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Review

BIOCHEMICAL INSIGHTS INTO CANNABIDIOL–ENDOCANNABINOID SYSTEM INTERACTIONS IN THE REGULATION OF METABOLIC PATHWAYS

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Cannabidiol (CBD), a non-psychoactive phytocannabinoid from *Cannabis sativa*, has emerged as an important compound of interest in biochemical and pharmaceutical research. Its molecular activity is closely linked to the endocannabinoid system (ECS), which plays a central role in the regulation of metabolic homeostasis. Dysregulation of the ECS has been associated with insulin resistance, lipid imbalance, obesity, and increased cardiovascular risk. This review summarizes the current biochemical evidence on the mechanisms by which CBD modulates metabolic pathways through interactions with cannabinoid receptors and related molecular targets. Special emphasis is placed on the antioxidant and anti-inflammatory properties of CBD, its capacity to influence mitochondrial function, and its impact on glucose and lipid metabolism. Furthermore, this review discusses the influence of physicochemical factors, such as bioavailability and route of administration, on the pharmacokinetic and pharmacodynamic behavior of CBD. Potential interactions with other biomolecules and therapeutic agents are also considered, highlighting the need for systematic biochemical and pharmacological evaluation. Overall, the synthesis of the available literature indicates that CBD is a promising candidate for further biochemical and preclinical studies aimed at elucidating its regulatory role in metabolic processes and its potential for the development of novel therapeutic strategies.

Keywords: CB_1 and CB_2 receptors; Diabetes mellitus (DM); metabolic (CKM) syndrome; insulin resistance; glucose metabolism; cardiovascular risk; inflammation; oxidative stress; lipid metabolism

БИОХЕМИСКИ АСПЕКТИ НА ИНТЕРАКЦИИТЕ ПОМЕЃУ КАНАБИДИОЛОТ И ЕНДОКАНАБИНОИДНИОТ СИСТЕМ ВО РЕГУЛАЦИЈАТА НА МЕТАБОЛНИТЕ ПРОЦЕСИ

Канабидиолот (CBD), непсихоактивен фитоканабиноид од *Cannabis sativa*, сè повеќе се издвојува како значајно соединение во биохемиските и фармаколошките истражувања. Неговото дејство е тесно поврзано со ендоканабиноидниот систем (ЕКС), што претставува клучен регулатор на метаболната хомеостаза. Постојат јасни индикации дека нарушената функција на ЕКС е поврзана со развој на инсулинска резистенција, дислипидемија, дебелина и зголемен кардиоваскуларен ризик. Оваа прегледна статија го сумира актуелното знаење за биохемиските механизми преку кои CBD може да влијае врз метаболните патишта, вклучувајќи ги неговите интеракции со канабиноидните рецептори и други молекуларни посредници. Посебно внимание е посветено на антиинфламаторните и антиоксидативните ефекти на CBD, неговата улога во модулацијата на функцијата на митоходнрии и неговото влијание врз метаболизмот на гликоза и липиди. Дополнително се разгледани и физикохемиските карактеристики што ја определуваат биорасположливоста на CBD, како и начинот на администрација кој го обликува неговиот

фармакокинетички и фармакодинамички профил. Опфатени се и потенцијалните интеракции со други биолошки активни молекули и лекови, со што се истакнува значењето на понатамошна систематска биохемиска и фармаколошка евалуација. Сумирано, достапната литература укажува дека CBD претставува ветувачка молекула за понатамошни истражувања насочени кон подобро разбирање на неговата регулаторна улога во метаболните процеси, но како и потенцијал за развој на нови терапевтски стратегии.

Клучни зборови: CB1 и CB2 рецептори; дијабетес мелитус; метаболен синдром; инсулинска резистенција; метаболизам на гликоза; кардиоваскуларни ризици; воспаление; оксидативен стрес; метаболизам на липиди

1. INTRODUCTION TO THE CANNABIDIOL (CBD) AND THE SIGNIFICANCE OF CANNABIS

The emerging use of CBD, one of the most notable cannabis compounds, in everyday life has expanded significantly in recent years, largely due to a trend for increased consumption, potential health benefits, and non-intoxicating properties. In January 2019, the World Health Organization (WHO) officially recommended that cannabis and cannabis-related substances, including CBD, be reclassified under international treaties. Specifically, it suggested the removal of pure CBD products containing less than 0.2% Δ^9-tetrahydrocannabinol (Δ^9-THC) from the list of controlled substances. CBD is currently used in Europe for medical purposes through licensed therapeutic indications, additional specific indications, and as an investigational new drug or for supplementation.[1] It was first isolated from cannabis by Adams *et al.*[2] in the United Kingdom and from hashish by Jacob and Todd[3] in the United States in 1940. CBD has the potential to be a safe treatment for a variety of disorders. In contrast to Δ^9-THC, it does not induce severe adverse effects or toxicity in humans when administered in a broad spectrum of doses via diverse routes.[4] Research suggests that CBD may have a positive impact on insulin sensitivity, glucose metabolism, and inflammation, all of which play key roles in the development and progression of diabetes mellitus (DM).[4] There are data that CBD treatment decreases the levels of pro-inflammatory markers in mouse models of DM, leading to improved glucose metabolism and insulin sensitivity.[5] Extensive research has been conducted to further understand the effects of cannabis on pain management, Parkinson's disease, spasticity resulting from multiple sclerosis or paraplegia, epilepsy, ophthalmological diseases, and various mental disorders.[4] In recent years, there has been increasing attention on the potential therapeutic benefits of CBD in addressing conditions such as cancer, cardiovascular disease, metabolic disease, and neurodegenerative disease.[4]

Cannabis (*Cannabis sativa* L., Cannabaceae) has been a subject of scientific interest for more than 50 years due to its pharmacological properties and potential therapeutic benefits.[6] From a chemical perspective, cannabis comprises approximately 565 distinct compounds belonging to 23 classes, categorized into cannabinoids and non-cannabinoids.[7] The most recognized class of compounds in cannabis are the eponymous cannabinoids, which are unique components of the plant.[8] Over 120 unique cannabinoids have been identified in *C. sativa*, with several demonstrating pharmacological activity, classified into 11 subclasses.[8] The primary compounds derived from *Cannabis sativa* include Δ^9-THC, Δ^9-tetrahydrocannabivarin (Δ^9-THCV), cannabinol (CBN), CBD, cannabidivarin (CBDV), cannabigerol (CBG), and cannabichromene (CBC).[4] The most abundant phytocannabinoids found in the cannabis plant are Δ^9-THC and CBD (Fig. 1). Δ^9-THC is well-known for its psychoactive properties,[7,9] but CBD does not have this effect.[4] Furthermore, factors such as genotype, soil quality, pollution, pesticide application, light exposure, temperature, and insect interactions can influence the composition of compounds in cannabis, thereby impacting its pharmacological properties.[7]

In general, cannabinoids isolated from the cannabis plant are distinguished as phytocannabinoids, natural cannabinoids, or external cannabinoids, whereas those synthesized chemically are termed synthetic cannabinoids.[10] Phytocannabinoids interact with the endocannabinoid system (ECS) by binding to cannabinoid receptors in the body, influencing various physiological processes. The ECS plays a crucial role in maintaining homeostasis by regulating metabolism, neurological functions, immune responses, cardiovascular health, and reproductive processes. Exogenous cannabinoids can mimic the effects of endocannabinoids produced naturally in the body.[11,12] While chronic cannabis consumption induces ECS hyperactivity in both the central and peripheral regions, there is evidence suggesting that long-term usage of

cannabis reduces obesity and other metabolic processes, indicating that it may have a role in controlling hunger.[13]

From chemical and biochemical perspectives, the study of CBD naturally begins with understanding its molecular structure and the features that determine its physicochemical and biological properties. CBD's structural features – a resorcinol moiety, a lipophilic pentyl side chain, and its terpenophenolic backbone – govern its physicochemical properties, stability, and interactions with biological targets, including endocannabinoid receptors and related metabolic enzymes. The structure of CBD consists of a cyclohexene ring, a β-resorcylic acid (aromatic ring), and an *n*-pentyl side chain, whereas CBDA also contains a carboxyl group (Fig. 1).

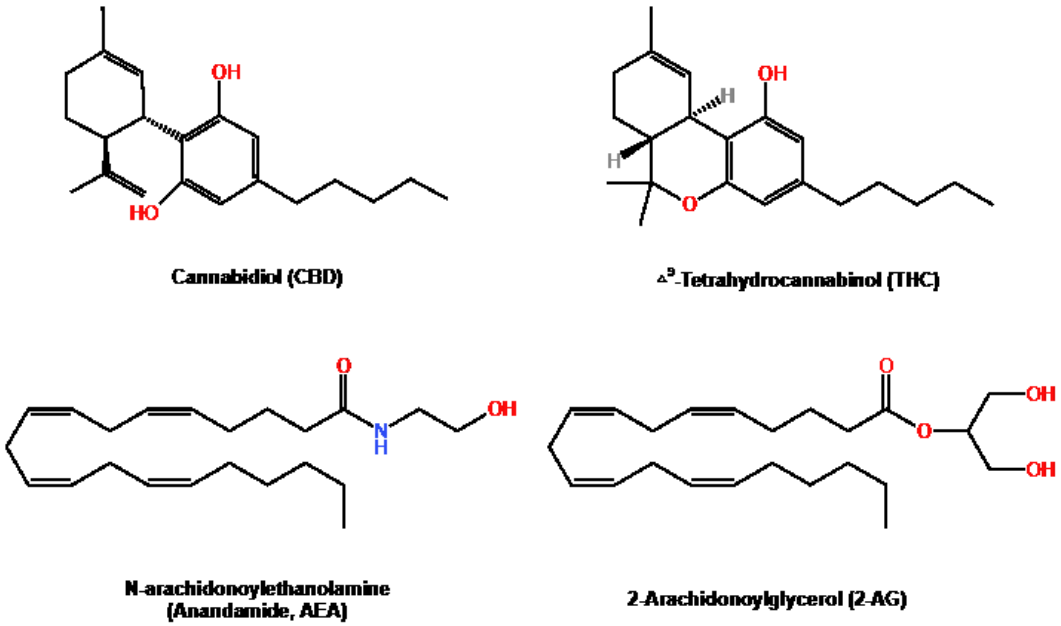

Fig. 1. Structural formulas of CBD, Δ⁹-THC, AEA, and 2-AG

The chemical characterization of CBD and its metabolites, particularly through chromatographic and spectroscopic techniques, provides insights into its bioavailability, degradation pathways, and potential interactions with lipids and proteins in metabolic regulation.[14] In addition, the growing complexity of cannabis-based products and shifting legal frameworks have increased the need for accurate, reproducible, and matrix-tailored analytical techniques that ensure product quality, potency, and regulatory compliance. CBD is present in a variety of matrices –including plant material, oils, pharmaceuticals, and edible products – and influences the selection of extraction, purification, and quantification strategies. Matrix interferences from lipids, pigments, terpenes, and polysaccharides can significantly compromise analytical precision. Therefore, careful optimization of sample preparation remains essential to achieve high recovery rates and to minimize bias.[15] Conventional methods such as solid–liquid extraction (SLE), liquid–liquid extraction (LLE), pressurized liquid extraction (PLE), solid-phase extraction (SPE), ultrasonic extraction (USE), focused ultrasonic extraction (FUSE), and microwave-assisted hydrodistillation (MAHD) have gradually been complemented or replaced by greener alternatives. Recent innovations emphasize the principles of green analytical chemistry, favoring solvent-free or low-solvent approaches like headspace solid-phase microextraction (HS-SPME) and supercritical fluid extraction (SFE), which improve efficiency, automation, reproducibility, and analytical throughput.[16,17]

Chromatographic techniques continue to form the foundation of CBD quantification. Thin-layer chromatography (TLC) and high-performance thin-layer chromatography (HPTLC) remain useful as rapid screening tools and are listed in pharmacopoeial monographs for cannabinoid identification. More sophisticated methods, including high-performance liquid chromatography with diode-array detection (HPLC-DAD), gas chromatography (GC), and liquid chromatography coupled to mass spectrometry (LC–MS or LC–MS/MS), are most common in current analytical workflows. GC is widely applied in forensic toxicology, pharmacokinetics, and phytochemical

analyses and is officially validated for determining terpenes, pesticides, and residual solvents – critical parameters for both industrial and regulatory assessments. HPLC, ultra-high-performance liquid chromatography (UHPLC), and supercritical fluid chromatography (SFC), have the ability to maintain chemical integrity makes LC-based techniques indispensable for accurate potency testing and pharmacological correlation studies.[18]

In addition to chromatographic techniques, nuclear magnetic resonance (NMR) spectroscopy and vibrational spectroscopies – including near-infrared (NIR), Fourier-transform infrared (FTIR), and Raman spectroscopy – have gained prominence as complementary analytical tools. Although they are less sensitive than chromatographic methods, these spectroscopic techniques provide fast, non-destructive, and environmentally friendly options for qualitative and quantitative analyses.[15,19] In this context, our group has already contributed to the advancement of analytical techniques for phytocannabinoid profiling of cannabis and cannabis-derived products, emphasizing chromatographic and spectroscopic approaches.[18,20] NIR and FTIR spectroscopy, in particular, have shown strong potential in process analytical technology (PAT), allowing *in situ* monitoring of decarboxylation, cannabinoid degradation, and overall process consistency. Furthermore, we have demonstrated the application of mid-infrared spectroscopy for *in situ* monitoring of phytocannabinoid decarboxylation (for both tetrahydrocannabinolic acid [THCA][21] and CBDA[22]), enabling real-time quantification and kinetic modeling. These studies have established spectroscopic markers for tracking the transformation of cannabinoid acids into their pharmacologically active neutral forms, an essential step in optimizing product quality and therapeutic efficacy.

2. THE ECS

The presence of the ECS in humans was first revealed in the 1990s,[3] and since there has been increased interest from the scientific community.[7] The ECS consists of three major constituents: endocannabinoids, cannabinoid receptors, and enzymes[23] responsible for synthesis and degradation, signaling pathways, and associated transport mechanisms.[7,24] Endocannabinoids, which are also known as endogenous ligands, belong to a large group of compounds with a similar structure and biological activity. They are chemical derivatives of dibenzopyrene or monoterpenoid compounds, possessing specific structural and functional characteristics.[25] The most studied endogenous endocannabinoids include arachidonoylethanolamide (AEA), also known as anandamide, and 2-arachidonoylglycerol (2-AG) (Fig 1).[6,23] AEA and 2-AG are derived from cell membrane phospholipids and are responsible for maintaining signaling with cannabinoid receptors.[23]

The interaction among the different components of the ECS, including endogenous ligands, receptors, and metabolic enzymes such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), regulates the typical level of ECS activity, known as the ECS tone, and has significant effects in diverse pathophysiological mechanisms.[4] Overexpression or downregulation of the ECS components affects several physiological functions and contributes to various diseases. Therefore, Meccariello *et al.*[7] proposed that manipulation of the ECS using drugs could be important in treating various disorders. The ECS is an intricate signaling system that governs multiple physiological and metabolic pathways. It is widely distributed throughout the organism, occurring at several levels including tissue, cellular, and sub-cellular levels,[7] and so has an important role in in the central nervous system as well as peripheral tissues.[26] It regulates and controls processes occurring at every stage of life, including prenatal development, puberty, adolescence, adulthood, and old age.[7]

Endocannabinoids are produced "on demand": AEA predominantly via hydrolysis of *N*-arachidonoyl phosphatidylethanolamine by phospholipase D and 2-AG from diacylglycerol-by-diacylglycerol lipase (DGL). Once synthesized, AEA or 2-AG are immediately released to target their receptors and then rapidly degraded by FAAH or MAGL, respectively.[23,27]

Enzymes that regulate the production and degradation of endocannabinoids, along with the cannabinoid 1 (CB_1) receptor and the cannabinoid 2 (CB_2) receptor through which they signal, play a crucial role in various biochemical processes.[23,25,28] These receptors, widely distributed both centrally and peripherally throughout the body,[4,7] have gained attention as pharmacotherapy targets due to their ability to mediate the effects of both phytocannabinoids and endocannabinoids.[23] Activation of CB_1 and CB_2 receptors, which are inhibitory G-protein coupled receptors (GPCRs), triggers a range of responses, including inhibition of voltage-gated Ca^{2+} channels and adenylate cyclase activity, leading to reduced cyclic adenosine monophosphate (cAMP) levels. This, in turn, stimulates multiple signaling pathways such as mitogen-activated protein kinases

(MAPK), phosphoinositide kinase 3 (PI3K), and cyclooxygenase (COX) 2 pathways, some of which operate through G protein-independent mechanisms.[27,29]

CB_1 receptors are notably more abundant than CB_2 receptors in both central and peripheral locations within the body. Both receptors exhibit polymorphic variants,[30,31] which account for the wide range of possible functions associated with their activation.[7] CB_1 is the predominant GPCR in the brain,[7] with notably elevated levels observed in (rank order): the substantia nigra, globus pallidus, hippocampus, cerebral cortex, putamen, caudate, cerebellum, and amygdala. Furthermore, CB_1 receptors are also present in peripheral sensory neurons, the immune system, the gastrointestinal tract, adipose tissue, the liver, the pancreas, reproductive organs, skeletal muscle, and cardiovascular tissues.[4] These receptors are localized at the subcellular level within the mitochondria in the brain and striated muscle.[7]

CB_2 receptors are predominantly localized in the periphery, specifically on immune cells.[32] They are also expressed in all hematopoietic cells, including neutrophils, monocytes, B-lymphocytes, natural killer cells,[33] macrophages[34] and pancreatic cells.[35] Even though CB_2 receptors were initially found in immune cells, later it was also found in the brain to a lesser degree. Based on preclinical research, activation of these receptors has been implicated in the management of numerous disease conditions, including pain,[36,37] inflammation,[37] atherosclerosis,[38,39] DM,[23] cancer,[40] and cardiovascular diseases.[39,41] CB_2 receptors can be greatly activated by cannabis and their expression can increase by 100 times in response to tissue injury and inflammatory processes.[42,43]

Although both cannabinoid receptors exhibit similar functions, there are distinct variations between them. They are metabotropic receptors associated with Gi/o proteins. Adenylyl cyclase is inhibited and MAPK is activated when CB_1 and CB_2 receptors are stimulated. Calcium and potassium channels are also modulated (but only for CB_1 receptors).[44] Even though CBD has low affinity for the cannabinoid receptors (i.e., micromolar concentrations),[45] it modulates the activity of these receptors and regulates insulin levels, reduces inflammation, and improves overall metabolic function.

The extensive distribution and diverse functions of cannabinoid receptors, both in the nervous system and metabolism, have led researchers to suggest the use of cannabinoids as homeostatic modulators for enhancing health and treating diseases. As recently suggested, this may be achieved through epigenetic modulation of the ECS.[12] Nevertheless, the available evidence from experiments and clinical studies is still inadequate, and additional research is necessary.[7]

Besides their interaction with CB_1 and CB_2 receptors, endocannabinoids, phytocannabinoids, and synthetic cannabinoids are very flexible molecules. They can also activate other GPCRs (e.g., GPR18, GPR19, and GPR55), transient receptor potential vanilloid-1 (TRPV1), subunit alpha 1 of the glycine receptor (GlyR), peroxisome proliferator-activated receptors (PPAR), and subunit beta 2 of the gamma-aminobutyric acid A (GABA-A) receptor.[42] GPR55 and TRPV1 play a role in regulating bone density and blood pressure, and promoting cancer growth.[7] They are also involved in detecting pain, heat, osmoregulation, neurotransmission, neuronal stabilization, and other sensory functions. PPAR is linked to the regulation of energy balance, inflammation, and insulin sensitivity.[42,46]

3. THE ECS AND DM

DM has emerged as a significant global health issue due to its widespread prevalence. Its associated complications are partly attributed to the prevailing global lifestyle characterized by physical inactivity, consumption of high-fat diets, obesity, and prolonged life spans. As of 2021, approximately 537 million adults (20–79 years) worldwide are living with DM, accounting for about 10.5% of the global adult population. This number is projected to rise to 643 million by 2030 and 783 million by 2045.[47] The WHO estimated that over 1.6 million individuals died of diabetic complications in 2021.[48] Furthermore, it is projected that the mortality rate will increase by 50% by the year 2030.[49]

DM is a multifaceted disorder of human metabolism primarily characterized by an inability to tolerate glucose and/or insulin resistance, abnormal levels of lipids in the blood, high blood pressure, and/or obesity.[49] People with DM have an inherent increased vulnerability to both microvascular and macrovascular diseases.[50] The disease is named after a Greek term that means “going through” and a Latin word that means “honey” or “sweet,”[51] likely due to the production of a large amount of urine with a honey-like taste.[52] It results in chronic hyperglycemia and disturbances in the metabolism of carbohydrates, proteins, and fats. These disruptions typi-

cally arise from an imbalance between the availability of insulin and the body's insulin requirements.[49,52]

The concept of so-called syndrome X or insulin-resistance syndrome[50] encompasses a range of interconnected metabolic abnormalities, including obesity and various cardiovascular risk factors.[26] In the absence of adequate interventions, this syndrome contributes to the development of chronic diseases like atherosclerosis, hypertension, and insulin-resistant-type 2 diabetes mellitus (T2DM),[26] as well as related cardiovascular complications such as coronary heart disease or stroke and non-vascular pathologies such as cancer, infections, liver diseases and mental and nervous systems disorders.[50] Cardiovascular diseases are the primary cause of mortality in patients with T2DM. The ECS is associated with metabolic processes parameters through cannabinoids that impact obesity, glucose metabolism, plasma lipids, blood pressure and non-alcoholic fatty liver disease. The role of the ECS in the development of metabolic syndrome is associated mainly with obesity and T2DM.[53] These pathophysiological mechanisms have a similar effect on the body as overstimulation of the ECS.[7] The ECS affects many pathways in the hypothalamus, leading to an increase in food intake and a decreased feeling of fullness.[53] Similarly, the pathophysiological mechanisms in metabolic syndrome modify various metabolic pathways, leading to insulin resistance, dyslipidemia, and an increase in body weight and visceral fat.[7] This ultimately results in the development of obesity, T2DM, and other abnormalities associated with metabolic disorders.

At the peripheral level, the ECS also affects the endocrine system, which is responsible for metabolism, by playing a role in suppressing insulin release and the uptake and breakdown of glucose in muscle and adipose tissue. This system also increases the concentration of the hunger hormone ghrelin in the bloodstream, stimulates the production of fat (lipogenesis) and the release of free fatty acids (FFAs) from the liver, promotes the formation of fat in adipose tissue, and reduces the levels of adiponectin.[13] Sensations of appetite and satiety result from coordinated communication between sensory neurons in the hypothalamus, among other regions, and peripheral signals (leptin, insulin, and ghrelin). Ghrelin levels are elevated during periods of negative energy balance, such as fasting and anorexia nervosa, and decreased during positive energy balance, specifically in obesity. Therefore, ghrelin, leptin, and insulin are an essential part of a set of peripheral signals that provide the brain with information regarding the current state of energy storage and contribute to the regulation of weight over the long term.[54] Higher levels of hypothalamic endocannabinoids have been linked to impaired leptin signaling. Leptin is a crucial signaling molecule that plays a role in communication between fat tissue and the central parts of the body that control weight and eating regulation. It also contributes to the way cannabinoids operate. Stimulating the leptin receptors in the hypothalamus promotes the release of pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART). This leads to a suppression of feeding and inhibits the release of neuropeptide Y (NPY) and agouti-related protein (AGRP), which are usually responsible for promoting feeding to maintain energy balance.[55] In addition to increasing visceral fat accumulation and obesity, an activated ECS decreases energy consumption and stimulates the production of fat.[56] Regardless of weight gain in the liver, adipose tissue, and skeletal muscle, the ECS influences insulin sensitivity.[7]

Interestingly, hyperphagia (overeating) and obesity both enhance endocannabinoid signaling at peripheral CB_1 receptors. This creates a harmful cycle that might potentially worsen and exacerbate DM.[57] Activation of CB_1 receptors play a role in causing inflammation and the production of reactive oxygen species (ROS) in DM. This leads to tissue damage; an increase in lipogenesis, plasma triglycerides, and insulin; and leptin resistance. It also results in a decrease in adiponectin, fatty acid oxidation, high-density lipoprotein (HDL) cholesterol, glucose tolerance, and thermogenesis. Furthermore, it stimulates hunger and consumption of food, particularly sugary and palatable food, by activating many pathways related to the brain's "reward" system and also affecting organs such as the pancreas, liver, adipose tissue, skeletal muscle, and central nervous system.[58,59] The overall result is high blood sugar levels, excessive body weight, an elevated risk of heart disease, enhanced ROS production by mitochondria, and increased expression of angiotensin II receptor type 1. Activation of CB_1 receptors enhances the inflammatory response and induces cell death through MAPK signaling, affecting cardiomyocytes, endothelial cells, smooth muscle (resulting in increased cell death and increased proliferation/migration), and fibroblasts. This ultimately leads to a pro-fibrotic response and abnormalities in the endothelium and the cardiovascular system.[60]

Stimulating CB_1 receptors also leads to systemic inflammation by activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which increases the expression of tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) as well as the presence of inflammatory cells such as polymorphonuclear cells, lymphocytes, monocytes, and macrophages. This stimulation also leads to an increase in the generation of ROS, resulting in the production of more endocannabinoids. This process causes tissue damage and contributes to the development of diabetic complications such as retinopathy, cardiomyopathy, neuropathy, and nephropathy.[24] Activation of CB_1 receptors plays a role in promoting cell proliferation and the development of adipocytes. It also influences the release of adipokines and the process of lipogenesis.[61] On the other hand, reducing CB_1 receptor signaling has positive effects on insulin sensitivity, metabolic diseases, and atherosclerosis. This reduction also provides cytoprotection by decreasing ROS levels.[7,62,63]

CB_1 receptor antagonists, such as rimonabant, have been investigated for their potential therapeutic effects in metabolic disorders, including DM. By blocking CB_1 receptor activation, these antagonists reduce food intake, enhance glucose uptake, and improve insulin sensitivity in peripheral tissues. Despite their beneficial metabolic effects, centrally acting CB_1 antagonists like rimonabant were withdrawn due to psychiatric side effects, prompting the development of peripherally restricted CB_1 inhibitors with fewer adverse effects.[27,64] In contrast, activation of CB_2 receptors exerts anti-inflammatory and β-cell-protective effects, which may be beneficial in DM treatment. CB_2 receptor agonists modulate immune responses, reduce inflammation, and protect pancreatic β-cells from apoptosis, thereby preserving insulin secretion and mitigating disease progression.[65,66] Additionally, non-selective CB receptor agonists, such as THC, have been reported to influence glucose metabolism, although their clinical relevance remains debated due to psychoactive effects and the potential for metabolic dysregulation.[67] Further research is necessary to develop selective CB receptor modulators that maximize therapeutic benefits while minimizing undesirable side effects.

4. CBD AND DM MANAGEMENT

Given its complexity, DM must be managed carefully to prevent serious complications. Metabolic abnormalities associated with DM can be difficult to treat and might require a mix of lifestyle modifications, medications, and further interventions. There has been a marked increase in research regarding the medicinal applications of *C. sativa* in recent years. An increasing body of evidence indicates the potential benefits of phytocannabinoids due to their anti-inflammatory, antioxidant and neuroprotective properties that could benefit individuals with DM. As an exogenous phytocannabinoid, CBD does not appear to induce respiratory depression and exerts minimal impact on vital signs (e.g., heart rate and blood pressure). CBD exhibits minimal toxicity, lacks psychotomimetic properties, poses a very low risk of abuse, and is well tolerated by adults.[68,69]

CBD has been studied for its potential effects on insulin sensitivity, particularly in the context of DM and related metabolic disorders. Studies suggest that CBD improves insulin sensitivity and reduces inflammation through various mechanisms, including the enhancement of anti-inflammatory effects, a direct effect on insulin secretion, modulation of the ECS by inhibiting specific receptors, a reduction of oxidative stress, neuroprotective effect, improvement in adipose tissue function, and modulation of metabolic pathways.

CBD exerts its effects on glucose and lipid metabolism through a network of cannabinoid and non-cannabinoid signaling pathways. Unlike THC, CBD has a low binding affinity for CB_1 and CB_2 receptors; however, it modulates the ECS indirectly.[70] Within the ECS, CBD functions as a negative allosteric modulator of CB_1 receptors and a partial antagonist or inverse agonist of CB_2 receptors,[71,72] thereby attenuating receptor overactivation associated with obesity, insulin resistance, and dyslipidemia.[27] CBD activates TRPV1 channels, which facilitate intracellular Ca^{2+} influx, supporting β-cell insulin secretion and contributing to glucose homeostasis.[73]

Beyond the ECS, CBD inhibits equilibrative nucleoside transporter (ENT), which increases the extracellular adenosine concentration and thus A2A receptor activation, and triggers anti-inflammatory signaling cascades that suppress the NF-κB pathway and downregulate pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.[72] Moreover, CBD inhibits FAAH,[27] leading to elevated levels of AEA. This

molecule binds to and activates the CB_1 and CB_2 receptors, which concurrently modulate intracellular signaling via the PI3K–Raf–mitogen-activated protein kinase (MEK)–extracellular signal-regulated protein kinase (ERK)–cyclic AMP binding protein (CREB) axis. CREB is phosphorylated and promotes the transcription of CRE-regulated genes, and PPARγ is activated. These molecular events enhance lipid and glucose metabolism, characterized by decreased levels of low-density lipoprotein (LDL) cholesterol and triglycerides, increased HDL cholesterol, and improved insulin sensitivity in peripheral tissues.[74]

Additionally, CBD exerts antioxidant effects by reducing mitochondrial ROS generation, thereby preserving cellular redox balance and preventing oxidative stress-induced β-cell dysfunction. The combined influence of these mechanisms –anti-inflammatory, antioxidant, and insulin sensitizing – establishes a comprehensive framework through which CBD contributes to metabolic stabilization, improved glycemic control, and attenuation of DM-related complications (Fig. 2).[75]

Table 1 summarizes the current evidence supporting the role of the ECS and cannabinoids in carbohydrate and lipid metabolism. Given the potential anti-inflammatory and metabolic-regulating properties of CBD, it is plausible that CBD could have a positive impact on individuals with DM[4] and its associated metabolic complications.

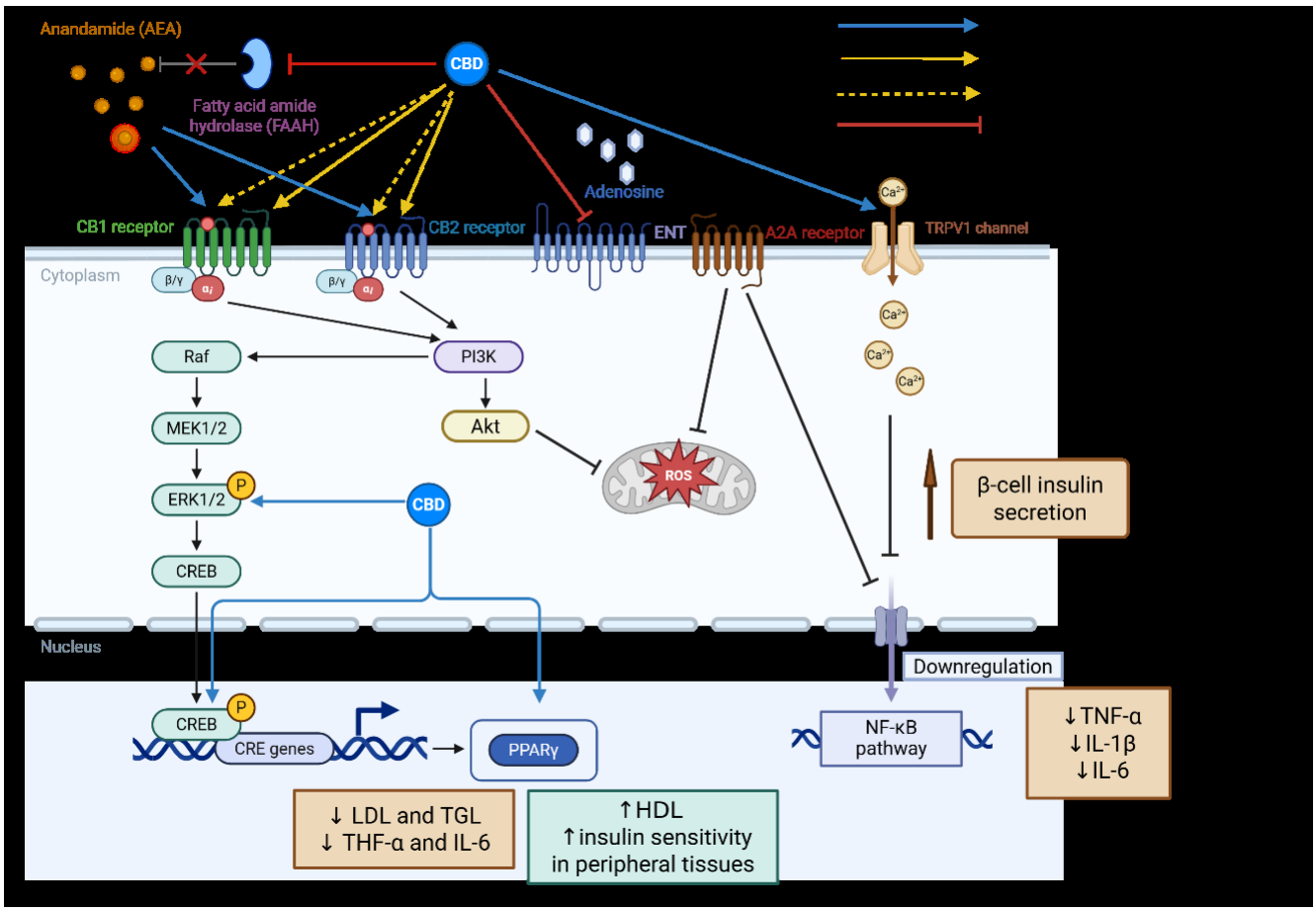

Fig. 2 Proposed mechanistic model of CBD-mediated regulation of metabolic, inflammatory, and insulin-signaling pathways. CBD interacts with ECS and non-ECS targets, enhancing insulin secretion by β-cells; reducing inflammatory cytokine expression; and improving lipid and glucose metabolism through TRPV1, A2A, and PPARγ activation, as well as FAAH inhibition and CB_1/CB_2 modulation.

Table 1

The current evidence supporting the role of the ECS and cannabinoids in carbohydrate and lipid metabolism

Reference	Receptor agonists/ antagonists	Studied mechanism and statistically significant changes	Characteristics of the examined group and study design	Treatment or drug used for research
Després *et al.*[76]	Selective CB_1 receptor antagonist rimonabant	Rimonabant decreases insulin levels and improves glucose tolerance in patients with obesity Obesity and IR	1036 patients with overweight or obesity with untreated dyslipidemia Randomized, placebo-controlled study	Rimonabant
Kim *et al.*[77]	CB_1 receptor agonists AEA and 2-AG and CB receptor antagonists AM251 and AM630	Inhibition of CB_1 receptors enhances pancreatic ß-cell signaling and proliferation in isolated islets, and also improves glucose tolerance and insulin sensitivity (in db/db mice) IR	Isolated human and mouse islets	CB_1 receptor antagonists, glucose, and KCl
Liu *et al.*[78]	CB_1 receptor agonist anandamide	A HFD induces hepatic IR in wild-type but not in CB_1-KO mice; CB_1 receptor activation contributes to diet-induced IR via hepatic CB_1 receptor–mediated inhibition of insulin signaling Obesity-related IR	Wild-type mice, CB_1-KO mice, or mice with hepatocyte-specific deletion or transgenic overexpression of CB_1 receptors	CB_1 receptor antagonists and HFD
Shin *et al.*[79]	CB receptor agonists 2-AG, ACEA, and WIN55212; CB receptor antagonist AM251	CB_1 agonists diminishes insulin secretion in a β-cell line and islets, whereas silencing CB_1 receptors in β-cells increases expression of proinsulin, glucokinase and GLUT2, which is also observed in CB_1-KO mice IR and T2DM	Mouse β-cell lines; human islets; CB_1-KO mice (used to observe changes in β-cell function without CB_1 receptor signaling) Experimental study, involving both *in vitro* and *in vivo* models	CB_1 receptor agonists
Motaghedi and McGraw[80]	CB receptor agonist 2-AG; CB_1 receptor antagonist rimonabant	2-AG improves insulin sensitivity by increasing insulin-stimulated AKT phosphorylation in adipocytes, which is attenuated by rimonabant IR	Cultured adipocytes (fat cells) Experimental, *in vitro* study using cultured adipocytes	2-AG and rimonabant
Hirsch and Tam[81]	CB_1 receptor antagonists	Decrease in food intake, body weight, obesity, T2DM, fatty liver, and IR; increase in glucose homeostasis Obesity, metabolic processes, and T2DM	Various animal models Preclinical studies in animal models	Peripheral CB_1 receptor antagonists
Di Marzo[82]	CB_1, CB_2 receptor and TRPV1 agonists AEA and 2-AG; CB receptor antagonists rimonabant and taranabant	CB_1 receptor antagonists decrease hyperglycemia and dyslipidemia, and increase insulin resistance and glucose tolerance T2DM	Humans with obesity and animal models of T2DM Clinical trials (for human studies) and preclinical studies (for animal models)	CB_1 receptor antagonists/inverse agonists
Nagappan *et al.*[83]	CB_1 receptor agonists; overexpression of CB_1 receptor antagonists	CB_1 receptor activation modulates insulin signaling pathway and leads to insulin resistance Obesity, IR, and T2DM	Obese mice and humans Preclinical studies and clinical trials	Several types of drugs and treatments related to CB_1 receptor antagonism

Reference	Receptor agonists/ antagonists	Studied mechanism and statistically significant changes	Characteristics of the examined group and study design	Treatment or drug used for research
Zanoni *et al.*[84]		Inhibition of HMG-CoAR activity Increase in LDLR and PCSK9 expression	Human hepatic HepG2 cells *In vitro* study	Ninety different peptides derived from *Cannabis sativa* hydrolysis
Afshar *et al.*[85]		Decrease in total cholesterol and LDL cholesterol	Individuals with T2DM (mean age 55.7 years)	Sublingual spray CBDEX10® twice daily (200 μg/20 μg CBD/Δ^9-THC)
Abuhasira *et al.*[86]		Positive correlation between 2-AG and triglyceride change and negative correlation between OEA and PEA and the HDL/LDL ratio	Individuals with hypertension and Parkinson's disease (mean age 69 years)	Herbal cannabis supplements with different CBD:Δ^9-THC ratios and different dosing patterns
Cusihuaman *et al.*[87]		Increase in HDL at 120 min	Healthy daily smokers of cannabis for at least 12 months (mean age 31 years)	0.2 g of *Cannabis* spp. administration via the pyrolytic route
Li *et al.*[88]		Inhibition of HMG-CoAR activity, increase in LDLR expression, and decrease in PCSK9	Human hepatic HepG2 cells *In vitro* study	*Cannabis sativa* peptide H3 (IGFLIIWV)
Huang *et al.*[89]		Decrease in TG and LDL at week 6	ApoE-KO mice (model of atherosclerosis) fed a high-cholesterol diet	30 μL of cannabis seed oil per day (7.4% palmitic acid, 3.0% stearic acid, 10.8% oleic acid, 55.8% linoleic acid, 14.0% α-linolenic acid, and 2.5% γ-linolenic acid)
Abbotts *et al.*[90]		Decrees in postprandial triglycerides at 30 min	Mean age of 26 years and mean BMI 29.7 kg/m^2	Five different formulations, each containing 30 mg of CBD; seven doses (two followed by a meal, five unrelated to a meal)
Alonso *et al.*[91]		Positive correlation between cannabis use and HDL cholesterol	Patients with schizophrenia	Declared daily cannabis use
Reyes-Cuapio *et al.*[92]		Decrease in triglycerides	Juvenile Wistar rats at 30 postanal day	Intraperitoneal CBD injections (5, 10, or 30 mg/kg)
Kaushal *et al.*[93]		Decrease in triglycerides, LDL cholesterol, and total cholesterol; increase in HDL cholesterol	Wistar rats fed an HFD(model of induced hypercholesterolemia)	Special composition of a hemp seed diet for 1 or 2 months
Ben-Cnaan *et al.*[94]		Decrease in triglycerides and total cholesterol; increase in the HDL/LDL ratio	Mouse models of obesity induced by diet and genetics	Intraperitoneal administration of CBDA-*O*-methyl ester (HU-580 and EPM301) at 40 mg/kg/day
Stiles *et al.*[95]		Decrease in triglycerides	Mean age of 23.4 years old; first episode of psychosis	Analysis of data obtained from the RAISE-ETP study*
Farokhnia *et al.*[13]	CB_1 and CB_2 receptor agonist	Investigate the effects of cannabis administered by different routes on appetitive and metabolic hormones	20 participants Randomized, crossover, double-blind, placebo-controlled study	Oral cannabis, smoked cannabis, vaporized cannabis, or placebo

Reference	Receptor agonists/ antagonists	Studied mechanism and statistically significant changes	Characteristics of the examined group and study design	Treatment or drug used for research
		Cannabis use modulates blood concentrations of some appetitive and metabolic hormones, chiefly insulin		
Ngueta and Ndjaboue[96]	CB_1 and CB_2 receptor agonist	Examine the association between cannabis use and insulin resistance Cannabis use reduces fasting insulin and HOMA-IR in adults with obesity but not in adults without obesity, independently of the time of use	Prospective analysis (population survey)	Cannabis
Ngueta[97]	CB_1 receptor agonist	Explore the association between cannabis use with mean plasma fasting insulin levels and HOMA-IR Cannabis use reduces fasting insulin levels and HOMA-IR score in U.S. adults with obesity and HOMA-IR ≥ 2.13, but not in those with HOMA-IR < 2.13 or ≥ 5.72; more significant impact of cannabis use after long-term exposure and is independent of BMI	Prospective analysis (population survey)	Cannabis
Okafor *et al.*[98]	CB_1 receptor agonist	Determine whether the self-reported frequency of cannabis use is associated with incident T2DM Reduced risk of T2DM in cannabis users compared with non-users, although all no significant associations; similar results for HIV-positive and HIV-negative participants	Prospective analysis (population survey)	Cannabis
Ross *et al.*[99]		Examine the associations between cannabis use and BMI Negative association between cannabis use and BMI	Prospective analysis from a longitudinal study	Cannabis
Roberts *et al.*[100]		Analyze appetite- and eating-related aspects of cannabis self-administration Cannabis influences both the motivational factors that lead to the initiation of eating and the hedonic factors implicated in encouraging and maintaining eating	Survey-based, observational study	Cannabis
Alshaarawy *et al.*[101]		Examine cannabis-attributable immunomodulation Cannabis use was not associated with any of the studied biomarkers; former Cannabis use is inversely associated with fibrinogen levels, whereas the associations are	Prospective analysis (population survey)	Cannabis

Reference	Receptor agonists/ antagonists	Studied mechanism and statistically significant changes	Characteristics of the examined group and study design	Treatment or drug used for research
		weaker for serum CRP and IL-6		
Kalla *et al.*[102]		Examine the prevalence of cardiovascular risk factors and events among patients who use cannabis; cannabis use increases the prevalence of most risk factors, including hypertension, obesity, tobacco use, and alcohol use; DM observed more frequently in those who do not use cannabis Similar hyperlipidemia between the groups	Patients aged 18–55 years with cannabis use identified in the National Inpatient Sample 2009-2010 Prospective analysis (population survey)	Cannabis
Auer *et al.*[103]	CB_1 and CB_2 receptor agonist	Determine the association between lifetime exposure to cannabis and subclinical atherosclerosis in mid-life Cumulative marijuana use is not associated with measures of atherosclerosis among middle-aged adults never exposed to tobacco; a trend for an increased risk of atherosclerosis with very high exposure to cannabis	A total of 3498 participants in the CARDIA study: a cohort of black and white men and women aged 18–30 years at baseline in 1985–1986, with up to seven follow-up examinations over 25 years Prospective analysis (population survey)	Cannabis
Chia *et al.*[104]	Insulinotropic polypeptide (GIP) and GLP-1	Nabilone stimulation of the ECS regulates incretin secretion; obesity and incretin secretion Highly significant increase in post-dose fasting GIP levels as a consequence of increased endocannabinoid levels by nabilone; post-dose fasting increase in insulin	20 lean and 20 participants with obesity from the Baltimore Longitudinal Study of Aging Randomized, double-blind, crossover study	Nabilone

* Recovery After an Initial Schizophrenia Episode – Early Treatment Program

Abbreviations: Δ^9-THC, tetrahydrocannabinol; 2-AG, 2-arachidonoylglycerol; ACEA, arachidonyl-2-chloroethyl amide; AEA, anandamide; AKT, protein kinase B; ApoE, apolipoprotein E; BMI, body mass index; CB_1 and CB_2, cannabinoid receptors type 1 and 2; CBD, cannabidiol; CRP, C-reactive protein; DM, diabetes mellitus; ECS, endocannabinoid system; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GLUT2, glucose transporter 2; HDL, high-density lipoprotein; HFD, high-fat diet; HIV, human immunodeficiency virus; HMG-CoAR, 3-hydroxy-3-methyl-glutaryl-coenzyme-A reductase; HOMA-IR, homeostatic model assessment of insulin resistance; IL-6, interleukin 6; IR, insulin resistance; KCl, potassium chloride; KO, knockout; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; OEA, oleoylethanolamide; PCSK9, proprotein convertase subtilisin/kexin 9; PEA, palmitoylethanolamide; T2DM, type 2 diabetes mellitus; TRPV1-transient receptor potential vanilloid 1.

4.1. *CBD and metabolic regulation in DM management*

The WHO defines obesity as a body mass index (BMI) ≥ 30 kg/m². Over the last few decades, obesity has become a global concern, with over 650 million people classified as obese and nearly 2 billion considered over-weight.[105] The tendency of obesity to induce insulin resistance is the primary link between obesity and T2DM. Insulin resistance is characterized by impaired suppression of hepatic glucose output and decreased insulin-stimulated glucose transport and metabolism in skeletal muscle and adipocytes, evident in obesity and T2DM.[106] These functional defects result from impaired insulin signaling in key tissues such as the liver, muscle, and white adipose tissue (WAT).[106]

The ECS has emerged as a significant therapeutic target in glucose homeostasis. While the effects of plant-derived cannabinoids on appetite and

body weight have been recognized for centuries, the precise mechanisms have only recently been elucidated with the identification of the CB_1 and CB_2 receptors and their endogenous ligands, 2-AG and AEA.[106] CBD improves insulin sensitivity in both *in vitro* and *in vivo* models.[107] Chronic inflammation is associated with insulin resistance, and CBD's anti-inflammatory properties contribute to its ability to enhance insulin sensitivity.[4] Moreover, CBD improves glycemic control in animal models of DM, with CB_2 receptor blockade inhibiting this beneficial effect.[108]

Another mechanism by which CBD enhances insulin sensitivity is through the upregulation of adiponectin, which is associated with improvements in lipid metabolism and the inhibition of hepatosteatosis development.[107,109] Additionally, CBD has been shown to inhibit insulin signaling and clearance through hepatic CB_1 receptor–mediated mechanisms, which may contribute to its benefits in individuals with obesity.[78] Furthermore, CBD restores adipose tissue sensitivity to insulin by influencing sphingolipid metabolism under conditions of increased fatty acid availability.[110] A randomized, double-blind, placebo-controlled pilot study indicated that CBD decreases resistin levels and increases glucose-dependent insulinotropic peptide in patients with T2DM.[111] In type 1 diabetes mellitus (T1DM) models, CBD has demonstrated potential in reducing β-cell destruction, leading to improved glucose utilization and lower blood glucose levels.[112]

CBD may also offer therapeutic benefits for managing complications associated with DM. It has been reported to alleviate diabetic neuropathy pain and to improve the overall quality of life for individuals with DM.[113] Some studies suggest that CBD could serve as an adjunct therapy alongside traditional DM medications, enhancing their efficacy. Due to its anti-inflammatory properties, CBD can mitigate inflammation-related diabetic complications.[25,114] Additionally, by targeting insulin resistance and exerting cardiovascular protective effects, CBD may help reduce the risk of heart disease in individuals with DM.[44,115]

In terms of glucose metabolism, CBD has been identified as a potential therapeutic agent for glucose homeostasis disorders. Research suggests that CBD treatment improves metabolic dysfunctions in adult diabetic rats by reducing hyperglycemia and increasing insulinemia.[5,108] Additionally, CBD administration has been found to ameliorate DM manifestations in non-obese diabetic (NOD) mice, further supporting its potential in T1DM management.[116] Studies have also shown that CBD significantly increases insulin levels and reduces glycemia in diabetic rats at higher doses (30 mg/kg).[117] Investigations into metabolic processes highlight the influence of CBD on microbiome-related metabolic parameters, where rats fed and high-fat, high-cholesterol diet and receiving CBD exhibited lower fasting glucose levels and improved glucose tolerance compared to their untreated counterparts.[118]

Regarding lipid metabolism, CBD has demonstrated the ability to reduce total cholesterol, LDL cholesterol, and triglyceride levels in adult diabetic rats.[5] Additionally, CBD reduces lipid accumulation and inhibits hepatosteatosis.[107] Improvements in lipid parameters have been observed in mice on high-fat, high-cholesterol diets treated with CBD.[118] The capacity of CBD to lower fasting insulin levels and improve insulin sensitivity in obese rats, along with reducing cholesterol and triglyceride levels in diabetic mice, suggests its potential role in regulating both blood sugar and lipid profiles.

The effects of CBD on weight management and appetite regulation have also been studied extensively. By interacting with the ECS, CBD may help regulate appetite and metabolism and thus offer potential benefits for overall metabolic health.[119] Intraperitoneal injection of CBD influences sphingolipid metabolism in insulin-resistant animal models. The findings indicate that when the animals are fed a high-fat diet, CBD sensitizes adipose tissue to insulin by modulating sphingolipid metabolism, highlighting its potential as a therapeutic target for reducing insulin resistance in T2DM.[110] Moreover, a study on men with overweight and obesity revealed that CBD administration, in conjunction with a mixed macronutrient meal, does not alter glucose responses compared to placebo but does lower insulin concentrations.[90]

Overall, the research on the role of CBD in DM management and metabolic processes is promising. Studies have shown that CBD improves insulin sensitivity, reduces inflammation, and may lower the risk of cardiovascular complications associated with DM. Its influence on glucose metabolism, lipid profiles, and weight regulation suggests that CBD could be a valuable therapeutic agent in the management of metabolic disorders and DM-related complications (Fig. 3).

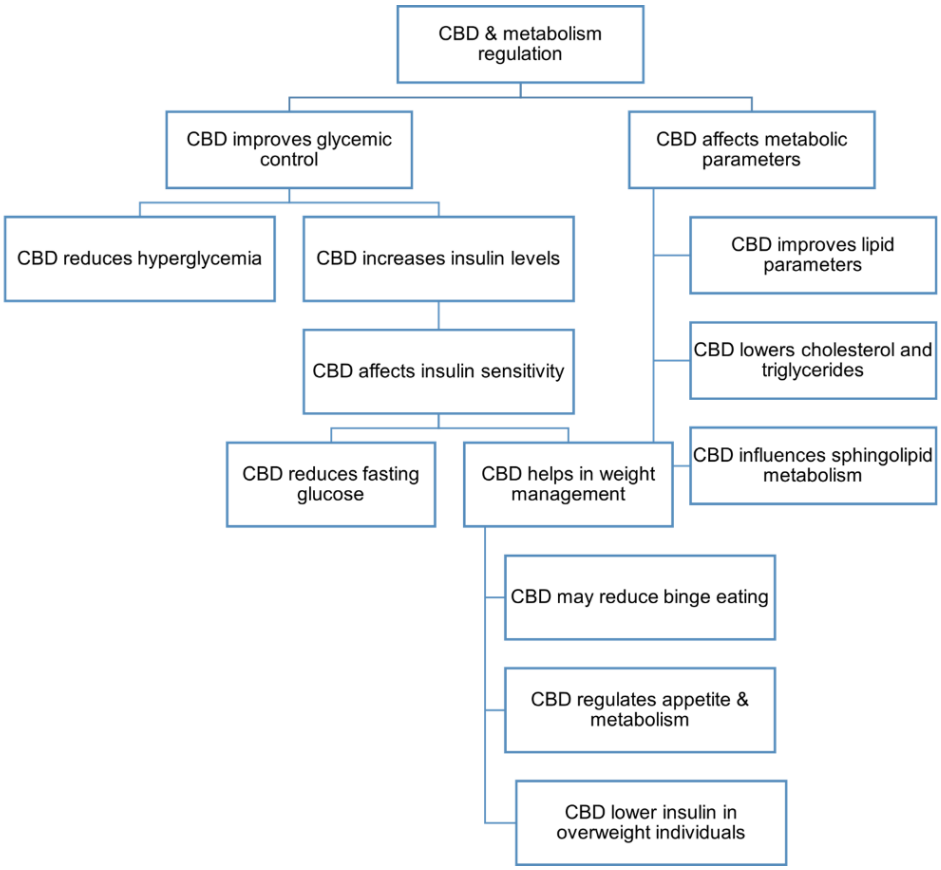

Fig. 3 The role of CBD in metabolic regulation: The effects on glycemic control, lipid metabolism, and weight management

4.2. *CBD and cardiovascular–kidney–metabolic (CKM) health*

Recent insights highlight the interconnected nature of cardiovascular, kidney, and metabolic health, collectively termed CKM syndrome. This paradigm shift, recognized by the American Heart Association, emphasizes the complex interplay between metabolic disorders, cardiovascular diseases, and kidney dysfunction.[120] Studies suggest that both endogenous and exogenous cannabinoids induce changes in the cardiovascular system of humans and animals.[121,122] CBD has potential beneficial properties in cardiovascular disorders by decreasing organ damage, dysfunction, oxidative stress, and inflammatory processes.[123] It has shown positive effects in experimental models of heart diseases.[123] These properties align with the emerging CKM syndrome framework, where systemic inflammation and metabolic dysregulation contribute to cardiovascular and renal pathologies. By targeting inflammatory markers (via its predominantly anti-inflammatory effect *in vivo*[124]) and insulin resistance, CBD could help improve overall cardiovascular health[123] and reduce the risk of heart disease[123] in individuals with metabolic syndrome.[125] CBD protects against vascular damage caused by high glucose, inflammation, or T2DM, and reduces vascular hyperpermeability.[126] CBD shows protection against cardiac injuries through its properties.[125] It has also been reported to reduce acute myocardial infarction size.[127] CBD reduces resting blood pressure and the blood pressure increases stress in humans, associated with increased heart rate.[128] CBD has a cardioprotective effect from ischemia, reducing infarct size by 66% and preserving the shortening fraction in ischemic rat hearts.[129] Taken together, the anti-inflammatory and antioxidant properties of CBD position it as a potential natural and holistic approach to improving heart health in individuals with metabolic syndrome. As more research is conducted, the role of CBD in preventing heart disease and managing risk factors may become clearer, providing a new avenue for treatment and prevention strategies (Fig. 3).

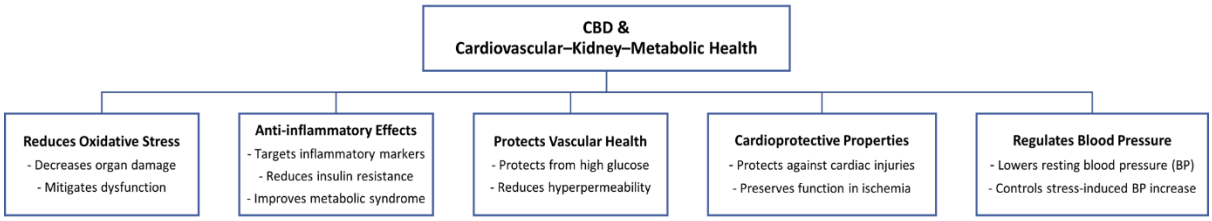

Fig. 4 The role of CBD in managing cardiovascular–kidney–metabolic health and associated risk factors

Given the close association between CKM syndrome and inflammation, CBD represents a promising therapeutic avenue. By regulating inflammatory markers and acting as a functional antagonist of the GPR55 receptor, CBD may control the release of pro-inflammatory cytokines such as IL-12 and TNF-α, both of which have been implicated in obesity and metabolic dysfunction.[4] Lehmann *et al.*[133] reported that experimental CBD treatment reduced markers of pancreatic inflammation, which may have implications for the management of CKM syndrome. Moreover, studies using mouse models indicate that CBD can decrease insulitis and inflammatory cytokine production, thereby reducing the incidence of DM.[131] CBD has also shown potential in modulating oxidative stress, a key driver of CKM syndrome. CBD reduces oxidative stress levels in diabetic rats,[132] supporting its possible role in mitigating DM-related complications. In adipose tissue, CBD modulates chemokine and cytokine pathways, which could contribute to reduced obesity and improved metabolic outcomes.[118] As the understanding of CKM syndrome evolves, the potential role of CBD in mitigating cardiovascular, kidney, and metabolic dysfunction warrants further investigation. While preliminary findings are promising, additional research is needed to determine the long-term safety and efficacy of CBD as an adjunctive therapy for CKM syndrome.

Another primary research interest is how to reduce inflammation and oxidative stress to manage DM. In this context, the anti-inflammatory properties of CBD are particularly promising: It may help improve overall health outcomes for individuals with DM and potentially reduce the risk of complications associated with the disease.[25] In an *in vivo* study, experimental CBD treatment could reduce markers of inflammation in the pancreatic microcirculation.[133] In mouse models, CBD decreases the production of destructive insulitis in pancreatic islets and a decrease in inflammatory cytokine production, thus significantly reducing the incidence of DM in these mice.[112] CBD has anti-inflammatory effects in adipose tissue by modulating chemokines/cytokines and receptor-mediated pathways,[134] which could potentially decrease the risk of developing T2DM. Another study showed that CBD decreases oxidative stress in diabetic rats.[135] While these initial findings are promising, it is important to note that more research is needed to determine the long-term effects and safety of using CBD for DM treatment. Additionally, the studies mentioned were conducted on animals and may not necessarily translate directly to human patients.

5. CBD DOSING FOR MANAGING DM AND RELATED METABOLIC DISORDERS

The current treatment for DM includes a range of medications such as insulin, alpha-glucosidase inhibitors, biguanides, glucagon-like peptide-1 (GLP-1) receptor agonists, dopamine-2 agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, sodium-glucose transporter 2 (SGLT2) inhibitors, thiazolidinediones, and sulfonylureas. Additionally, lifestyle modifications, including a balanced diet and regular exercise, play a crucial role in disease management. While these treatments can be effective in controlling blood sugar levels, they may also come with side effects and limitations. For example, some medications can cause weight gain or hypoglycemia, and lifestyle changes may be difficult to maintain in the long term. As a result, there is a growing interest in exploring alternative therapies like CBD for DM and metabolic processes management. It is important to note that the American Diabetic Association emphasizes that CBD should not be used in place of conventional DM treatment.[136] However, CBD shows promise as an adjuvant therapy in DM management due to its anti-inflammatory, neuroprotective, cardioprotective, and metabolic regulatory properties. By reducing pro-inflammatory cytokines and oxidative stress, CBD may mitigate insulin resistance and improve glucose metabolism through PPARγ activation and AMP-activated protein kinase (AMPK) stimulation. These mechanisms complement the actions of GLP-1 receptor agonists, which enhance insulin secretion and suppress glucagon release, and SGLT2 inhibitors, which lower blood glucose levels

by increasing urinary glucose excretion.[137] CBD also offers cardiovascular benefits by lowering blood pressure, reducing endothelial dysfunction, and preventing arrhythmias, aligning with the cardioprotective effects observed with GLP-1 receptor agonists and SGLT2 inhibitors.[137] CBD's neuroprotective and analgesic effects may help alleviate diabetic neuropathy, while its modulation of CB_1 receptors supports weight management by reducing appetite and fat accumulation, reinforcing the metabolic benefits of dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonists such as tirzepatide.[138] Furthermore, CBD's renoprotective effects – reducing inflammation, oxidative damage, and fibrosis – could enhance diabetic nephropathy treatment alongside SGLT2 inhibitors.[137] While CBD is not a replacement for conventional antidiabetic therapies, its myriad of benefits suggest that it could enhance overall treatment efficacy, particularly in reducing inflammation, improving insulin sensitivity, protecting against diabetic complications, and supporting weight management when combined with GLP-1 receptor agonists, SGLT2 inhibitors, and dual GLP-1/GIP receptor agonists.

There is extensive evidence that CBD improve insulin sensitivity in obese rats, leading to better blood sugar control and reduced inflammation.[139–141] These findings suggest that CBD may be beneficial in managing DM and metabolic disorders. Chaves *et al.*[117] found that a 30 mg/kg dose of CBD reduces depressive and anxiogenic behaviors in diabetic rats, and increases weight gain and insulin levels, suggesting that it could be a useful therapeutic strategy for treating psychiatric comorbidities in patients with DM. Treatment with the same dose of CBD significantly increases insulin levels and reduces glycemia in diabetic rats.[117] Zorzenon *et al.*[5] reported similar findings: A 10 mg/kg dose improves metabolic dysfunctions in adult diabetic rats with chronic cerebral hypoperfusion, leading to reduced hyperglycemia, improved lipid profiles, and decreased liver enzyme levels. Two studies reported positive effects on lipid and glycemic parameters in patients with DM, although the treatments were different: Afshar *et al.*[85,] used a sublingual spray (CBDEX1®) and Jadoon *et al.*[85,111] tested the effects of CBD and THCV.[111] Sublingual administration of the 100 μg/10 μg CBD/Δ^9-THC regimen was well tolerated by the patients.[85] A study involving 62 patients with noninsulin-treated T2DM investigated the impact of CBD at a dosage of 100 mg taken twice daily, in combination with THCV at a dosage of 5 mg taken twice daily, on glycemic control.[111] The authors reported a statistically significant drop in resistin and a rise in glucose-dependent insulinotropic peptide compared with the start of the study but not compared with the placebo. Other results suggested that glycemic control had improved. Although THCV had positive benefits on fasting plasma glucose levels and pancreatic β-cell function, CBD did not. A recent case report described a 62-year-old Hispanic man with obesity (weighing 113 kg, with a BMI of 39 kg/m^2) who had been diagnosed with T2DM 11 years earlier and started using CBD oil orally as a substitute for insulin degludec to manage his blood glucose levels. This product was initiated by the patient based on personal research indicating that CBD might be beneficial for individuals with T2DM, in contrast to the clinician's recommendation.[142] The patient's use of CBD did not cause harm or worsen DM control.

Recent *in vivo* preclinical investigations have provided additional support for the antidiabetic potential of CBD. Rafailovska *et al.*[143] demonstrated that CBD exerts dose- and route-dependent effects in streptozotocin-induced diabetic rats, with oral administration at 50 mg/kg producing the most pronounced benefits. At this dose, CBD significantly reduced blood glucose levels, improved insulin secretion, and modulated hepatic carbohydrate metabolism by inhibiting gluconeogenic enzymes (glucose-6-phosphatase and fructose-1,6-bisphosphatase), while increasing glucose-6-phosphate concentrations and reducing hepatic glucose output. Moreover, the authors observed improvements in lipid homeostasis, including decreased triacylglycerols and increased HDL cholesterol. These findings highlight that CBD's therapeutic efficacy follows a non-linear, inverted-U dose–response relationship, with optimal metabolic regulation achieved at moderate doses.[143] Simultaneously, significant progress has been seen in the development of formulations and delivery technologies, which has broadened the prospective use of cannabinoids as a highly effective medical treatment.[144]

It is important to note that the optimal dosage of CBD for managing DM may vary depending on individual factors such as weight, metabolism, and the severity of symptoms. In general, it is recommended to start with a low dose such as 200 mg or less per day and gradually increase until the desired effects are achieved. It is advisable to consult with a healthcare provider before starting any CBD regimen to ensure safety and effectiveness.[145] The oral route of cannabinoids is preferred over alternative routes due to its numerous advantages, such as increased safety, improved patient adherence, conven-

ient intake, pain mitigation, and adaptability to accept diverse drug formulations. Moreover, the duration of exposure is extended, and the adverse effects are noticeably milder.[144] CBD is commonly administered orally through oils or capsules, while edibles provide a convenient and discreet option for individuals with active lifestyles. Furthermore, using CBD oil sublingually or in capsule form has been shown to have a longer-lasting effect compared with edibles, making it a more effective option for managing blood sugar levels throughout the day.

6. CBD ADMINISTRATION

The dominant method of administering cannabis-derived medications is through inhalation. Intrapulmonary delivery rapidly delivers cannabinoids to the central nervous system, high systemic bioavailability, and rapid onset of action (5–10 min). Moreover, this route of administration is advantageous for individuals who are incapable of ingesting medications orally (e.g., those experiencing severe vertigo and vomiting). Another widely used approach to administration is vaporization, which has been suggested since the 1990s as an alternative to combustion, to prevent the generation of hazardous by-products. This involves heating cannabis to the temperature at which cannabinoid vaporizes, but below the point at which combustion occurs.[144]

An alternative is transmucosal administration, where a drug enters the systemic circulation via the mucosal epithelium. The principal transmucosal routes are rectal, intranasal, and oral transmucosal. The latter relies on the drug being absorbed directly by the oral mucosa, which is highly vascularized. A variety of pharmaceutical dosage forms have been created to deliver their active ingredients: orally disintegrating tablets, buccal mucoadhesive tablets, films and patches, sublingual disintegrating thin films, sprays, chewing gum, and lozenges. Upon delivery, the formulation dissolves in a small amount of saliva. The drug that is released diffuses across the epithelial barrier, ultimately entering the systemic circulation while avoiding first-pass liver metabolism. This route is expected to improve adherence and reception among older adult and pediatric patients, who frequently encounter difficulties in ingesting traditional tablets. A major obstacle in oral transmucosal delivery is to ensure the drug remains stable within the oral cavity to allow its absorption. While there have been suggestions for using CBD oil in commercial products for transmucosal distribution, there is a lack of information on therapeutic items in the literature and patents. Leaf Vertical Inc., formerly known as Diverse Biotech Inc. (Orlando, FL, USA), is currently developing an oral sublingual formulation of CBD (BRCX 014) for the treatment of different types of malignancies.[144]

Because of its relative ease of access, the skin is an ideal route for the administration of drugs. Dermal formulations are classified as either transdermal (for systemic effects) or topical (for local effects on the skin). Medicines given transdermally must meet the following physicochemical parameters (recommendations): high potency (less than 10 mg/day), a low molecular weight (less than 500 g/mol), moderate lipophilicity (logP 1–5), and a melting point of less than 250 °C.[130] Transdermal uses of CBD are currently gaining significant attention. Paudel *et al.*[146] provided preclinical data on the pharmacokinetics of CBD patches. The authors of another study investigated the effects of applying CBD via the skin using a hydroalcoholic gel on reducing inflammation and pain in a rat model of arthritis induced in one knee joint.[132] The findings confirmed that CBD administered transdermally may have a lasting therapeutic effect. Futura Medical (UK) is developing CBD 100, a topical CBD gel intended for the management of pain and potentially other indications.[144] Botanix Pharmaceuticals (Perth, Australia) uses synthetic iterations of CBD through their Permetrex™ (dermal/transdermal medication delivery system) to manage a range of skin disorders, such as acne, plaque psoriasis, rosacea, atopic dermatitis, and bacterial skin diseases.[144]

7. POTENTIAL SIDE EFFECTS AND INTERACTIONS OF CBD

Potential concerns or side effects associated with using CBD for managing DM and related metabolic disorders include interactions with other medications, digestive issues, changes in appetite, and potential liver toxicity. Beyond developing a more comprehensive understanding of the efficacy of CBD as a therapeutic treatment option, future research should continue to evaluate the safety of CBD, to determine the optimal dosage and form of administration, and its potential interactions with other medications. Specifically, CBD may inhibit several cytochrome P450 enzymes (CYPs), which are involved in the metabolism of many common prescription and over-the-counter drugs.[147] When CBD is administered alongside medications that are metabolized by specific CYPs (e.g., CYP2C9 and CYP2D6), the metabolism of these medications may be delayed. Small trials and recent case reports have described such drug–drug interactions.[148,149] CBD may interact with some blood pressure and

cholesterol medications.[69] In addition, CBD may lead to changes in appetite or weight, fatigue, and diarrhea. The health consequences of cannabis are poorly understood, particularly in individuals who have long-term illnesses. It is important for individuals with DM and related metabolic disorders to consult their healthcare providers before incorporating CBD into their treatment plans to ensure it does not interfere with their current medications or exacerbate their condition.

8. CONCLUSIONS

DM, CKM syndrome, and related metabolic disorders are strongly linked to modern lifestyle factors such as physical inactivity, high-fat diets, and increased lifespan. With a global prevalence approaching 10% and rising incidence, these conditions pose major risk factors for cardiovascular disease and other metabolic abnormalities. CBD, a non-psychoactive compound derived from cannabis, has gained attention following its deregulation, due to both lifestyle trends and potential therapeutic benefits. Research on the ECS has highlighted its role in metabolic regulation and the pathophysiology of DM. ECS components, including CB_1 and CB_2 receptors, influence glucose metabolism, insulin sensitivity, and inflammatory pathways. Overactivation of CB_1 receptors is associated with obesity and metabolic syndrome, while CB_2 receptors provide protective effects against inflammation and tissue damage.

The growing interest in CBD as a complementary therapy for DM stems from its ability to modulate ECS activity. Based on preclinical and emerging clinical evidence, CBD can improve insulin sensitivity, reduce inflammation, and mitigate complications such as neuropathy and cardiovascular disorders. CBD may protect cardiovascular health by reducing vascular damage caused by hyperglycemia, inflammation, or T2DM, and it has shown potential in regulating lipid profiles, increasing adiponectin levels, and combating oxidative stress. Advances in formulation and delivery technologies have expanded the potential applications of cannabinoids. CBD can be administered orally, transdermally, or topically, with each route offering distinct advantages in terms of safety, convenience, and targeted delivery. While oral administration remains the most widely used due to its practicality, transdermal and topical systems are gaining interest for sustained and localized effects. Further research is needed to establish optimal dosing, safety profiles, and potential drug interactions.

Overall, CBD shows promise as an adjunct therapy for managing DM and related metabolic disorders. However, challenges remain in integrating it into standard treatment protocols, including determining long-term safety, effective dosing strategies, and the efficacy of different delivery methods. Rigorous clinical trials are essential to validate its therapeutic potential and optimize its use.

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