19. Additionally, Epidiolex labeling suggests potential dual inhibition/induction of CYP1A2 and CYP2B6 (Jiang et al. 2011). CBD also inhibits UGT1A9 and UGT2B7, reducing excretion and increasing bioavailability of substrates like acetaminophen,

Table 1 Pharmacokinetics studies related to CBD dosage and parameters in preclinical and clinical studies

Species/ Condition	Dose	Dosage form	PK parameters	References
Preclinical studies				
Mice	5–10 mg/kg	I.P	n/a	(Ward et al. 2011)
Rat	10 mg	Oral capsules	T_{max} = 1 h; C_{max} = 2.1; AUC_{0-last} = 6.9	(Cherniakov et al. 2017)
Cat	4 mg/kg/day	Soft chew	C_{max} = 43 ± 9 ng/mL AUC = 164 ng-h/mL T_{max} = 2 h	(Deabold et al. 2019)
Dog	1.7–64.7 mg/kg	Predominant oil	Half-life = 6 h	(Vaughn et al. 2020)
Dog	2 mg/kg/day With 10–15 mg CBD	Small and large soft chew	C_{max} = 301 ng/mL AUC = 1297 ng-h/mL T_{max} = 1.4 h	(Deabold et al. 2019)
Dog	20 mg intranasal (IN), 100 mg intrarectal (IR) and oral (PO)	For IN, CBD in PEG:NaCl solution For IR, CBD suppositories Tablets for PO	IN T_{max} = 0.5 h IN AUC = 61 ng/ml-h IN C_{max} = 28 ng/mL PO T_{max} = 3.5 h PO AUC = 1376 ng/ml-h PO C_{max} = 217 ng/mL	(Bartner et al. 2018; Polidoro et al. 2022a, b)
Dog	1 mg/kg	Hemp extract	C_{max} = 145 ± 69 ng/mL	(Wakshlag et al. 2020)
Dog	1, 2, 4 and 12 mg/kg	Oil	AUC_{0-last} = 183 ± 43,287 ± 178,859 ± 475,1,430 ± 610, Half-life (h) = 5.6 ± 1.0,9.3 ± 6.6,5.4 ± 1.4,7.2 ± n/a	(Vaughn et al. 2021)
Guinea pig	25–50 mg/kg	Oil	C_{max} = 42 & 96.8 ng/mL	(Spittler et al. 2021)
Horse	0.35 or 2.0 mg/kg	Oral pellets	C_{max} = 6.6 ± 2.1 ng/mL T_{max} = 1.8 ± 1.2 h	(Williams et al. 2022)
Clinical studies				
Healthy individuals	5.4 mg once a week for 3 weeks	Oral capsules	T_{max} = 0.5–2 h; C_{max} = 0–2.6; AUC_{0-last} = 2.7–5.6	(Nadulski et al. 2005)
Cannabis smokers	2 mg once	Cigaratte	T_{max} = 0.25–0.50 h; C_{max} = 2 h	(Schwope et al. 2011)
Healthy men	100 mg	Oral gelatin matrix pellet	T_{max} = 3.5 h; C_{max} = 47.44 h; AUC_{0-last} = 149.54 h; Half-life = 3.59 h	(Atsmon et al. 2018)
Children with Dravet syndrome	2.5, 5, 10 and 20 mg/kg/day	Oral solution	AUC_{0-last} = 70.23, 241, 722, 963	(Devinsky et al. 2018)

C_{max}, Maximum concentration; *AUC*, Area under the curve

ibuprofen, and valproic acid, requiring caution in co-administration. A study showed CBD decreased UGT1A9 activity by 49% and UGT2B7 by 70%, though clinical relevance remains unclear (Al Saabi et al. 2013). The inactive 7-COOH-CBD metabolite inhibits breast cancer resistance protein (BCRP), potentially affecting drug efflux and increasing substrate side effects. BCRP substrates, including glyburide, methotrexate, and statins, may have altered distribution and excretion. Toxicity monitoring and dose adjustments are recommended when co-administering CBD with these drugs (Brown and Winterstein 2019) Table 2.

Similarly, safety studies of CBD across various clinical conditions have demonstrated a generally favorable profile, though dose-dependent adverse events are reported. In cancer pain management, Sativex® (THC: CBD oromucosal spray) was associated with dose-dependent side effects, with high-dose groups experiencing a worse safety profile than placebo. The most common adverse events included nausea, dizziness, vomiting, and somnolence, though no serious safety concerns were reported (Portenoy et al. 2012; Fallon et al. 2017). In lymphoma and chronic lymphocytic leukemia patients, a single-dose THC/CBD treatment led to grade 1–2 adverse events in 91% of patients, with dry mouth (78%), vertigo (70%), and somnolence (43%) as the most frequent side effects (Melén et al. 2022). Similarly, for multiple sclerosis (MS), CBD-based therapies were well tolerated, though dizziness, dry mouth, and somnolence were more commonly reported than in placebo groups (Rog et al. 2005). A large-scale study on MS spasticity (N = 1,615) revealed that 18.7% of patients discontinued treatment due to adverse events, highlighting individual variability in tolerability (Patti et al. 2016). Similarly, in inflammatory bowel diseases (IBD), CBD-rich cannabis oil was well tolerated, with no significant adverse effects reported (Naftali et al. 2021). In gastroparesis, CBD administration led to mild-to-moderate adverse effects, with diarrhea (14), fatigue (8), headache (8), and nausea (7) among 44 patients (Zheng et al. 2023). Studies in rheumatoid arthritis and ankylosing spondylitis focused on long-term CBD and THC exposure, with serious adverse events monitored, though specific safety data were not detailed (Hendricks et al. 2019). In hand osteoarthritis and psoriatic arthritis, CBD showed no serious safety concerns, with similar adverse event rates between CBD and placebo groups (Vela et al. 2022) Table 3. Overall, CBD appears safe and well tolerated, though higher doses may increase the risk of adverse events, and individual variability in response necessitates further investigation across different autoimmune and chronic pain conditions.

4 CBD receptors and pharmacodynamics

CBD is a complex multi-target molecule that exerts diverse pharmacological effects by interacting with a wide range of molecular targets. These targets include G-protein coupled receptors (GPCRs), ion channels, enzymes, serotonin receptors, and nuclear receptors. In vivo investigations have identified several critical molecular targets for CBD, such as CB1, CB2, transient receptor potential vanilloid 1 (TRPV1), G protein-coupled receptor 55 (GPR55), Mu-opioid receptor (MOR), 5-hydroxytryptamine receptor 1A (5-HT1A), dopamine (DA) receptors, toll like receptor-4 (TLR-4), and ion channels (Castillo-Arellano et al. 2023).

Cannabinoid receptors, CB1 and CB2 (CB1R/CB2R), are GPCRs and primary targets of the endocannabinoid system. CB1 receptors are predominantly expressed in the central and peripheral nervous systems, controlling excitatory and inhibitory neurotransmitter release, which impacts physiological processes such as memory, learning, and synaptic plasticity (Pertwee 2001; Busquets Garcia et al. 2016). CB2R's, classified as peripheral receptors, are expressed in immune cells and play significant roles in immunity,

Table 2 CBD drug interactions with enzyme substrates, inducers, inhibitors and transport proteins (Brown and Winterstein 2019)

CYP3A4		
Substrates	*Inducers*	*Inhibitors*
Chemotherapeutics, immunosuppressants, antipsychotics, calcium channel blockers, statins	Phenytoin, Carbamazepine, topiramate, phenobarbital, rifampicin, efavirenz, pioglitazone	Protease inhibitors, ketoconazole, nefazodone, loperamide
CYP2C19		
Substrates	*Inducers*	*Inhibitors*
Antidepressants, proton pump inhibitors, clopidogrel, propranolol, warfarin	Rifampin, carbamazepine, phenobarbital, phenytoin	Fluvoxamine, fluoxetine, cimetidine, ketoconazole, fluconazole, efavirenz
Transport proteins		
UGT1A9	*UGT2B7*	*BCRP*
Regorafenib, haloperidol, ibuprofen, acetaminophen, canagliflozin, sorafenib, propofol, mycophenolate	Hydromorphone, losartan, naproxen, ezetimibe, simvastatin, valproate, carbamazepine	Glyburide, imatinib, methotrexate, mitoxantrone, nitrofurantoin, prazosin, statins, dipyridamole

Table 3 In vitro cell type-specific immunosuppressive effects of CBD

Cell type	CBD Dose	Effects	Ref
Humans			
PBMCs	0.1–10 µg/mL or 0.3–32 µM	↓IFN-γ secretion and mRNA expression	(Jenny et al. 2009)
Hsp70-activated human NK cells	10 µM for 3 days	↓IFN-γ, IL-4, TNF-α, and GrzB	(Wang et al. 2024)
THP-1 cells	0.1 µg/ml, 1–10 µg/ml	1.5–twofold ↑IFN-γ secretion, ↓IFN-γ secretion	(Jenny et al. 2009)
Human neutrophils	100 nM, 1 µM, 3 µM	↓ROS	(Wang et al. 2017)
HaCaT human keratinocytes	1, 5, 10, 20 µM	↓IL-6, IL-8, TNF-α	(Petrosino et al. 2018)
Human liver sinusoidal endothelial cells	3 or 10 mg/kg	↓Adhesion molecules, ↓Liver inflammation, oxidative/nitrative stress and TNF-α	(Mukhopadhyay et al. 2011)
Human monocytic cells (U937)	10.6 µM, 21.2 µM, 31.8 µM, and 42.4 µM	↓MCP-1, CCL-5 ↑IL-6, IL-8, IL-16, and IL-32	(Muthumalage and Rahman 2019)
Animals			
B6C3F1 female splenocytes	1, 5, 10, 15, 20 µM	↓IL-2	(Kaplan et al. 2003)
C57BL/6 male Kupffer cells	3 or 10 mg/kg	↓TNF-α	(Mukhopadhyay et al. 2011)
C57BL/6 or BALB/c female splenocytes	5,10,15 µg/ml	↓Proliferation and cytokines	(Khuja et al. 2019)
RAW 264.7 cells	Pretreatment with 5 µM CBD for 2 h	↓Inflammasome pathways ↓TNF-α, MCP-1, IL-1β and NF-kB	(Huang et al. 2019)
BV-2 microglial cells	10 µM	↓Ccl-2, ↓oxidative stress	(Juknat et al. 2012)

particularly in macrophage populations and B cells (Parolaro 1999). Despite CBD's low binding affinity for CB1R/CB2R (Thomas et al. 2007), it enhances CB1 activity through the phosphoinositide 3-kinase/protein kinase b (PI3K/AKT) pathway, promoting cellular differentiation, mitochondrial polarization, and reduced inflammation (Blando et al. 2022). CBD also enhances endocannabinoid activity by inhibiting fatty acid amide hydrolase (FAAH), the enzyme responsible for the degradation of anandamide (AEA). This inhibition increases AEA and 2-arachidonoylglycerol (2-AG) availability, enhancing their anti-inflammatory and neuroprotective actions (Bisogno et al. 2001). AEA, an endocannabinoid, exerts tonic inhibitory effects on inflammation, further supported by CBD's ability to block its transporter-mediated uptake (Watanabe et al. 1996).

CBD also interacts with the serotonin receptor 5-HT1A, an important GPCR implicated in depression, anxiety, and aggression. Acting as a partial agonist, CBD increases serotoninergic and glutamatergic transmission, contributing to its anxiolytic effects (Martinez Naya et al. 2023). This interaction involves the GTP-binding proteins that couple 5-HT1A activation to downstream signaling (Russo et al. 2005). Through its interaction with transient receptor potential ankyrin 1 (TRPA1), CBD excites vagal afferent neurons, inducing inward currents and modulating sodium conductance, which may influence vagal signaling and adapt with chronic cannabis exposure (Kowalski et al. 2020). CBD is also an antagonist of GPR55 which is co-localized with cannabinoid receptors in brain regions like the putamen and caudate nucleus. By blocking GPR55, CBD contributes to the prevention of pro-inflammatory cytokine production (Mishiro et al. 2021).

CBD's interaction with TLR4 pathway further highlights its anti-inflammatory properties. TLR4 activation increases the phosphorylation of TAK1 (TGF-β-activated kinase 1), which further activates the IKK (IκB kinase) complex. The IKK complex phosphorylates IκB (inhibitor of κB), leading to its degradation, thereby releasing NF-κB (nuclear factor κB), which translocates to the nucleus and induces pro-inflammatory cytokine production (Liu et al. 2017). CBD inhibits the NF-κB pathway and the production of pro-inflammatory cytokines by preventing IκB degradation (Kim et al. 2014; Dos-Santos-Pereira et al. 2020). In the context of opioid receptors, CBD acts as an allosteric modulator, showing subtype-selective inhibition at both μ and δ opioid receptors (Kathmann et al. 2006). These interactions suggest CBD's potential in addressing drug addiction and abuse (Kalsoom et al. 2024).

At the ion channel level, CBD inhibits L-type calcium channels in rat and rabbit ventricular cardiomyocytes (Ali et al. 2015; Isaev et al. 2022). Mechanistically these cardioprotective effects of CBD are mediated by hippo and calcium signaling pathways in doxorubicin induced myocardial infarction (Dong et al. 2025). Additionally, CBD functions as a nonselective sodium channel inhibitor, stabilizing the inactivated state of these channels and

preventing their activation (Ghovanloo et al. 2018; Le Marois et al. 2020). CBD's effects on nuclear receptors such as peroxisome proliferator-activated receptor gamma (PPARγ) further underscore its anti-inflammatory properties. Activation of PPARγ decreases inducible nitric oxide synthase (iNOS) expression, reduces pro-inflammatory cytokines, and mitigates inflammation in cardiovascular cells, particularly endothelial cells (Maguire et al. 2021).

In summary, CBD demonstrates a wide range of therapeutic effects, including anti-inflammatory, antioxidant, neuroprotective, anxiolytic, and cardioprotective properties. These effects stem from its ability to modulate key signaling pathways and molecular targets, making it a promising candidate for addressing various physiological and pathological conditions (Fig. 1).

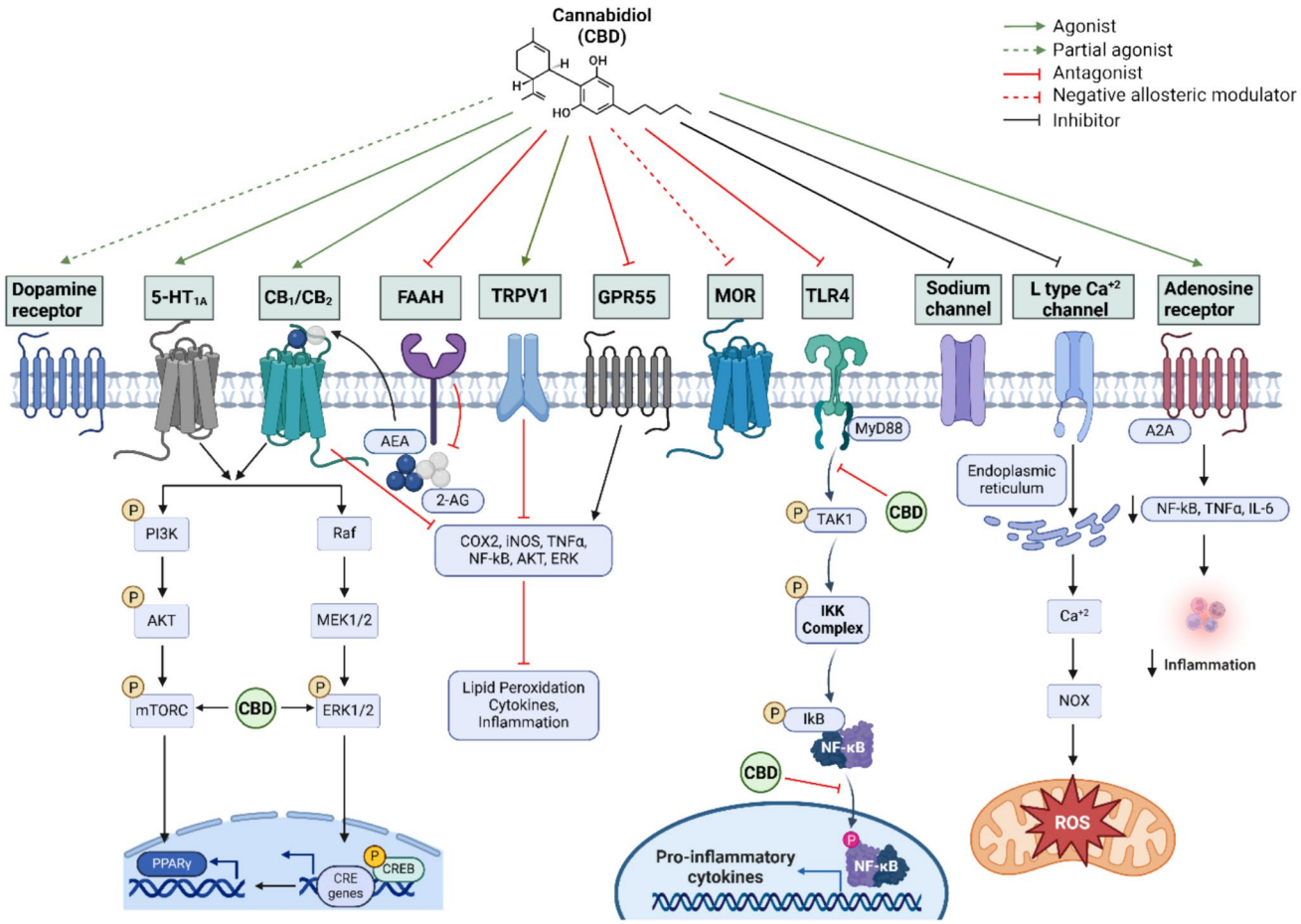

Fig. 1 Pharmacodynamically CBD interacts with multiple molecular targets. CBD interacts with various receptors and ion channels including DA receptors, 5-HT1A receptors, CB1R/CB2R, FAAH, TRPV1, GPR55, MOR, TLR4, sodium channels, and L-type Ca^{2+} channels. As an agonist for CB1R/CB2R, it regulates pain, inflammation, and metabolism by activating PI3K/AKT and MAPK/ERK pathways, promoting cell survival, immune modulation, and inflammation reduction. Inhibition of FAAH elevates endogenous anandamide levels, further enhancing CB1R/CB2R activity. Full agonism of serotonin 5-HT1A receptors supports anxiolytic and neuroprotective effects via PI3K/AKT activation, regulating synaptic plasticity and stress responses. Agonism of TRPV1 channels influences pain and inflammation by modulating COX-2, iNOS, TNF-α, NF-κB, AKT, and ERK pathways, reducing oxidative stress and cytokine production. Activation of adenosine A1 receptors exerts anti-inflammatory effects by suppressing NF-κB, TNF-α, and IL-6 signaling, supporting therapeutic potential in inflammation and metabolic disorders. Partial agonism at DA receptors influences cognitive function and emotional regulation. Antagonism of FAAH prevents anandamide degradation, sustaining CB1R/CB2R activation, exerting anti-inflammatory and neuroprotective actions, while GPR55 antagonism regulates calcium mobilization, inflammation, and metabolic balance, reducing pro-inflammatory effects. TLR4 antagonism inhibits MyD88-dependent NF-κB signaling through TAK1/IKK suppression, decreasing pro-inflammatory cytokine expression. Inhibition of sodium and L-type calcium channels modulates neuronal excitability and mitochondrial calcium homeostasis, affecting ion transport and oxidative stress. Recreated with permission from (de Almeida and Devi 2020). CB1R/CB2R, CB1/CB2 receptors; FAAH, fatty acid amide hydrolase; TRPV1, transient receptor potential vanilloid 1; GPR55, G protein-coupled receptor 55; MOR, μ-opioid receptor; TLR4, toll-like receptor 4; DA, dopamine receptor; 5-HT1A, serotonin 5-hydroxytryptamine 1A receptor; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; AEA, anandamide; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase

5 CBD role in immune system regulation

Immunity relies on the coordinated action of various cell types, including T cells, dendritic cells, neutrophils, macrophages, and other myeloid cells, to defend against pathogens while avoiding self-reactivity (Parkin and Cohen 2001). Innate immune cells rapidly destroy pathogens and can activate the adaptive immune response, led by T and B cells, when necessary (Iwasaki and Medzhitov 2015). CBD modulates both innate and adaptive immune responses by targeting cellular receptors and signaling pathways involved in immune regulation (Nichols and Kaplan 2020) (Fig. 2) Table 3.

5.1 CBD effects on lymphocytes

Most studies exploring the effects of CBD on the immune system have focused on its role in T cells. Early research

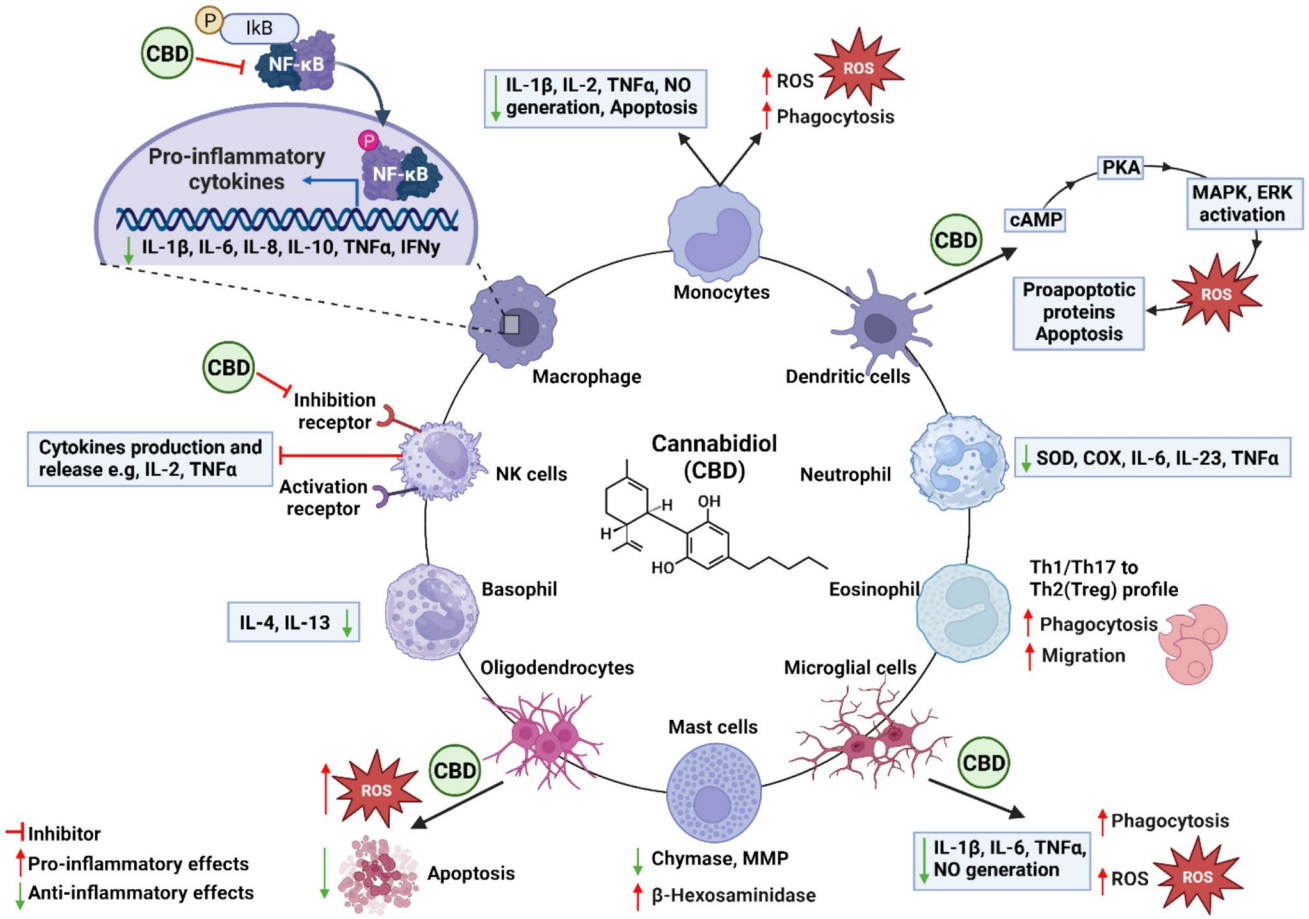

Fig. 2 CBD modulates immune cell functions. It interacts with macrophages, monocytes, dendritic cells, neutrophils, eosinophils, basophils, mast cells, NK cells, and microglial cells, regulating key immune processes. It influences pathways related to cytokine production, ROS generation, apoptosis, phagocytosis, and cell migration, contributing to immune homeostasis. In macrophages and monocytes, it suppresses inflammatory cytokines by inhibiting NF-κB signaling, reducing pro-inflammatory responses. In dendritic cells, it alters cAMP signaling and MAPK/ERK activation, leading to proapoptotic protein expression and apoptosis. In neutrophils, it suppresses inflammatory cytokine secretion and ROS production while promoting a shift toward an anti-inflammatory phenotype, reducing excessive phagocytic activity. In eosinophils, it suppresses inflammatory cytokine production and promotes a shift from a Th1/Th17 to a Th2/Treg immune profile, reducing migration and phagocytosis. In basophils, it downregulates IL-4 and IL-13 secretion, limiting type 2 immune responses and allergic inflammation. In mast cells, it inhibits the release of chymase and MMP, dampening inflammatory signaling and allergic responses. In NK cells, it inhibits activation receptors, leading to reduced cytokine production and cytotoxic activity. In microglial cells, it promotes apoptosis and reduces neuroinflammatory responses, demonstrating potential neuroprotective effects. Recreated with a permission from (Martini et al. 2023). NK, natural killer; ROS, reactive oxygen species; NF-κB, nuclear factor kappa B; COX, cyclooxygenase; SOD, superoxide dismutase; NO, nitric oxide; MMP, matrix metalloproteinases; cAMP, cyclic adenosine monophosphate; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; IL, interleukin; Th, T helper cells; Treg, regulatory T cells

investigating rosette formation in response to sheep red blood cells (sRBCs), which is primarily considered a T cell-mediated response, demonstrated that CBD at concentrations of 1 µM and 100 µM reduced this response (Cushman 1976). Similarly, CBD was shown to inhibit IFN-γ production in lymph node cells isolated from arthritic mice, following ex vivo stimulation with collagen (Malfait et al. 2000). Further evidence of CBD's immunosuppressive effects was observed when CBD (0.1–10 µg/mL or 0.3–32 µM) suppressed IFN-γ mRNA expression in human peripheral blood mononuclear cells (PBMCs) stimulated with phytohemagglutinin (PHA) (Jenny et al. 2009). Additionally, CBD at concentrations of 1–20 µg/mL (3.2–64 µM) inhibited IL-17A production in human CD3 + T cells derived from healthy individuals, as well as from patients with multiple sclerosis (MS) or nonseminomatous germ cell tumors, when stimulated ex vivo with phorbol 12-myristate 13-acetate / ionomycin (Zgair et al. 2017). Notably, one of these studies was conducted on human T cells, where CBD (5 µM) was found to suppress both total and phosphorylated p38 expression 16 h after treatment. Importantly, the inhibition of phosphorylated p38 was reversed by the addition of SR144528 (a CB2R antagonist) or tocopherol, suggesting that CBD's effects are mediated via CB2 and involve the production of reactive oxygen species (ROS) (RJ 2006).

5.2 CBD effects on Macrophages

Macrophages, a key component of stromal and parenchymal cells in metabolic organs such as the liver, pancreas, and adipose tissue, play a vital role in maintaining metabolic homeostasis (Wynn et al. 2013). In bacterial infections, the activation of macrophages significantly impacts the production of cytokines, including TNF-α, IL-6, and IL-1β, which are critical mediators of inflammation (Fujiwara and Kobayashi 2005). Studies demonstrated the suppressive activity of CBD in RAW 264.7 monocytes and peritoneal macrophages, observing a marked reduction in the production of IL-6, IL-1β, and TNF-α (Huang et al. 2019; Yekhtin et al. 2022). CBD also exerts pro-inflammatory effects in RAW 264.7 macrophages, stimulating the production of IL-12 while inhibiting anti-inflammatory cytokines such as IL-10 in a dose-dependent manner (Sacerdote et al. 2005). Similarly, in U937 macrophage cell line, CBD increased the expression of pro-inflammatory cytokines, including IL-6, IL-8, IL-16, and IL-32, underscoring its potential to amplify inflammatory responses under certain conditions (Muthumalage and Rahman 2019). Beyond cytokine modulation, CBD regulates chemotaxis and tissue infiltration by suppressing CXCL9, CXCL10, and IL-1β, reducing inflammatory macrophage infiltration, promoting myeloid-derived suppressor cells (MDSCs), and inhibiting gasdermin-mediated pyroptosis in the gastrointestinal (GI) tract without altering microbiota composition (Dopkins et al. 2022). CBD enhances the activation of the autophagy receptor p62/SQSTM1, facilitating stimulator of interferon genes (STING) degradation and attenuating type I interferon responses in macrophages (Tomer et al. 2022). Given these conflicting results, the precise effects of CBD on macrophages appear context dependent.

5.3 CBD effects on natural killer cells

Natural killer (NK) cells constitute 5–10% of circulating leukocytes and play a pivotal role in immune surveillance by targeting tumors, inhibiting metastasis, and maintaining immune homeostasis (Chiossone et al. 2018; Zitti and Bryceson 2018). These cells secrete cytokines, particularly IFN-γ, which are crucial for modulating adaptive immune responses and ensuring immune system balance (Vivier et al. 2011). NK cells express cannabinoid receptors CB1, CB2, and GPR55 and release substantial amounts of endocannabinoids such as AEA and 2-AG, which are involved in regulating their activity (Chiurchiù et al. 2015). CB2R are highly expressed on NK cells, where their activation influences the release of inflammatory cytokines, suggesting a regulatory role of CB2 and its ligands in modulating NK cell function (Kishimoto et al. 2005; Ferrini et al. 2017). CBD impacts NK cell activity through its interaction with these pathways. For instance, CBD treatment reduced IL-17 production while increasing IFN-γ levels in psoriasis patients, highlighting its dual regulatory effects on cytokine secretion (Tsiogkas et al. 2024). Similarly, CBD inhibited tumor-derived Hsp70 peptide (TKD) + IL-2-induced release of IFN-γ, IL-4, TNF-α, and GrzB but had no effect on IFN-α release when NK cells were co-incubated with tumor target cells (Wang et al. 2024).

5.4 CBD effects on mast cells

Mast cells, historically associated with allergic reactions and immediate hypersensitivity, play crucial roles in defending against microorganisms and in the pathophysiology of various diseases, including multiple sclerosis, rheumatoid arthritis, chronic pain, and heart failure (Krishnaswamy et al. 2005). These cells contain cytoplasmic granules that store and release chemical mediators such as heparin, histamine, and neutral proteases, which are essential for inflammatory and immune responses (Galli et al. 2020). Electroacupuncture (EA) has demonstrated anti-inflammatory effects in allergic contact dermatitis (ACD) by upregulating CB2R expression in mast cells, thereby inhibiting p38 MAPK phosphorylation, suppressing IgE and cytokine production, and reducing mast cell infiltration and degranulation. These effects were reversed by the CB2R antagonist AM630 but remained unaffected by the CB1R antagonist AM251,

underscoring CB2R's key role in EA-mediated immunomodulation (Wang et al. 2019). CBD enhances β-hexosaminidase release in antigen-stimulated and unstimulated in a rat basophilic leukemic mast cell model (RBL-2H3) mast cells by increasing intracellular calcium ([$Ca2^{+}$]i) levels, independent of Gi/Go protein-coupled receptors and VR1 channels (Giudice et al. 2007). Although cannabinoids have been recognized for their role in regulating mast cell activity, research focusing specifically on CBD's effects remains limited.

5.5 CBD effects on dendritic cells

Dendritic cells (DCs), derived from bone marrow, reside in secondary lymphoid organs, peripheral tissues, mucosal tissues, and skin, where they act as crucial regulators of immune responses serving as antigen-presenting cells (APCs) (Lipscomb and Masten 2002). Murine bone marrow-derived DCs express CB1R/CB2R, and their activation has been shown to induce apoptosis in these cells, suggesting a regulatory role for cannabinoids in immune modulation (Matias et al. 2002). Interestingly, endogenous and exogenous cannabinoids, such as anandamide and THC, inhibit immune responses by inducing apoptosis in DCs, emphasizing their importance in controlling immune activation (Matias et al. 2002). CBD modulates human monocyte-derived dendritic cells (moDCs) by promoting a tolerogenic phenotype, enhancing IL-6, TNF-α, and IL-10 secretion in response to LPS while reducing their ability to activate naïve T cells. These effects were observed in both TLR4 and TLR7/8 signaling pathways, supporting CBD's potential immunomodulatory role in DCs regulation (Pénzes et al. 2023). Although these findings suggest that CBD may influence immune and inflammatory responses through the regulation of DCs, the precise mechanisms by which CBD impacts dendritic cell function remain insufficiently explored. These preliminary insights underscore the need for further research into the potential immunomodulatory role of CBD via DC pathways.

5.6 CBD effects on polymorphonuclear neutrophils

Neutrophils, a key component of the immune response during acute inflammation, exhibit prolonged lifespans under inflammatory conditions, ensuring their availability at inflammation sites in inflammatory diseases (Wright et al. 2010). CBD interacts with neutrophils, where a study showed its ability to reduce neutrophil accumulation, respiratory burst, and oxidative stress markers (NOX2, lipid peroxidation, 3-nitrotyrosine), highlighting its role in modulating neutrophil-driven inflammation (Wang et al. 2017). CBD also reduces neutrophil extracellular trap (NET) formation (NETosis) in psoriasis patients, potentially mitigating oxidative stress and tissue damage in chronic diseases (Wójcik et al. 2020). Another study showed that topical application of CBD reduced neutrophil infiltration and inflammation in corneal injury by acting via 5-HT1A receptors, independent of CB1R and CB2R, highlighting its role in modulating immune responses and pain (Thapa et al. 2018). CBD also interacts with neutrophils in lung inflammation, but its effects appear context dependent. For example, in acute lung injury models, CBD significantly reduced neutrophil migration, myeloperoxidase (MPO) activity, and pro-inflammatory cytokines (TNF-α, IL-6, MCP-1, MIP-2) via adenosine A2A receptor activation, highlighting its potential anti-inflammatory role (Ribeiro et al. 2012). However, in a model of airway hyperresponsiveness, CBD had no effect on TNF-α–enhanced airway contractions, bronchoconstriction, or neutrophil recruitment, in contrast to Δ9-THC, which inhibited these responses through CB1R/CB2R activation, emphasizing differential cannabinoid mechanisms in lung inflammation (Makwana et al. 2015).

5.7 CBD effects on eosinophils and basophils

Eosinophil granulocytes, originally identified by Paul Ehrlich, are fully developed cells derived from the bone marrow myeloid lineage. They make up 1–5% of circulating mononuclear cells and are primarily found as plasma cells in inflammatory skin disorders (Limberg et al. 2023). Eosinophils play a pivotal role in immune and allergic responses, particularly in mediating hypersensitivity reactions within the host (Gleich 1986). A study showed that the CB2R is expressed in human eosinophils but not in neutrophils, and its endogenous ligand, 2-AG, induces eosinophil migration via CB2R activation, suggesting a role in allergic inflammation (Oka et al. 2004). In a murine asthma model, CBD extract downregulated IgE, suppressed pro-asthmatic cytokines, and reduced leukocyte, eosinophil, and neutrophil infiltration (Aswad et al. 2024).

Basophils, like mast cells, contribute to the connection between innate and adaptive immunity. They are distinguished by their rapid induction of IL-4 and IL-13, which are crucial for Th2-mediated responses, along with their ability to release histamine and other proteins during activation (Stone et al. 2010). While the endocannabinoid system has been found to influence the activity of eosinophils and basophils (Cabral et al. 2015; Frei et al. 2016), no direct evidence currently exists to demonstrate CBD's regulatory effects on these cells. Further investigation is required to determine CBD's potential role in modulating their functions.

5.8 CBD effects on glial cells

Astrocytes are the most abundant glial cells in the central nervous system (CNS) (Markiewicz and Lukomska 2006),

while microglial cells, which constitute 5–20% of glial cells, are equally important for maintaining physiological balance and contributing to the progression and treatment of CNS diseases (Saijo and Glass 2011). Recent findings suggest that CBD influences microglial cells through various targets, including TRPV1, GPR55, and CB1/2 receptors, although specific connections to these receptors were not observed in some studies. For example, CBD induces apoptosis in primary microglial cells in a time- and concentration-dependent manner, activating caspase-8 and −9. This effect is independent of CB1, CB2, vanilloid receptors, and oxidative stress and is hypothesized to act through targets such as 5-HT1A, TRPV2, and PPARγ (Wu et al. 2012). This hypothesis is supported by other research demonstrating the suppression of microglial activation following the engagement of TRPV1, PPARγ, and 5-HT1A pathways (Landucci et al. 2022). Moreover, during neuroinflammation, microglial cells migrate toward dying neurons, a process driven by 2-AG via CB2 and abnormal CBD sensitive receptors, activating the ERK1/2 pathway. Notably, CBD inhibits 2-AG-induced migration by antagonizing these receptors, suggesting its potential as a nonpsychotropic therapeutic for limiting microglial recruitment in neuroinflammatory lesions (Walter et al. 2003). Similarly, oligodendrocytes, derived from oligodendrocyte progenitor cells (OPCs), are essential for producing the myelin sheath, a lipid-rich layer that wraps around axons to facilitate rapid nerve impulse conduction. OPCs are highly proliferative and migratory in the CNS, and their differentiation into mature oligodendrocytes is crucial for maintaining efficient neuronal communication (Snaidero and Simons 2017). CBD protects OPCs from oxidative stress and LPS/IFNγ-induced apoptosis by reducing ROS production and caspase-3 activation, independent of CB1, CB2, TRPV1, or PPARγ receptors (Mecha et al. 2012). Although CBD demonstrates neuroprotective and immunomodulatory effects in glial cells, further research is required to clarify its precise mechanisms, receptor interactions, and long-term therapeutic potential in neuroinflammatory and demyelinating diseases.

6 Clinical manifestations of CBD in autoimmune diseases

To evaluate the therapeutic potential of CBD in autoimmune diseases, this review summarizes key studies and clinical trials (Table 4) investigating their role in modulating immune responses, alleviating symptoms, and improving patient outcomes along with safety concerns.

6.1 Multiple Sclerosis (MS)

Multiple sclerosis (MS) is a progressive autoimmune disease that affects CNS, primarily regulated by T lymphocytes. Inflammation in MS results in the destruction of the blood–brain barrier (BBB), leading to edema, activation of macrophages, and the secretion of cytotoxic proteins and cytokines, such as metalloproteinases (Bjelobaba et al. 2017). Experimental models of MS, such as Experimental Autoimmune Encephalomyelitis (EAE) in mice, have demonstrated the critical role of CB1 receptors in regulating neuroinflammation. CB1-deficient mice exhibit heightened sensitivity to inflammatory and excitotoxic stimuli, leading to significant neurodegeneration during immunological responses (Pryce et al. 2003). Furthermore, CB1 knockout mice have revealed increased neurofilament damage, caspase-3 activation, and axonal marker dephosphorylation during chronic recurrent EAE (Jackson et al. 2005). CB1 receptor stimulation in motor-related regions of the CNS has been linked to improved motor symptoms such as reduced tremor, ataxia, and spasticity in mice and rat models (Berrendero et al. 2001; Pryce and Baker 2007).

In EAE rats, diminished levels of 2-AG and AEA were observed in motor-related regions such as the striatum and midbrain. Rolipram, a phosphodiesterase type IV inhibitor, has been shown to restore CB1 gene expression in the basal ganglia of EAE rats, reduce motor deficits, and delay clinical deterioration (Cabranes et al. 2005). CB2R deficient T cells in the CNS during EAE exhibit reduced apoptosis and increased inflammatory cytokine production, leading to more severe clinical outcomes. Selective glial staining for FAAH, CB1, and CB2R has further highlighted their involvement in MS pathogenesis (Arévalo-Martín et al. 2003). AEA, a natural endocannabinoid, plays a significant role in modulating inflammation in MS. AEA protects neurons by suppressing inflammatory cytokines (IL-6, IL-1β, TNF-α), reducing microglial activation and spinal cord infiltration, and inducing mitogen-activated protein kinase phosphatase-1 (MKP-1) via CB1/CB2-mediated mechanisms (Eljaschewitsch et al. 2006).

6.2 Inflammatory Bowel Disease (IBD)

Cannabis has been widely used to manage bowel inflammation and related conditions, particularly through its interaction with CB1R and CB2R, which regulate both peripheral and central mechanisms (Schicho and Storr 2014). IBD, including Crohn's disease (CD) and ulcerative colitis (UC), is characterized by variable expression of these receptors, suggesting their involvement in the disease's progression and potential therapeutic role (Ambrose and Simmons 2019).

CBD has shown significant potential in managing bowel inflammation, particularly in conditions like CD and UC by targeting key pathways involved in immune and inflammatory regulation. A study demonstrated that CBD exerts anti-inflammatory effects in intestinal inflammation by modulating CREB, JNK, NF-κB, p38, ERK1/2, Akt, p70S6k, and

Table 4 Clinical trial studies related to CBD therapeutic effects in autoimmune diseases

Clinical trial	Intervention	Outcomes	Safety	Ref
Cancer				
Sativex® for Pain Relief in Patients with Advanced Malignancy (SPRAY)	Sativex® (THC 2.7 mg + CBD 2.5 mg per spray) or placebo (1–16 sprays/day) Low: 1–4 sprays/day Medium: 6–10 sprays/day High: 11–16 sprays/day	≥ 30% pain reduction on NRS at any dose Significant pain relief (cumulative NRS) in low and medium doses Significant sleep improvement in low dose No change in MADRS (depression scale)	Dose-dependent adverse events Only high-dose group had worse safety profile than placebo Most common side effects: nausea, dizziness, vomiting, and somnolence No serious safety concerns	(Portenoy et al. 2012)
Sativex oromucosal spray for relieving uncontrolled persistent pain in patients with advanced cancer	Nabiximols (THC 2.7 mg + CBD 2.5 mg per spray) or placebo, self-administered (3–10 sprays/day) for 2–7 weeks (Nabiximols) or 5 weeks (Placebo)	No significant pain NRS score improvement Significant effect on US patients < 65 years Improved quality of life with Sativex No safety concerns or misuse	Consistent safety profile with previous studies Common adverse events: Somnolence, dizziness, nausea and vomiting No evidence of abuse or misuse	(Fallon et al. 2017)
Effects of Sativex on blood leukocytes in patients with lymphoma/chronic lymphocytic leukemia	Single-dose THC/CBD (Sativex) ranging from 2.7 mg THC + 2.5 mg CBD (1 spray) to 18.9 mg THC + 17.5 mg CBD	11% reduction in leukemic B cells within 2 h Effect lasted 6 h, disappeared by 24 h No apoptosis or proliferation observed Reduction of non-leukemic B and T cells	Grade 1–2 adverse events in 91% of patients Dry mouth (78%), vertigo (70%), somnolence (43%)	(Melén et al. 2022)
Multiple sclerosis				
THC:CBD oromucosal spray as adjunctive analgesic treatment in patients with MS and central pain states	Each spray delivered 2.7 mg THC + 2.5 mg CBD, with self-titration up to 48 sprays/24 h	Reduced pain and sleep disturbances	Well tolerated, but more dizziness, dry mouth, and somnolence vs. placebo	(Rog et al. 2005)
THC: CBD Oromucosal spray for MS spasticity	Sativex (THC: CBD oromucosal spray) assessment in 1,615 MS patients across 30 centers in Italy over 6 months using the 0–10 NRS scale	70.5% had ≥ 20% improvement (IR), 28.2% had ≥ 30% improvement (CRR) Mean NRS reduction: 22.6% (from 7.5 to 5.8) Higher response in progressive MS	39.5% (631 patients) discontinued within 6 months Lack ofcefficacy (26.2%) Adverse events (18.7%)	(Patti et al. 2016)
Inflammatory bowel diseases (UC and CD)				
CBD-rich cannabis oil for induction of remission in Crohn's disease	CBD-rich cannabis oil (160 mg/mL CBD, 40 mg/mL THC) or placebo Oral administration for 8 weeks	Clinical improvement (CDAI reduction, but non-significant endoscopic (SES-CD) or inflammatory marker (CRP, calprotectin) changes Quality of life (QOL) improved significantly in the cannabis group CBD and THC well absorbed, but no remission induction at the inflammatory level	Well tolerated, with no significant adverse effects reported	(Naftali et al. 2021)

Table 4 (continued)

Clinical trial	Intervention	Outcomes	Safety	Ref
Diabetes				
CBD in patients with idiopathic or diabetic (diabetes mellitus) gastroparesis	CBD (Epidiolex, up to 20 mg/kg/day) or placebo Twice daily for 4 weeks in idiopathic and diabetic gastroparesis	Reduced symptom severity, meal intolerance, vomiting episodes, and total Gastroparesis Cardinal Symptom Index score Improved liquid nutrient tolerance but slowed gastric emptying (GES)	Diarrhea (14), fatigue (8), headache (8), and nausea (7) in 44 patients	(Zheng et al. 2023)
Rheumatoid Arthritis				
CBD and THC for pain management in rheumatoid arthritis and ankylosing spondylitis	CBD (oral) vs. placebo for 12 weeks Non-responders receive open-label THC add-on for 12 weeks Follow up at 36 weeks	Primary: Pain reduction (VAS ≥ 20 improvement) Secondary: Quality of life, cognitive function, sleep, disease activity, and adverse events assessment	——	(Hendricks et al. 2019)
Psoriasis				
CBD as add-on analgesic therapy in patients with hand osteoarthritis or psoriatic arthritis	Synthetic CBD (20–30 mg daily) or placebo for 12 weeks	Non-significant reduction in pain intensity Non-significant effects on sleep quality, depression, anxiety, or pain catastrophe	Similar adverse event rates between CBD and placebo groups No serious safety concerns reported	(Vela et al. 2022)

NRS, Numerical Rating Scale; *VAS*, Visual Analog Scale; *QOL*, Quality of life; *MADRS*, Montgomery-Asberg Depression Rating Scale; *CRP*, C-reactive protein; *SES-CD*, Simple Endoscopic Score for Crohn's Disease; *CDAI*, Crohn's Disease Activity Index; *GES*, Gastric emptying of solids; *EudraCT*, European Union Drug Regulating Authorities Clinical Trials

STAT3/5 signaling pathways, reducing pro-inflammatory cytokines (IL-8, IL-6, IL-17, MCP-1) in acutely inflamed human colon (Couch et al. 2017). CBD's activation of PPARγ plays a pivotal role in its anti-inflammatory effects by inhibiting pro-inflammatory transcription factors such as NF-κB, STAT, and AP-1. This mechanism supports the management of UC and CD and reduces the risk of inflammation-associated conditions like colon cancer (Lewis et al. 2011). Furthermore, by modulating inflammatory pathways, CBD protects the colonic epithelium, promotes epithelial wound healing, and decreases the activity of immune cells such as T cells, neutrophils, and monocytes in inflamed regions (Wright et al. 2005).

In ulcerative pancolitis, CB2R and diacylglycerol lipase-α (DAGLα) expression increase in mild-to-moderate cases, while N-acyl-phosphatidylethanolamine phospholipase D (NAPE-PLD) decreases in more severe cases, suggesting a role of endocannabinoid signaling in disease modulation (Marquéz et al. 2009). Observational studies suggest that CBD alleviates symptoms in CD, improving disease management and reducing reliance on conventional medications, though complete remission has not been consistently achieved. (Naftali et al. 2013, 2014). Although CBD shows promise in managing IBD by alleviating inflammation and improving symptoms, CBD's role in IBD remains uncertain due to study limitations, as seen in a trial facing challenges such as a small sample size, high withdrawal rates, and missing endoscopy scores, with the lack of centralized scoring remaining a concern (Irving et al. 2018). Therefore, larger, well-controlled trials with standardized assessment methods, adequate sample sizes, and long-term follow-ups are needed to confirm CBD's therapeutic efficacy, optimize dosing strategies, and ensure its safety profile in IBD treatment.

6.3 Cancer

CBD has emerged as a promising therapeutic agent in cancer research, demonstrating potential benefits across various cancer types (Wang and Multhoff 2021). In epithelial ovarian cancer, CBD disrupts the tumor microenvironment, inhibiting angiogenesis, inflammation, cancer cell migration, and invasion by downregulating MMP2 and MMP9 and modulating the EGFR/AKT/MMP signaling pathway in a dose-dependent manner (Cao et al. 2024). Similarly, in TRPV2-overexpressed endometrial cancer cells, CBD enhances chemotherapeutic efficacy, reduces cell viability, and promotes autophagy and apoptosis (Marinelli et al. 2020).

Clinical trials have also explored CBD's role in improving cancer patient outcomes. For example, a randomized placebo-controlled trial evaluated oral CBD (50–600 mg/day) in advanced cancer patients receiving palliative care. The study focused on overall symptom burden and identified tolerable doses that provided symptom relief with minimal side effects (Good et al. 2019). Another clinical trial showed that CBD attenuates early symptoms of chemotherapy-induced peripheral neuropathy (CIPN) in patients receiving oxaliplatin- or paclitaxel-based chemotherapy, with no major safety concerns (Nielsen et al. 2022). In leukemia models, including aggressive pediatric T-cell acute lymphoblastic leukemia (T-ALL), CBD targets the mTOR pathway, reducing phosphorylation of AKT, mTOR, and ribosomal S6, which affects leukemia cell proliferation. It also induces mitochondrial stress, disrupts membrane potential, and increases cytochrome c release, activating caspases 8, 9, 2, and 10. Additionally, CBD triggers ROS production via upregulation of NADPH oxidases Nox4 and p22phox, contributing to cancer cell apoptosis (Andradas et al. 2021). Mechanistically, CBD induces apoptosis by increasing apoptotic effectors such as Bax, caspase-3, and caspase-9, and disrupting mitochondrial function. It regulates cytoplasmic Ca^{2+} distribution and activates mitochondrial permeability transition pore (mPTP), leading to apoptosis. CBD also downregulates epidermal growth factor receptor (EGFR) and antagonistically interacts with GPR55, inhibiting pathways such as PI3K/AKT, rat sarcoma/rapidly accelerated fibrosarcoma/extracellular signal-regulated kinase (RAS/RAF/ERK), and tumor protein 53 (P53), while regulating tumor-related genes like inhibitor of DNA binding 1 (ID1), forkhead box M1 (FOXM1), and growth differentiation factor 15 (GDF15), which are linked to tumor proliferation and differentiation (Yan et al. 2023) (Fig. 3). Despite its therapeutic potential, CBD's effectiveness in managing cancer-related pain remains inconclusive due to limited data. Factors such as age, cancer type, pain characteristics, co-morbidities, and concurrent medications require further investigation. Future studies should focus on specific cancer types and compare CBD's efficacy across different treatment modalities, including surgery, radiation, chemotherapy, targeted therapy, and immunotherapy (Green et al. 2022).

6.4 Rheumatoid arthritis

The degradation of articular cartilage is a hallmark of both degenerative and inflammatory joint disorders such as rheumatoid arthritis (RA) (Cush 2022). In RA, cartilage breakdown is driven by elevated levels of cytokines, including TNF and IL-1, which stimulate chondrocytes and synovial cells to release matrix metalloproteinases (MMPs), particularly MMP-3 and MMP-13, accelerating cartilage degeneration (Goldring and Otero 2011). In vitro research has revealed that CBD reduces the release of MMPs and cytokines from fibroblast-like synovial cells, thereby mitigating cartilage extracellular matrix (ECM) breakdown caused by proteoglycan and collagen degradation (Johnson et al. 2007; Selvi et al. 2008; Zurier et al. 2009). CBD also

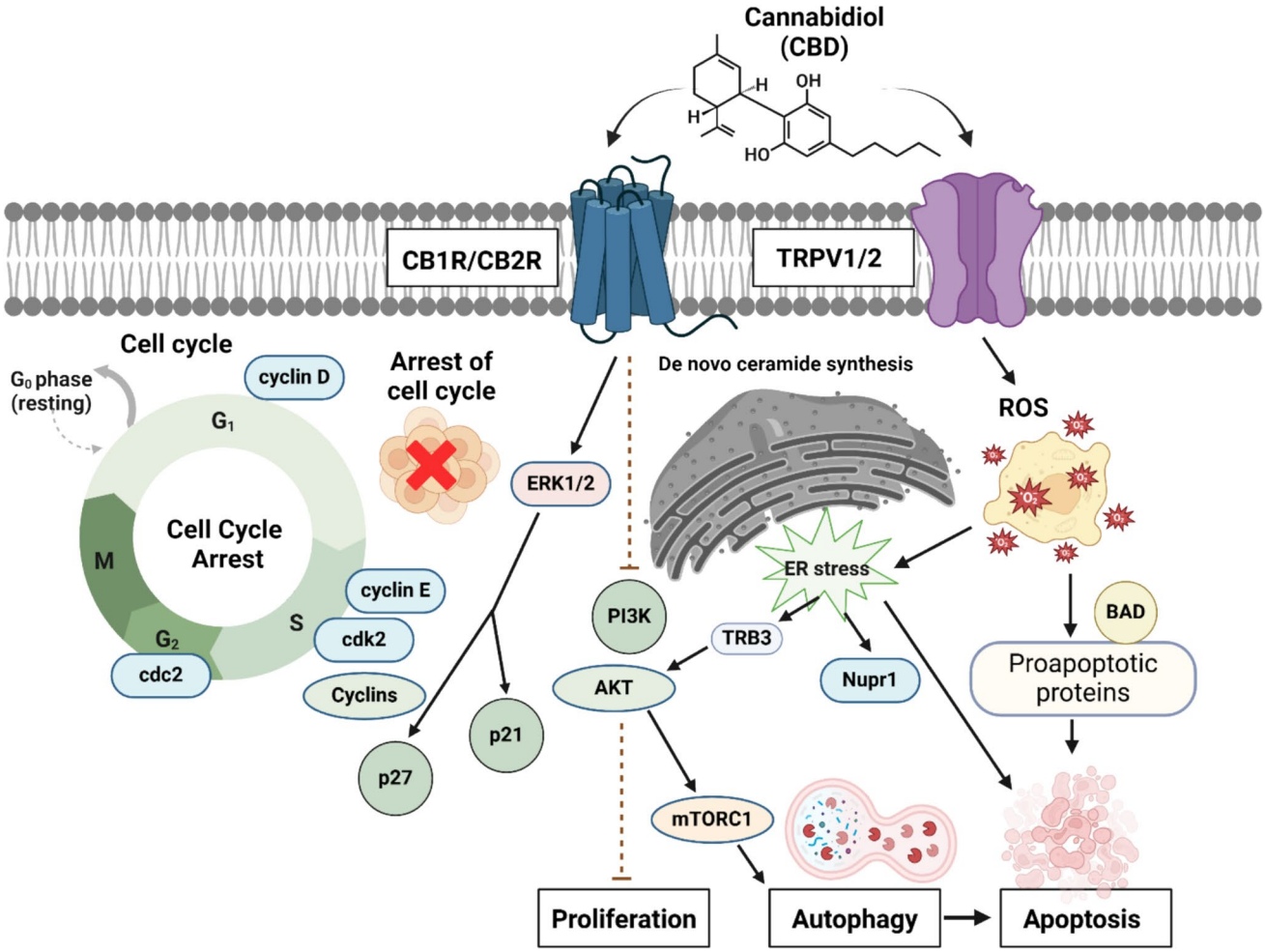

Fig. 3 Mechanisms of CBD in cancer therapy. CBD interacts with CB1, CB2, TRPV1, and TRPV2 receptors to modulate key signaling pathways involved in cancer cell fate. Activation of these receptors stimulates ERK1/2 signaling, leading to upregulation of p27 and p21, which suppress cyclins D and E, cdc2, and cdk2, ultimately causing cell cycle arrest. Inhibition of the PI3K/AKT/mTORC1 pathway reduces AKT activity, suppressing cell proliferation and promoting autophagy through mTORC1 downregulation. CBD also induces ER stress via de novo ceramide synthesis, leading to an increase in stress proteins p8/Nupr1, TRIB3, and ATF4, which contribute to apoptosis. The accumulation of ROS further promotes apoptosis by activating pro-apoptotic proteins such as BAD, exerting anti-cancer effects by suppressing tumor growth and enhancing programmed cell death. Recreated with permission from (Mangal et al. 2021). CB1R, CB2R, cannabinoid receptor 1 and 2; TRPV1, TRPV2, transient receptor potential vanilloid 1 and 2; ER, endoplasmic reticulum; ERK1/2, extracellular signal-regulated kinases 1 and 2; PI3K, phosphoinositide 3-kinase; TRB3, tribbles pseudokinase 3; ATF4, activating transcription factor 4; Nupr1, nuclear protein 1; BAD, Bcl-2-associated death promoter; cdk2, cyclin-dependent kinase 2; cdc2, cell division cycle protein 2; mTORC1, mechanistic target of rapamycin complex 1; ROS, reactive oxygen species

inhibits inflammatory processes by targeting pro-inflammatory cytokines, including IL-6, through mechanisms linked to CB2 receptor activation (Selvi et al. 2008). Additionally, CBD demonstrates efficacy in reducing reactive oxygen species (ROS) and TNF levels, further supporting its potential role in protecting cartilage and modulating inflammation (Sumariwalla et al. 2004).

CBD modulates CB1R/CB2R activity as a non-competitive negative allosteric modulator (NAM), reducing the efficacy of cannabinoid receptor agonists, including endogenous endocannabinoids such as AEA and 2-AG, which are involved in nociceptive processing (Castillo-Arellano et al. 2023). Synovial biopsies from patients with osteoarthritis and RA have confirmed the presence of CB1R and CB2R mRNA and proteins, as well as elevated levels of endocannabinoids such as AEA and 2-AG in synovial fluid, suggesting the activation of endocannabinoid pathways in diseased joints (Richardson et al. 2008). Overall, CBD exhibits significant potential in reducing inflammation, modulating cartilage degradation, and alleviating pain in arthritis, offering a promising therapeutic avenue for managing RA and osteoarthritis. However, further clinical studies in humans are required to validate their efficacy and mechanisms.

6.5 Scleroderma

Scleroderma fibroblasts overexpress cannabinoid receptors CB1 and CB2 compared to normal fibroblasts, and their activation has been implicated in modulating fibrotic pathways, influencing collagen metabolism and extracellular matrix remodeling (Dziadzio et al. 2004). Given the fibrotic nature of scleroderma, IL-6 has also been shown to stimulate collagen and glycosaminoglycan production in dermal fibroblasts, further supporting its role in fibrotic skin disorders. However, its direct contribution to fibroblast transdifferentiation in scleroderma remains unclear (Duncan and Berman 1991). Adenosine A2A receptor activation further modulates fibrosis by interacting with CB1R/CB2R to regulate collagen biosynthesis and myofibroblast differentiation, highlighting a potential antifibrotic role of cannabinoid receptor signaling (Lazzerini et al. 2012). Moreover, the CBD derivative VCE-004.3 demonstrated anti-inflammatory and antifibrotic effects in scleroderma by acting as a dual PPARγ/CB2 agonist and CB1 modulator, further expanding the therapeutic potential of cannabinoids in fibrotic diseases (Del Rio et al. 2018). However, further studies are needed to fully elucidate the antifibrotic effects of CBD and its derivatives in scleroderma and other fibrotic skin disorders.

6.6 Psoriasis

Psoriasis is a chronic autoimmune disorder characterized by excessive keratinocyte proliferation and inflammation. Cannabinoids, particularly CBD, have shown promise in managing psoriasis by targeting key pathways involved in the disease's pathophysiology (Stanescu et al. 2024). CBD plays a critical role in reducing keratinocyte proliferation through the activation of PPARγ, which has been identified as a primary mechanism for its therapeutic effects in psoriasis (Wilkinson and Williamson 2007). CBD selectively modulates immune responses in psoriasis by decreasing IL-17 production in CD3, Th, and NKT cells and reducing IFNγ production in CD3 + cells from psoriatic patients, while paradoxically increasing IFNγ production in Th, Tc, and NK cells from healthy individuals (Tsiogkas et al. 2024). The activation of CB1 receptors by cannabinoids contributes to feedback inhibition of keratin K6 and K16 expression, further regulating keratinocyte activity and providing a secondary mechanism of inhibition (Ramot et al. 2013). CBD also interacts with the cholinergic anti-inflammatory pathway, modulating both immunological and neurological systems to exert its anti-inflammatory effects (Derakhshan and Kazemi 2016). These findings suggest that CBD offers significant therapeutic potential in managing psoriasis by reducing inflammation, keratinocyte overgrowth, and immune dysregulation. However, CBD's impact on psoriasis faces multiple therapeutic challenges, particularly in topical formulations, as skin penetration varies with the gelling agent used, highlighting the need for optimized delivery systems. Its high lipophilicity (LogP = 5.79) and poor solubility hinder effective absorption, causing accumulation in sebaceous glands rather than reaching psoriatic lesions. Given the skin's barrier properties, only molecules with specific characteristics (LogP 1–3, MW < 500 Da, low melting point) can efficiently penetrate (Ferreira et al. 2023). These limitations underscore the need for advanced formulation strategies to enhance CBD's therapeutic efficacy in psoriasis.

6.7 Type 1 diabetes

Type 1 diabetes is characterized by the destruction of pancreatic beta cells, primarily caused by the activity of Th1, CD4 +, and CD8 + T lymphocytes (Atkinson and Leiter 1999; Mandrup-Poulsen 2003). During the onset of insulitis, the primary histological abnormality in this disorder, leukocytes, predominantly lymphocytes, infiltrate and encircle the pancreatic islets (Di Marzo et al. 2011). CBD has demonstrated significant potential in reducing the incidence of diabetes in non-obese diabetic (NOD) mice. In mice treated with CBD between 6 and 12 weeks of age, the incidence of diabetes dropped from 86% in untreated controls to 30%, accompanied by reduced insulitis and preservation of pancreatic islets (Weiss et al. 2006). This effect was linked to CBD's ability to suppress Th1-associated cytokines like INF-γ and TNF-α while increasing Th2 cytokines such as IL-4 and IL-10, promoting an anti-inflammatory environment.

When tested in older NOD mice (11–14 weeks old), CBD therapy again showed promising results. Diabetes incidence decreased to 32% in CBD-treated mice compared to 86% and 100% in untreated and emulsifier-treated groups, respectively. Histological examinations revealed intact pancreatic islets in CBD-treated mice, highlighting its potential to delay or prevent beta-cell destruction (Weiss et al. 2008). The mechanism underlying CBD's efficacy is thought to involve a shift from a destructive Th1 response to a protective Th2 response. This shift could make CBD a valuable therapeutic option for preventing and managing type 1 diabetes in high-risk individuals or those with early-onset diseases. If the Th1/Th2 shift induced by CBD is permanent, treatment could potentially be discontinued once autoimmunity is halted, reducing long-term safety concerns (Weiss et al. 2006). However, if CBD acts as a general immunosuppressant, lifelong treatment may be required, raising potential risks such as increased susceptibility to infections and cancer (Satoh et al. 1999). Cytokines play a critical role in Th1/Th2 differentiation, with monocyte-secreted cytokines influencing the immune response balance (Swain 1995). For instance, IL-12 promotes Th1 differentiation and drives beta-cell destruction by activating

cytotoxic T cells, enhancing TNF-α, IL-1, and IL-6 production (Skeen et al. 1996; Trinchieri 2003). CBD's ability to modulate these cytokines may contribute to its protective effects in diabetes. Overall, while CBD shows potential in managing diabetes and its complications, its safety and efficacy remain uncertain, as a clinical trial in diabetic patients treated with CBD reported adverse events, including diarrhea (14 patients), fatigue (8 patients), headache (8 patients), and nausea (7 patients) among 44 total patients (Zheng et al. 2023), highlighting the need for cautious evaluation before clinical application. Further research, particularly large-scale clinical trials, is needed to establish its therapeutic benefits.

7 Nanotechnology based improvements in CBD therapeutics

The integration of CBD with advanced nanotechnology has revolutionized its therapeutic applications by addressing challenges like poor solubility, bioavailability, and stability, while enabling targeted and controlled drug delivery. These innovations enhance CBD's efficacy across a range of diseases, offering safer and more effective treatment options (Singh et al. 2024). For example, CBD-loaded lipid nanoparticles combined with tocilizumab improve anti-inflammatory effects in COVID-19 by modulating ACE2 expression and cytokine storms, providing enhanced bioavailability and therapeutic potential (Zielińska et al. 2023). Similarly, CBD encapsulated in carbon nanodots (CNDs) increases solubility, stability, and targeted delivery, showing significant anticancer efficacy and cardioprotective effects in cardiovascular diseases (Ibrahim et al. 2023). In cancer and chronic pain management, CBD-loaded bigel formulations, incorporating 3D printed hyaluronic acid, enhance bioavailability and precision delivery, offering personalized therapeutic solutions (Gościniak et al. 2024). Additionally, CBD integrated with ultrastable Y-type zeolite (H-USY) facilitates controlled release, improving efficacy in cancer, inflammation, and neurological disorders (Dernaika et al. 2024).

Nanotechnology-based CBD formulations have also shown promise in wound healing and cardiovascular disease management. CBD-enriched chitosan films offer antimicrobial, antioxidant, and anti-inflammatory effects, promoting tissue regeneration through controlled release (Chelminiak-Dudkiewicz et al. 2022). In pain and inflammation management, CBD-encapsulated organosilica nanoparticles within PVA nanofiber mats ensure stability, solubility, and controlled transdermal delivery, offering an innovative non-invasive platform (Partalis 2022). Effervescent CBD-doped dissolving microneedles significantly improve melanoma therapy by enhancing CBD delivery, inducing apoptosis through TRPV1 activation, and modulating the tumor microenvironment to elicit anti-tumoral responses (Shi et al. 2023). Additionally, CBD-loaded Prussian blue nanoparticles with macrophage membrane coatings and hyaluronic acid target atherosclerotic plaques, reducing oxidative stress, modulating macrophage polarization, and restoring endothelial function for cardiovascular disease treatment (Liu et al. 2024). These nanotechnology-driven advancements highlight CBD's potential as a versatile and effective therapeutic agent in immune related disorders.

8 Conclusion, challenges and future perspectives

CBD demonstrates substantial immunomodulatory effects in both in vitro and in vivo models, with limited but encouraging evidence in humans. Clinical studies have shown improvements in autoimmune diseases such as multiple sclerosis, scleroderma, rheumatoid arthritis, and type 1 diabetes, as well as in neuropathic pain and inflammatory bowel disease. CBD has also reduced cytokine levels and inflammation in some conditions, such as ulcerative colitis, where it alleviated symptoms like diarrhea (Samara et al. 1988). However, its effects on various immune cells, including microglia, macrophages, mast cells, basophils, eosinophils, and T cells, remain inconsistent, with studies reporting both anti-inflammatory and pro-inflammatory responses. Despite the evidence, it is premature to recommend CBD as a therapeutic agent for autoimmune diseases due to limited understanding of its long-term safety, efficacy, drug-drug interactions, as well as reported adverse effects such as hepatotoxicity, neurotoxicity, and gastrointestinal disturbances (Huestis et al. 2019). The wide variability in reported immune responses to CBD underscores the need for further investigation to clarify its mechanisms and clinical applicability.

One significant limitation of CBD therapy is the challenge of achieving effective plasma levels due to its high lipophilicity, poor solubility, and extensive first-pass metabolism (Millar et al. 2020). In preclinical study, plasma levels of 40 ng/mL (0.12 μM) were observed after oral dosing of 75 mg/kg/day for three days in mice, while human trial with 20 mg/kg/day dosing reported plasma levels of 400 ng/mL (1.2 μM), demonstrating its potential clinical relevance (Nichols and Kaplan 2020). However, variations in bioavailability across species, routes of administration, and formulations remain a challenge, necessitating optimized delivery systems such as nanotechnology-based approaches.

CBD's mechanisms of action, such as cytokine suppression (e.g., TNF-α, IFN-γ, IL-6, IL-1β) and regulation of transcription factors like NF-κB and AP-1, have been well-documented. However, key gaps remain in understanding immunomodulatory mechanisms of CBD, particularly the roles of cannabinoid-associated receptors (TRPV1, GPR55,

PPAR-γ, and 5-HT1AR) and the enzyme FAAH in regulating inflammation and maintaining homeostasis (Aziz et al. 2023). Furthermore, underexplored immune cells, such as B cells, dendritic cells, and specific T cell subsets, require focused investigation to better understand the full scope of CBD's immune effects. Another critical challenge is the lack of data on how CBD interacts with various immune stimuli and disease-specific immune responses. The interplay between CBD and the immune system in outbred species, including humans, naturally exposed to diverse pathogens, remains poorly understood. Additionally, there is a need for controlled studies comparing different administration routes (e.g., oral, transdermal, inhalation), dose escalation, and pharmacokinetics to optimize therapeutic efficacy while minimizing side effects (Costiniuk et al. 2019).

Future clinical trials, such as the planned study in HIV + patients that explores dose escalation from 45–225 mg/kg/day, are expected to provide valuable insights into immune modulation and dose–response relationships (Costiniuk et al. 2019). These trials should also explore combined therapies, such as CBD and THC, to evaluate the synergistic or antagonistic effects on immune modulation. Furthermore, as CBD-based therapies gain momentum, understanding its interactions with conventional medications and its long-term safety profile becomes increasingly vital (Gottschling et al. 2020). Studies should investigate whether CBD-induced immunosuppression could increase susceptibility to infections or malignancies in patients requiring chronic treatment. Addressing these limitations will pave the way for CBD's integration into precision medicine as a reliable therapeutic option for autoimmune and inflammatory diseases.

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References

Adams R, Hunt M, Clark J (1940) Structure of cannabidiol, a product isolated from the marihuana extract of Minnesota wild hemp. I. J Am Chem Soc 62:196–200

Agurell S, Carlsson S, Lindgren JE, Ohlsson A et al (1981) Interactions of delta 1-tetrahydrocannabinol with cannabinol and cannabidiol following oral administration in man. Assay of cannabinol and cannabidiol by mass fragmentography. Experientia 37:1090–1092. https://doi.org/10.1007/bf02085029

Al Saabi A, Allorge D, Sauvage F-L, Tournel G et al (2013) Involvement of UDP-glucuronosyltransferases UGT1A9 and UGT2B7 in ethanol glucuronidation, and interactions with common drugs of abuse. Drug Metab Dispos 41:568–574. https://doi.org/10.1124/dmd.112.047878

Ali RM, Al Kury LT, Yang K-HS, Qureshi A et al (2015) Effects of cannabidiol on contractions and calcium signaling in rat ventricular myocytes. Cell Calcium 57:290–299. https://doi.org/10.1016/j.ceca.2015.02.001

Ambrose T, Simmons A (2019) Cannabis, Cannabinoids, and the Endocannabinoid System-Is there Therapeutic Potential for Inflammatory Bowel Disease? J Crohns Colitis 13:525–535. https://doi.org/10.1093/ecco-jcc/jjy185

Andradas C, Truong A, Byrne J, Endersby R (2021) The role of cannabinoids as anticancer agents in pediatric oncology. Cancers (Basel) 13. https://doi.org/10.3390/cancers13010157

Arévalo-Martín A, Vela JM, Molina-Holgado E, Borrell J et al (2003) Therapeutic action of cannabinoids in a murine model of multiple sclerosis. J Neurosci 23:2511–2516. https://doi.org/10.1523/jneurosci.23-07-02511.2003

Aswad M, Pechkovsky A, Ghanayiem N, Hamza H et al (2024) High-CBD Extract (CBD-X) in Asthma Management: Reducing Th2-Driven Cytokine Secretion and Neutrophil/Eosinophil Activity. Pharmaceuticals 17:1382. https://doi.org/10.3390/ph17101382

Atkinson MA, Leiter EH (1999) The NOD mouse model of type 1 diabetes: as good as it gets? Nat Med 5:601–604. https://doi.org/10.1038/9442

Atsmon J, Heffetz D, Deutsch L, Deutsch F et al (2018) Single-dose pharmacokinetics of oral cannabidiol following administration of PTL101: a new formulation based on gelatin matrix pellets technology. Clinical Pharmacology in Drug Development 7:751–758. https://doi.org/10.1002/cpdd.408

Aziz AI, Nguyen LC, Oumeslakht L, Bensussan A et al (2023) Cannabinoids as Immune System Modulators: Cannabidiol Potential Therapeutic Approaches and Limitations. Cannabis Cannabinoid Res 8:254–269. https://doi.org/10.1089/can.2022.0133

Bardhi K, Coates S, Watson CJW, Lazarus P (2022) Cannabinoids and drug metabolizing enzymes: potential for drug-drug interactions and implications for drug safety and efficacy. Expert Rev Clin Pharmacol 15:1443–1460. https://doi.org/10.1080/17512433.2022.2148655

Bartner LR, McGrath S, Rao S, Hyatt LK et al (2018) Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs. Can J Vet Res 82:178–183

Berman P, Futoran K, Lewitus GM, Mukha D et al (2018) A new ESI-LC/MS approach for comprehensive metabolic profiling of phytocannabinoids in Cannabis. Sci Rep 8:14280. https://doi.org/10.1038/s41598-018-32651-4

Berrendero F, Sánchez A, Cabranes A, Puerta C et al (2001) Changes in cannabinoid CB(1) receptors in striatal and cortical regions of rats with experimental allergic encephalomyelitis, an animal model of multiple sclerosis. Synapse 41:195–202. https://doi.org/10.1002/syn.1075

Bisogno T, Hanuš L, De Petrocellis L, Tchilibon S et al (2001) Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol 134:845–852. https://doi.org/10.1038/sj.bjp.0704327

Bjelobaba I, Savic D, Lavrnja I (2017) Multiple Sclerosis and Neuroinflammation: The Overview of Current and Prospective Therapies. Curr Pharm des 23:693–730. https://doi.org/10.2174/1381612822666161214153108

Blando S, Raffaele I, Chiricosta L, Valeri A et al (2022) Cannabidiol promotes neuronal differentiation using Akt and Erk pathways triggered by Cb1 signaling. Molecules 27:5644. https://doi.org/10.3390/molecules27175644

Britch SC, Babalonis S, Walsh SL (2021) Cannabidiol: pharmacology and therapeutic targets. Psychopharmacology 238:9–28. https://doi.org/10.1007/s00213-020-05712-8

Brown JD, Winterstein AG (2019) Potential adverse drug events and drug-drug interactions with medical and consumer cannabidiol (CBD) use. J Clin Med 8. https://doi.org/10.3390/jcm8070989

Busquets Garcia A, Soria-Gomez E, Bellocchio L, Marsicano G (2016) Cannabinoid receptor type-1: breaking the dogmas. F1000Res 5. https://doi.org/10.12688/f1000research.8245.1

Cabral GA, Rogers TJ, Lichtman AH (2015) Turning Over a New Leaf: Cannabinoid and Endocannabinoid Modulation of Immune Function. J Neuroimmune Pharmacol 10:193–203. https://doi.org/10.1007/s11481-015-9615-z

Cabranes A, Venderova K, de Lago E, Fezza F et al (2005) Decreased endocannabinoid levels in the brain and beneficial effects of agents activating cannabinoid and/or vanilloid receptors in a rat model of multiple sclerosis. Neurobiol Dis 20:207–217. https://doi.org/10.1016/j.nbd.2005.03.002

Cao D, Lin Y, Lin C, Xu M et al (2024) Cannabidiol Inhibits Epithelial Ovarian Cancer: Role of Gut Microbiome. J Nat Prod 87:1501–1512. https://doi.org/10.1021/acs.jnatprod.3c00782

Castillo-Arellano J, Canseco-Alba A, Cutler SJ, León F (2023) The polypharmacological effects of cannabidiol. Molecules 28:3271. https://doi.org/10.3390/molecules28073271

Chelminiak-Dudkiewicz D, Smolarkiewicz-Wyczachowski A, Mylkie K, Wujak M et al (2022) Chitosan-based films with cannabis oil as a base material for wound dressing application. Sci Rep 12:18658. https://doi.org/10.1038/s41598-022-23506-0

Cherniakov I, Izgelov D, Domb AJ, Hoffman A (2017) The effect of Pro NanoLipospheres (PNL) formulation containing natural absorption enhancers on the oral bioavailability of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a rat model. Eur J Pharm Sci 109:21–30. https://doi.org/10.1016/j.ejps.2017.07.003

Chiossone L, Dumas PY, Vienne M, Vivier E (2018) Natural killer cells and other innate lymphoid cells in cancer. Nat Rev Immunol 18:671–688. https://doi.org/10.1038/s41577-018-0061-z

Chiurchiù V, Battistini L, Maccarrone M (2015) Endocannabinoid signalling in innate and adaptive immunity. Immunology 144:352–364. https://doi.org/10.1111/imm.12441

Costiniuk CT, Saneei Z, Routy JP, Margolese S et al (2019) Oral cannabinoids in people living with HIV on effective antiretroviral therapy: CTN PT028-study protocol for a pilot randomised trial to assess safety, tolerability and effect on immune activation. BMJ Open 9:e024793. https://doi.org/10.1136/bmjopen-2018-024793

Couch DG, Tasker C, Theophilidou E, Lund JN et al (2017) Cannabidiol and palmitoylethanolamide are anti-inflammatory in the acutely inflamed human colon. Clin Sci (Lond) 131:2611–2626. https://doi.org/10.1042/cs20171288

Cush JJ (2022) Rheumatoid Arthritis: Early Diagnosis and Treatment. Rheum Dis Clin North Am 48:537–547. https://doi.org/10.1016/j.rdc.2022.02.010

Cushman P Jr (1976) Cannabinols and the rosette forming properties of lymphocytes in vitro. Life Sci 19:875–885. https://doi.org/10.1016/0024-3205(76)90315-5

de Almeida DL, Devi LA (2020) Diversity of molecular targets and signaling pathways for CBD. Pharmacol Res Perspect 8:e00682. https://doi.org/10.1002/prp2.682

Deabold KA, Schwark WS, Wolf L, Wakshlag JJ (2019) Single-dose pharmacokinetics and preliminary safety assessment with use of CBD-rich hemp nutraceutical in healthy dogs and cats. Animals (Basel) 9. https://doi.org/10.3390/ani9100832

Del Rio C, Cantarero I, Palomares B, Gómez-Cañas M et al (2018) VCE-004.3, a cannabidiol aminoquinone derivative, prevents bleomycin-induced skin fibrosis and inflammation through PPARγ- and CB(2) receptor-dependent pathways. Br J Pharmacol 175:3813–3831. https://doi.org/10.1111/bph.14450

Derakhshan N, Kazemi M (2016) Cannabis for refractory psoriasis—High hopes for a novel treatment and a literature review. Curr Clin Pharmacol 11:146–147. https://doi.org/10.2174/1574884711666160511150126

Dernaika F, Halawy L, Zeaiter J, Kawrani S et al (2024) Development and characterization of a zeolite based drug delivery system: Application to cannabidiol oral delivery. Heliyon 10:e37373. https://doi.org/10.1016/j.heliyon.2024.e37373

Devinsky O, Patel AD, Thiele EA, Wong MH et al (2018) Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology 90:e1204–e1211. https://doi.org/10.1212/wnl.0000000000005254

Di Marzo V, Piscitelli F, Mechoulam R (2011) Cannabinoids and endocannabinoids in metabolic disorders with focus on diabetes. Handb Exp Pharmacol 75–104. https://doi.org/10.1007/978-3-642-17214-4_4

Di Salvo A, Conti MB, Della Rocca G (2023) Pharmacokinetics, efficacy, and safety of cannabidiol in dogs: an update of current knowledge. Frontiers in Veterinary Science 10:1204526

Dong T, Li J, Liang X, Wang W et al (2025) Cannabidiol Ameliorates Doxorubicin-Induced Myocardial Injury via Activating Hippo Pathway. Drug des Devel Ther 19:569–583. https://doi.org/10.2147/dddt.S497323

Dopkins N, Miranda K, Wilson K, Holloman BL et al (2022) Effects of Orally Administered Cannabidiol on Neuroinflammation and Intestinal Inflammation in the Attenuation of Experimental Autoimmune Encephalomyelitis. J Neuroimmune Pharmacol 17:15–32. https://doi.org/10.1007/s11481-021-10023-6

Dos-Santos-Pereira M, Guimarães FS, Del-Bel E, Raisman-Vozari R et al (2020) Cannabidiol prevents LPS-induced microglial inflammation by inhibiting ROS/NF-κB-dependent signaling

and glucose consumption. Glia 68:561–573. https://doi.org/10.1002/glia.23738

Duncan MR, Berman B (1991) Stimulation of collagen and glycosaminoglycan production in cultured human adult dermal fibroblasts by recombinant human interleukin 6. J Invest Dermatol 97:686–692. https://doi.org/10.1111/1523-1747.ep12483971

Dziadzio M, Smith RE, Abraham DJ, Stratton RJ et al (2004) Serological assessment of type I collagen burden in scleroderma spectrum disorders: a systematic review. Clin Exp Rheumatol 22:356–367

El Oihabi M, Soultana M, Ammari M, Allal LB et al (2024) Diversity and variability of bioactive compounds in Cannabis sativa: Effects on therapeutic and environmental uses and orientations for future research. Case Studies in Chemical and Environmental Engineering 9:100732. https://doi.org/10.1016/j.cscee.2024.100732

Eljaschewitsch E, Witting A, Mawrin C, Lee T et al (2006) The endocannabinoid anandamide protects neurons during CNS inflammation by induction of MKP-1 in microglial cells. Neuron 49:67–79. https://doi.org/10.1016/j.neuron.2005.11.027

Fallon MT, Albert Lux E, McQuade R, Rossetti S et al (2017) Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. Br J Pain 11:119–133. https://doi.org/10.1177/2049463717710042

Ferreira BP, Costa G, Mascarenhas-Melo F, Pires PC et al (2023) Skin applications of cannabidiol: sources, effects, delivery systems, marketed formulations and safety. Phytochem Rev 22:781–828. https://doi.org/10.1007/s11101-023-09860-5

Ferrini ME, Hong S, Stierle A, Stierle D et al (2017) CB2 receptors regulate natural killer cells that limit allergic airway inflammation in a murine model of asthma. Allergy 72:937–947. https://doi.org/10.1111/all.13107

Frei RB, Luschnig P, Parzmair GP, Peinhaupt M et al (2016) Cannabinoid receptor 2 augments eosinophil responsiveness and aggravates allergen-induced pulmonary inflammation in mice. Allergy 71:944–956. https://doi.org/10.1111/all.12858

Fujiwara N, Kobayashi K (2005) Macrophages in inflammation. Current Drug Targets-Inflammation & Allergy 4:281–286. https://doi.org/10.2174/1568010054022024

Galli SJ, Gaudenzio N, Tsai M (2020) Mast Cells in Inflammation and Disease: Recent Progress and Ongoing Concerns. Annu Rev Immunol 38:49–77. https://doi.org/10.1146/annurev-immunol-071719-094903

Ghovanloo M-R, Shuart NG, Mezeyova J, Dean RA et al (2018) Inhibitory effects of cannabidiol on voltage-dependent sodium currents. J Biol Chem 293:16546–16558. https://doi.org/10.1074/jbc.ra118.004929

Giudice ED, Rinaldi L, Passarotto M, Facchinetti F et al (2007) Cannabidiol, unlike synthetic cannabinoids, triggers activation of RBL-2H3 mast cells. J Leukoc Biol 81:1512–1522. https://doi.org/10.1189/jlb.1206738

Gleich GJ (1986) The pathology of asthma: with emphasis on the role of the eosinophil. N Engl Reg Allergy Proc 7:421–424. https://doi.org/10.2500/108854186778984718

Goldring MB, Otero M (2011) Inflammation in osteoarthritis. Curr Opin Rheumatol 23:471–478. https://doi.org/10.1097/BOR.0b013e328349c2b1

Good P, Haywood A, Gogna G, Martin J et al (2019) Oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer: a double-blind, placebo controlled, randomised clinical trial of efficacy and safety of cannabidiol (CBD). BMC Palliat Care 18:110. https://doi.org/10.1186/s12904-019-0494-6

Gościniak A, Kocaj F, Stasiłowicz-Krzemień A, Szymański M et al (2024) 3D printed bigel: A novel delivery system for cannabidiol-rich hemp extract. Gels 10: https://doi.org/10.3390/gels10120770

Gottschling S, Ayonrinde O, Bhaskar A, Blockman M et al (2020) Safety Considerations in Cannabinoid-Based Medicine. Int J Gen Med 13:1317–1333. https://doi.org/10.2147/ijgm.S275049

Green R, Khalil R, Mohapatra S S and Mohapatra S, (2022) Role of Cannabidiol for Improvement of the Quality of Life in Cancer Patients: Potential and Challenges. Int J Mol Sci 23: https://doi.org/10.3390/ijms232112956

Hendricks O, Andersen TE, Christiansen AA, Primdahl J et al (2019) Efficacy and safety of cannabidiol followed by an open label add-on of tetrahydrocannabinol for the treatment of chronic pain in patients with rheumatoid arthritis or ankylosing spondylitis: protocol for a multicentre, randomised, placebo-controlled study. BMJ Open 9:e028197. https://doi.org/10.1136/bmjopen-2018-028197

Hively RL, Mosher WA, Hoffmann FW (1966) Isolation of trans-Δ6-tetrahydrocannabinol from marijuana. J Am Chem Soc 88:1832–1833

Huang Y, Wan T, Pang N, Zhou Y et al (2019) Cannabidiol protects livers against nonalcoholic steatohepatitis induced by high-fat high cholesterol diet via regulating NF-κB and NLRP3 inflammasome pathway. J Cell Physiol 234:21224–21234. https://doi.org/10.1002/jcp.28728

Huestis MA, Solimini R, Pichini S, Pacifici R et al (2019) Cannabidiol Adverse Effects and Toxicity. Curr Neuropharmacol 17:974–989. https://doi.org/10.2174/1570159x17666190603171901

Ibrahim IA, Xu J, Robertson J, Ajayi BKO (2023) Exploring the synergy of carbon nanodots in enhancing cannabidiol delivery and therapeutic efficacy: A Comprehensive Review. https://doi.org/10.20944/preprints202310.1434.v1

Irving PM, Iqbal T, Nwokolo C, Subramanian S et al (2018) A randomized, double-blind, placebo-controlled, parallel-group, pilot study of cannabidiol-rich botanical extract in the symptomatic treatment of ulcerative colitis. Inflamm Bowel Dis 24:714–724. https://doi.org/10.1093/ibd/izy002

Isaev D, Shabbir W, Dinc EY, Lorke DE et al (2022) Cannabidiol inhibits multiple ion channels in rabbit ventricular cardiomyocytes. Front Pharmacol 13:821758. https://doi.org/10.3389/fphar.2022.821758

Iwasaki A, Medzhitov R (2015) Control of adaptive immunity by the innate immune system. Nat Immunol 16:343–353. https://doi.org/10.1038/ni.3123

Jackson SJ, Pryce G, Diemel LT, Cuzner ML et al (2005) Cannabinoid-receptor 1 null mice are susceptible to neurofilament damage and caspase 3 activation. Neuroscience 134:261–268. https://doi.org/10.1016/j.neuroscience.2005.02.045

Jenny M, Santer E, Pirich E, Schennach H et al (2009) Delta9-tetrahydrocannabinol and cannabidiol modulate mitogen-induced tryptophan degradation and neopterin formation in peripheral blood mononuclear cells in vitro. J Neuroimmunol 207:75–82. https://doi.org/10.1016/j.jneuroim.2008.12.004

Jiang R, Yamaori S, Takeda S, Yamamoto I et al (2011) Identification of cytochrome P450 enzymes responsible for metabolism of cannabidiol by human liver microsomes. Life Sci 89:165–170. https://doi.org/10.1016/j.lfs.2011.05.018

Johnson DR, Stebulis JA, Rossetti RG, Burstein SH et al (2007) Suppression of fibroblast metalloproteinases by ajulemic acid, a nonpsychoactive cannabinoid acid. J Cell Biochem 100:184–190. https://doi.org/10.1002/jcb.21046

Juknat A, Pietr M, Kozela E, Rimmerman N et al (2012) Differential transcriptional profiles mediated by exposure to the cannabinoids cannabidiol and Δ9-tetrahydrocannabinol in BV-2 microglial

cells. Br J Pharmacol 165:2512–2528. https://doi.org/10.1111/j.1476-5381.2011.01461.x
Kalsoom I, Shehzadi K, Li H-s, Wen H-l et al (2024) Unraveling the Mechanisms of Cannabidiol's Pharmacological Actions: A Comprehensive Research Overview. Top Curr Chem 382:20. https://doi.org/10.1007/s41061-024-00465-w
Kaplan BL, Rockwell CE, Kaminski NE (2003) Evidence for cannabinoid receptor-dependent and -independent mechanisms of action in leukocytes. J Pharmacol Exp Ther 306:1077–1085. https://doi.org/10.1124/jpet.103.051961
Kathmann M, Flau K, Redmer A, Tränkle C et al (2006) Cannabidiol is an allosteric modulator at mu-and delta-opioid receptors. Naunyn Schmiedebergs Arch Pharmacol 372:354–361. https://doi.org/10.1007/s00210-006-0033-x
Khuja I, Yekhtin Z, Or R, Almogi-Hazan O (2019) Cannabinoids reduce inflammation but inhibit lymphocyte recovery in murine models of bone marrow transplantation. Int J Mol Sci 20. https://doi.org/10.3390/ijms20030668
Kim K-A, Jang S-E, Jeong J-J, Yu D-H et al (2014) Doenjang, a Korean soybean paste, ameliorates TNBS-induced colitis in mice by suppressing gut microbial lipopolysaccharide production and NF-κB activation. Journal of Functional Foods 11:417–427. https://doi.org/10.1016/j.jff.2014.09.021
Kishimoto S, Muramatsu M, Gokoh M, Oka S et al (2005) Endogenous cannabinoid receptor ligand induces the migration of human natural killer cells. J Biochem 137:217–223. https://doi.org/10.1093/jb/mvi021
Knaub K, Sartorius T, Dharsono T, Wacker R et al (2019) A novel self-emulsifying drug delivery system (SEDDS) based on VESIsorb(®) formulation technology improving the oral bioavailability of cannabidiol in healthy subjects. Molecules 24. https://doi.org/10.3390/molecules24162967
Kowalski CW, Ragozzino FJ, Lindberg JE, Peterson B et al (2020) Cannabidiol activation of vagal afferent neurons requires TRPA1. J Neurophysiol 124:1388–1398. https://doi.org/10.1152/jn.00128.2020
Krishnaswamy G, Ajitawi O, Chi DS (2005) The human mast cell: an overview. Mast Cells: Methods and Protocols 13–34. https://doi.org/10.1385/1-59259-967-2:013
Landucci E, Mazzantini C, Lana D, Calvani M et al (2022) Cannabidiol inhibits microglia activation and mitigates neuronal damage induced by kainate in an in-vitro seizure model. Neurobiol Dis 174:105895. https://doi.org/10.1016/j.nbd.2022.105895
Lazzerini PE, Natale M, Gianchecchi E, Capecchi PL et al (2012) Adenosine A2A receptor activation stimulates collagen production in sclerodermic dermal fibroblasts either directly and through a cross-talk with the cannabinoid system. J Mol Med (Berl) 90:331–342. https://doi.org/10.1007/s00109-011-0824-5
Le Marois M, Ballet V, Sanson C, Maizières MA et al (2020) Cannabidiol inhibits multiple cardiac ion channels and shortens ventricular action potential duration in vitro. Eur J Pharmacol 886:173542. https://doi.org/10.1016/j.ejphar.2020.173542
Legare CA, Raup-Konsavage WM, Vrana KE (2022) Therapeutic potential of cannabis, cannabidiol, and cannabinoid-based pharmaceuticals. Pharmacology 107:131–149. https://doi.org/10.1159/000521683
Lewis SN, Brannan L, Guri AJ, Lu P et al (2011) Dietary α-eleostearic acid ameliorates experimental inflammatory bowel disease in mice by activating peroxisome proliferator-activated receptor-γ. PLoS ONE 6:e24031. https://doi.org/10.1371/journal.pone.0024031
Limberg MM, Weihrauch T, Gray N, Ernst N et al (2023) Eosinophils, basophils, and neutrophils in bullous pemphigoid. Biomolecules 13. https://doi.org/10.3390/biom13071019
Limsuwan S, Phonsatta N, Panya A, Asasutjarit R et al (2024) Pharmacokinetics behavior of four cannabidiol preparations following single oral administration in dogs. Front Vet Sci 11:1389810. https://doi.org/10.3389/fvets.2024.1389810
Lipscomb MF, Masten BJ (2002) Dendritic cells: immune regulators in health and disease. Physiol Rev 82:97–130. https://doi.org/10.1152/physrev.00023.2001
Liu T, Zhang L, Joo D, Sun S-C (2017) NF-κB signaling in inflammation. Signal Transduct Target Ther 2:1–9. https://doi.org/10.1038/sigtrans.2017.23
Liu B, Sun Y, Zhang H, Zhang H, Chang S, CHEN, C,…& Jiang Y (2024) Nano-Cannabidiol to Orchestrate Inflammatory Homeostasis Via Macrophage Metabolism Reprogramming for Targeted Treatment Atherosclerosis. SSRN. https://doi.org/10.2139/ssrn.4783451
Maguire RF, Wilkinson DJ, England TJ, O'Sullivan SE (2021) The pharmacological effects of plant-derived versus synthetic cannabidiol in human cell lines. Medical Cannabis and Cannabinoids 4:86–96. https://doi.org/10.1159/000517120
Makwana R, Venkatasamy R, Spina D, Page C (2015) The effect of phytocannabinoids on airway hyper-responsiveness, airway inflammation, and cough. J Pharmacol Exp Ther 353:169–180. https://doi.org/10.1124/jpet.114.221283
Malfait AM, Gallily R, Sumariwalla PF, Malik AS et al (2000) The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci U S A 97:9561–9566. https://doi.org/10.1073/pnas.160105897
Mandrup-Poulsen T (2003) Beta cell death and protection. Ann N Y Acad Sci 1005:32–42. https://doi.org/10.1196/annals.1288.005
Mangal N, Erridge S, Habib N, Sadanandam A et al (2021) Cannabinoids in the landscape of cancer. J Cancer Res Clin Oncol 147:2507–2534. https://doi.org/10.1007/s00432-021-03710-7
Marinelli O, Morelli MB, Annibali D, Aguzzi C et al (2020) The effects of cannabidiol and prognostic role of TRPV2 in human endometrial cancer. Int J Mol Sci 21. https://doi.org/10.3390/ijms21155409
Markiewicz I and Lukomska B (2006) The role of astrocytes in the physiology and pathology of the central nervous system. Acta neurobiologiae experimentalis 66:343–358. https://doi.org/10.55782/ane-2006-1623
Marquéz L, Suárez J, Iglesias M, Bermudez-Silva FJ et al (2009) Ulcerative colitis induces changes on the expression of the endocannabinoid system in the human colonic tissue. PLoS ONE 4:e6893. https://doi.org/10.1371/journal.pone.0006893
Martinez Naya N, Kelly J, Corna G, Golino M et al (2023) Molecular and cellular mechanisms of action of cannabidiol. Molecules 28:5980. https://doi.org/10.3390/molecules28165980
Martini S, Gemma A, Ferrari M, Cosentino M et al (2023) Effects of cannabidiol on innate immunity: experimental evidence and clinical relevance. Int J Mol Sci 24. https://doi.org/10.3390/ijms24043125
Matias I, Pochard P, Orlando P, Salzet M et al (2002) Presence and regulation of the endocannabinoid system in human dendritic cells. Eur J Biochem 269:3771–3778. https://doi.org/10.1046/j.1432-1033.2002.03078.x
Mecha M, Torrao A, d S, Mestre L, Carrillo-Salinas F, et al (2012) Cannabidiol protects oligodendrocyte progenitor cells from inflammation-induced apoptosis by attenuating endoplasmic reticulum stress. Cell Death Dis 3:e331–e331. https://doi.org/10.1038/cddis.2012.71
Mechoulam R, Shvo Y (1963) Hashish. I the Structure of Cannabidiol Tetrahedron 19:2073–2078. https://doi.org/10.1016/0040-4020(63)85022-x
Melén CM, Merrien M, Wasik AM, Panagiotidis G et al (2022) Clinical effects of a single dose of cannabinoids to patients with chronic lymphocytic leukemia. Leuk Lymphoma

63:1387–1397. https://doi.org/10.1080/10428194.2021.2020776
Millar SA, Stone NL, Yates AS, O'Sullivan SE (2018) A Systematic Review on the Pharmacokinetics of Cannabidiol in Humans. Front Pharmacol 9:1365. https://doi.org/10.3389/fphar.2018.01365
Millar SA, Maguire RF, Yates AS, O'Sullivan SE (2020) Towards better delivery of cannabidiol (CBD). pharmaceuticals (Basel) 13. https://doi.org/10.3390/ph13090219
Mishiro S, Igarashi-Takeuchi H, Numabe Y (2021) Expression of Cannabinoid Receptor GPR55 in Human Gingival Fibroblasts and Anti-inflammatory Effects of Cannabidiol via GPR55. Nihon Shishubyo Gakkai Kaishi (Journal of the Japanese Society of Periodontology) 63:11–23. https://doi.org/10.2329/perio.63.11
Mukhopadhyay P, Rajesh M, Horváth B, Bátkai S et al (2011) Cannabidiol protects against hepatic ischemia/reperfusion injury by attenuating inflammatory signaling and response, oxidative/nitrative stress, and cell death. Free Radic Biol Med 50:1368–1381. https://doi.org/10.1016/j.freeradbiomed.2011.02.021
Muthumalage T, Rahman I (2019) Cannabidiol differentially regulates basal and LPS-induced inflammatory responses in macrophages, lung epithelial cells, and fibroblasts. Toxicol Appl Pharmacol 382:114713. https://doi.org/10.1016/j.taap.2019.114713
Nadulski T, Sporkert F, Schnelle M, Stadelmann AM et al (2005) Simultaneous and sensitive analysis of THC, 11-OH-THC, THC-COOH, CBD, and CBN by GC-MS in plasma after oral application of small doses of THC and cannabis extract. J Anal Toxicol 29:782–789. https://doi.org/10.1093/jat/29.8.782
Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP et al (2013) Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Clin Gastroenterol Hepatol 11:1276-1280.e1271. https://doi.org/10.1016/j.cgh.2013.04.034
Naftali T, Mechulam R, Lev LB, Konikoff FM (2014) Cannabis for inflammatory bowel disease. Dig Dis 32:468–474. https://doi.org/10.1159/000358155
Naftali T, Bar-Lev Schleider L, Almog S, Meiri D et al (2021) Oral CBD-rich Cannabis Induces Clinical but Not Endoscopic Response in Patients with Crohn's Disease, a Randomised Controlled Trial. J Crohns Colitis 15:1799–1806. https://doi.org/10.1093/ecco-jcc/jjab069
Nasrin S, Watson CJ, Perez-Paramo YX, Lazarus P (2021) Cannabinoid metabolites as inhibitors of major hepatic CYP450 enzymes, with implications for cannabis-drug interactions. Drug Metab Dispos 49:1070–1080. https://doi.org/10.1124/dmd.121.000442
Nichols JM, Kaplan BLF (2020) Immune Responses Regulated by Cannabidiol. Cannabis Cannabinoid Res 5:12–31. https://doi.org/10.1089/can.2018.0073
Nielsen SW, Hasselsteen SD, Dominiak HSH, Labudovic D et al (2022) Oral cannabidiol for prevention of acute and transient chemotherapy-induced peripheral neuropathy. Support Care Cancer 30:9441–9451. https://doi.org/10.1007/s00520-022-07312-y
Oka S, Ikeda S, Kishimoto S, Gokoh M et al (2004) 2-arachidonoylglycerol, an endogenous cannabinoid receptor ligand, induces the migration of EoL-1 human eosinophilic leukemia cells and human peripheral blood eosinophils. J Leukoc Biol 76:1002–1009. https://doi.org/10.1189/jlb.0404252
Parkin J, Cohen B (2001) An overview of the immune system. The Lancet 357:1777–1789. https://doi.org/10.1016/s0140-6736(00)04904-7
Parolaro D (1999) Presence and functional regulation of cannabinoid receptors in immune cells. Life Sci 65:637–644. https://doi.org/10.1016/s0024-3205(99)00286-6
Partalis C (2022) Development of silica nanoparticle transdermal delivery systems for cannabidiol. Macquarie University 10(25949/21555219):v1
Patti F, Messina S, Solaro C, Amato MP et al (2016) Efficacy and safety of cannabinoid oromucosal spray for multiple sclerosis spasticity. J Neurol Neurosurg Psychiatry 87:944–951. https://doi.org/10.1136/jnnp-2015-312591
Pénzes Z, Alimohammadi S, Horváth D, Oláh A et al (2023) The dual role of cannabidiol on monocyte-derived dendritic cell differentiation and maturation. Front Immunol 14:1240800. https://doi.org/10.3389/fimmu.2023.1240800
Pertwee RG (2001) Cannabinoid receptors and pain. Prog Neurobiol 63:569–611. https://doi.org/10.1016/s0301-0082(00)00031-9
Petrosino S, Verde R, Vaia M, Allarà M et al (2018) Anti-inflammatory Properties of Cannabidiol, a Nonpsychotropic Cannabinoid, in Experimental Allergic Contact Dermatitis. J Pharmacol Exp Ther 365:652–663. https://doi.org/10.1124/jpet.117.244368
Polidoro D, Temmerman R, Devreese M, Charalambous M et al (2022a) Pharmacokinetics of cannabidiol following intranasal, intrarectal, and oral administration in healthy dogs. Frontiers in Veterinary Science 9:899940
Polidoro D, Temmerman R, Devreese M, Charalambous M et al (2022b) Pharmacokinetics of Cannabidiol Following Intranasal, Intrarectal, and Oral Administration in Healthy Dogs. Front Vet Sci 9:899940. https://doi.org/10.3389/fvets.2022.899940
Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R et al (2012) Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain 13:438–449. https://doi.org/10.1016/j.jpain.2012.01.003
Pryce G, Baker D (2007) Control of spasticity in a multiple sclerosis model is mediated by CB1, not CB2, cannabinoid receptors. Br J Pharmacol 150:519–525. https://doi.org/10.1038/sj.bjp.0707003
Pryce G, Ahmed Z, Hankey DJ, Jackson SJ et al (2003) Cannabinoids inhibit neurodegeneration in models of multiple sclerosis. Brain 126:2191–2202. https://doi.org/10.1093/brain/awg224
Ramot Y, Sugawara K, Zákány N, Tóth BI et al (2013) A novel control of human keratin expression: cannabinoid receptor 1-mediated signaling down-regulates the expression of keratins K6 and K16 in human keratinocytes in vitro and in situ. PeerJ 1:e40. https://doi.org/10.7717/peerj.40
Ribeiro A, Ferraz-de-Paula V, Pinheiro ML, Vitoretti LB et al (2012) Cannabidiol, a non-psychotropic plant-derived cannabinoid, decreases inflammation in a murine model of acute lung injury: role for the adenosine A(2A) receptor. Eur J Pharmacol 678:78–85. https://doi.org/10.1016/j.ejphar.2011.12.043
Richardson D, Pearson RG, Kurian N, Latif ML et al (2008) Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis. Arthritis Res Ther 10:R43. https://doi.org/10.1186/ar2401
Rj M (2006) Cannabidiol-induced apoptosis in human leukemia cells: A novel role of cannabidiol in the regulation of p22phox and Nox4 expression. Mol Pharmacol 70:897–908. https://doi.org/10.1124/mol.106.023937
Rog DJ, Nurmikko TJ, Friede T, Young CA (2005) Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 65:812–819. https://doi.org/10.1212/01.wnl.0000176753.45410.8b
Russo EB, Burnett A, Hall B, Parker KK (2005) Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem Res 30:1037–1043. https://doi.org/10.1007/s11064-005-6978-1
Sacerdote P, Martucci C, Vaccani A, Bariselli F et al (2005) The nonpsychoactive component of marijuana cannabidiol modulates chemotaxis and IL-10 and IL-12 production of murine macrophages both in vivo and in vitro. J Neuroimmunol 159:97–105. https://doi.org/10.1016/j.jneuroim.2004.10.003
Saijo K, Glass CK (2011) Microglial cell origin and phenotypes in health and disease. Nat Rev Immunol 11:775–787. https://doi.org/10.1038/nri3086

Samara E, Bialer M, Mechoulam R (1988) Pharmacokinetics of cannabidiol in dogs. Drug Metab Dispos 16:469–472. https://doi.org/10.1016/S0090-9556(25)06962-4

Samara E, Bialer M, Harvey DJ (1990) Pharmacokinetics of urinary metabolites of cannabidiol in the dog. Biopharm Drug Dispos 11:785–795. https://doi.org/10.1002/bdd.2510110906

Satoh J, Takahashi K, Nakazawa T, Sakata Y et al (1999) Current concept of the pathogenesis of autoimmune type 1 diabetes mellitus. Nihon Rinsho 57:528–533

Schicho R, Storr M (2014) Cannabis finds its way into treatment of Crohn's disease. Pharmacology 93:1–3. https://doi.org/10.1159/000356512

Schlag AK, O'Sullivan SE, Zafar RR, Nutt DJ (2021) Current controversies in medical cannabis: Recent developments in human clinical applications and potential therapeutics. Neuropharmacology 191:108586. https://doi.org/10.1016/j.neuropharm.2021.108586

Schwope DM, Karschner EL, Gorelick DA, Huestis MA (2011) Identification of recent cannabis use: whole-blood and plasma free and glucuronidated cannabinoid pharmacokinetics following controlled smoked cannabis administration. Clin Chem 57:1406–1414. https://doi.org/10.1373/clinchem.2011.171777

Selvi E, Lorenzini S, Garcia-Gonzalez E, Maggio R et al (2008) Inhibitory effect of synthetic cannabinoids on cytokine production in rheumatoid fibroblast-like synoviocytes. Clin Exp Rheumatol 26:574–581

Shi J, Ma Q, Su W, Liu C et al (2023) Effervescent cannabidiol solid dispersion-doped dissolving microneedles for boosted melanoma therapy via the "TRPV1-NFATc1-ATF3" pathway and tumor microenvironment engineering. Biomater Res 27:48. https://doi.org/10.1186/s40824-023-00390-x

Singh V, Vihal S, Rana R, Rathore C (2024) Nanocarriers for Cannabinoid Delivery: Enhancing Therapeutic Potential. Recent Adv Drug Deliv Formul 18:247–261. https://doi.org/10.2174/0126673878300347240718100814

Skeen MJ, Miller MA, Shinnick TM, Ziegler HK (1996) Regulation of murine macrophage IL-12 production. Activation of macrophages in vivo, restimulation in vitro, and modulation by other cytokines. J Immunol 156:1196–1206

Snaidero N, Simons M (2017) The logistics of myelin biogenesis in the central nervous system. Glia 65:1021–1031. https://doi.org/10.1002/glia.23116

Spittler AP, Helbling JE, McGrath S, Gustafson DL et al (2021) Plasma and joint tissue pharmacokinetics of two doses of oral cannabidiol oil in guinea pigs (Cavia porcellus). J Vet Pharmacol Ther 44:967–974. https://doi.org/10.1111/jvp.13026

Stanescu AMA, Bejan GC, Balta MD, Andronic O et al (2024) The Perspective of Cannabidiol in Psoriasis Therapy. Psoriasis (Auckl) 14:51–61. https://doi.org/10.2147/ptt.S469698

Stone KD, Prussin C, Metcalfe DD (2010) IgE, mast cells, basophils, and eosinophils. J Allergy Clin Immunol 125:S73-80. https://doi.org/10.1016/j.jaci.2009.11.017

Sumariwalla PF, Gallily R, Tchilibon S, Fride E et al (2004) A novel synthetic, nonpsychoactive cannabinoid acid (HU-320) with antiinflammatory properties in murine collagen-induced arthritis. Arthritis Rheum 50:985–998. https://doi.org/10.1002/art.20050

Swain SL (1995) T-cell subsets. Who does the polarizing? Curr Biol 5:849–851. https://doi.org/10.1016/s0960-9822(95)00170-9

Taylor L, Gidal B, Blakey G, Tayo B et al (2018) A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, Multiple Dose, and Food Effect Trial of the Safety, Tolerability and Pharmacokinetics of Highly Purified Cannabidiol in Healthy Subjects. CNS Drugs 32:1053–1067. https://doi.org/10.1007/s40263-018-0578-5

Thapa D, Cairns EA, Szczesniak AM, Toguri JT et al (2018) The Cannabinoids Δ(8)THC, CBD, and HU-308 Act via Distinct Receptors to Reduce Corneal Pain and Inflammation. Cannabis Cannabinoid Res 3:11–20. https://doi.org/10.1089/can.2017.0041

Thomas A, Baillie G, Phillips A, Razdan R et al (2007) Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. Br J Pharmacol 150:613–623. https://doi.org/10.1038/sj.bjp.0707133

Tomer S, Mu W, Suryawanshi G, Ng H et al (2022) Cannabidiol modulates expression of type I IFN response genes and HIV infection in macrophages. Front Immunol 13:926696. https://doi.org/10.3389/fimmu.2022.926696

Trinchieri G (2003) Interleukin-12 and the regulation of innate resistance and adaptive immunity. Nat Rev Immunol 3:133–146. https://doi.org/10.1038/nri1001

Tsiogkas SG, Apostolopoulou K, Papagianni ED, Mavropoulos A et al (2024) Cannabidiol Mediates In Vitro Attenuation of Pro-inflammatory Cytokine Responses in Psoriatic Disease. Cannabis and Cannabinoid Research 9:134–146. https://doi.org/10.1089/can.2023.0237

Ujváry I, Hanuš L (2016) Human Metabolites of Cannabidiol: A Review on Their Formation, Biological Activity, and Relevance in Therapy. Cannabis Cannabinoid Res 1:90–101. https://doi.org/10.1089/can.2015.0012

Vaughn D, Kulpa J, Paulionis L (2020) Preliminary Investigation of the Safety of Escalating Cannabinoid Doses in Healthy Dogs. Front Vet Sci 7:51. https://doi.org/10.3389/fvets.2020.00051

Vaughn DM, Paulionis LJ, Kulpa JE (2021) Randomized, placebo-controlled, 28-day safety and pharmacokinetics evaluation of repeated oral cannabidiol administration in healthy dogs. Am J Vet Res 82:405–416. https://doi.org/10.2460/ajvr.82.5.405

Vela J, Dreyer L, Petersen KK, Arendt-Nielsen L et al (2022) Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind, placebo-controlled trial. Pain 163:1206–1214. https://doi.org/10.1097/j.pain.0000000000002466

Vivier E, Raulet DH, Moretta A, Caligiuri MA et al (2011) Innate or adaptive immunity? The example of natural killer cells. Science 331:44–49. https://doi.org/10.1126/science.1198687

Wakshlag JJ, Schwark WS, Deabold KA, Talsma BN et al (2020) Pharmacokinetics of Cannabidiol, Cannabidiolic Acid, Δ9-Tetrahydrocannabinol, Tetrahydrocannabinolic Acid and Related Metabolites in Canine Serum After Dosing With Three Oral Forms of Hemp Extract. Front Vet Sci 7:505. https://doi.org/10.3389/fvets.2020.00505

Walter L, Franklin A, Witting A, Wade C et al (2003) Nonpsychotropic cannabinoid receptors regulate microglial cell migration. J Neurosci 23:1398–1405. https://doi.org/10.1523/jneurosci.23-04-01398.2003

Wang F, Multhoff G (2021) Repurposing cannabidiol as a potential drug candidate for anti-tumor therapies. Biomolecules 11. https://doi.org/10.3390/biom11040582

Wang Y, Mukhopadhyay P, Cao Z, Wang H et al (2017) Cannabidiol attenuates alcohol-induced liver steatosis, metabolic dysregulation, inflammation and neutrophil-mediated injury. Sci Rep 7:12064. https://doi.org/10.1038/s41598-017-10924-8

Wang Z, Lu M, Ren J, Wu X et al (2019) Electroacupuncture inhibits mast cell degranulation via cannabinoid CB2 receptors in a rat model of allergic contact dermatitis. Acupunct Med 37:348–355. https://doi.org/10.1136/acupmed-2017-011506

Wang T, Zakharov A, Gomez B, Lyubimov A et al (2022) Serum Cannabinoid 24 h and 1 Week Steady State Pharmacokinetic Assessment in Cats Using a CBD/CBDA Rich Hemp Paste. Front Vet Sci 9:895368. https://doi.org/10.3389/fvets.2022.895368

Wang F, Bashiri Dezfouli A, Multhoff G (2024) The immunomodulatory effects of cannabidiol on Hsp70-activated NK cells and tumor target cells. Mol Immunol 174:1–10. https://doi.org/10.1016/j.molimm.2024.07.008

Ward SJ, Ramirez MD, Neelakantan H, Walker EA (2011) Cannabidiol prevents the development of cold and mechanical allodynia in paclitaxel-treated female C57Bl6 mice. Anesth Analg 113:947–950. https://doi.org/10.1213/ANE.0b013e3182283486

Watanabe K, Kayano Y, Matsunaga T, Yamamoto I et al (1996) Inhibition of anandamide amidase activity in mouse brain microsomes by cannabinoids. Biol Pharm Bull 19:1109–1111. https://doi.org/10.1248/bpb.19.1109

Weiss L, Zeira M, Reich S, Har-Noy M et al (2006) Cannabidiol lowers incidence of diabetes in non-obese diabetic mice. Autoimmunity 39:143–151. https://doi.org/10.1080/08916930500356674

Weiss L, Zeira M, Reich S, Slavin S et al (2008) Cannabidiol arrests onset of autoimmune diabetes in NOD mice. Neuropharmacology 54:244–249. https://doi.org/10.1016/j.neuropharm.2007.06.029

Wilkinson JD, Williamson EM (2007) Cannabinoids inhibit human keratinocyte proliferation through a non-CB1/CB2 mechanism and have a potential therapeutic value in the treatment of psoriasis. J Dermatol Sci 45:87–92. https://doi.org/10.1016/j.jdermsci.2006.10.009

Williams MR, Holbrook TC, Maxwell L, Croft CH et al (2022) Pharmacokinetic evaluation of a cannabidiol supplement in horses. J Equine Vet 110:103842. https://doi.org/10.1016/j.jevs.2021.103842

Wójcik P, Garley M, Wroński A, Jabłońska E et al (2020) Cannabidiol modifies the formation of NETs in neutrophils of psoriatic patients. Int J Mol Sci 21. https://doi.org/10.3390/ijms21186795

Wright K, Rooney N, Feeney M, Tate J et al (2005) Differential expression of cannabinoid receptors in the human colon: cannabinoids promote epithelial wound healing. Gastroenterology 129:437–453. https://doi.org/10.1016/j.gastro.2005.05.026

Wright HL, Moots RJ, Bucknall RC, Edwards SW (2010) Neutrophil function in inflammation and inflammatory diseases. Rheumatology 49:1618–1631

Wu HY, Goble K, Mecha M, Wang CC et al (2012) Cannabidiol-induced apoptosis in murine microglial cells through lipid raft. Glia 60:1182–1190. https://doi.org/10.1002/glia.22345

Wynn TA, Chawla A, Pollard JW (2013) Macrophage biology in development, homeostasis and disease. Nature 496:445–455. https://doi.org/10.1038/nature12034

Yan C, Li Y, Liu H, Chen D et al (2023) Antitumor mechanism of cannabidiol hidden behind cancer hallmarks. Biochim Biophys Acta Rev Cancer 1878:188905. https://doi.org/10.1016/j.bbcan.2023.188905

Yekhtin Z, Khuja I, Meiri D, Or R et al (2022) Differential effects of D9 tetrahydrocannabinol (THC)- and cannabidiol (CBD)-based cannabinoid treatments on macrophage immune function In Vitro and on gastrointestinal inflammation in a murine model. Biomedicines 10. https://doi.org/10.3390/biomedicines10081793

Zgair A, Wong JC, Lee JB, Mistry J et al (2016) Dietary fats and pharmaceutical lipid excipients increase systemic exposure to orally administered cannabis and cannabis-based medicines. Am J Transl Res 8:3448–3459

Zgair A, Lee JB, Wong JCM, Taha DA et al (2017) Oral administration of cannabis with lipids leads to high levels of cannabinoids in the intestinal lymphatic system and prominent immunomodulation. Sci Rep 7:14542. https://doi.org/10.1038/s41598-017-15026-z

Zheng T, BouSaba J, Taylor A, Dilmaghani S et al (2023) A Randomized, Controlled Trial of Efficacy and Safety of Cannabidiol in Idiopathic and Diabetic Gastroparesis. Clin Gastroenterol Hepatol 21:3405-3414.e3404. https://doi.org/10.1016/j.cgh.2023.07.008

Zielińska A, Eder P, Karczewski J, Szalata M et al (2023) Tocilizumab-coated solid lipid nanoparticles loaded with cannabidiol as a novel drug delivery strategy for treating COVID-19: A review. Front Immunol 14:1147991. https://doi.org/10.3389/fimmu.2023.1147991

Zitti B, Bryceson YT (2018) Natural killer cells in inflammation and autoimmunity. Cytokine Growth Factor Rev 42:37–46. https://doi.org/10.1016/j.cytogfr.2018.08.001

Zurier RB, Sun YP, George KL, Stebulis JA et al (2009) Ajulemic acid, a synthetic cannabinoid, increases formation of the endogenous proresolving and anti-inflammatory eicosanoid, lipoxin A4. Faseb j 23:1503–1509. https://doi.org/10.1096/fj.08-118323