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THEMED ISSUE REVIEW

Is there a role for cannabidiol in obesity, metabolic syndrome and binge eating?

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Cannabidiol (CBD) is one of the most abundant phytocannabinoids isolated from the *Cannabis sativa* plant. CBD is a lipophilic, non-intoxicating substance that differently from Δ^9-tetrahydrocannabinol (Δ^9-THC) does not present the typical profile of a drug of abuse. It shows powerful anti-inflammatory and anti-oxidative properties that might be helpful for treating several pathologies. The aim of this review is to describe the potential role of CBD in the control of food intake and metabolism, with implications for the treatment of obesity and metabolic syndrome, and to discuss the underlying potential mechanisms of action. The preclinical evidence mentioned reveals that CBD influences eating behaviour, exerting anorexigenic effects and affecting the non-homeostatic aspect of food intake, via modulation of dopamine signalling in the brain reward system. Data from animal models of diet-induced obesity (DIO) and metabolic syndrome show that CBD improves glucose and lipid metabolism, inflammation and ameliorates psychiatric alterations not only in obese animals but also in the offspring born from obese mothers. These effects are achieved targeting multiple proteins expressed both in the central nervous system and peripheral tissues. The evidence collected from preclinical research, together with preliminary findings from clinical studies, supports further investigation of CBD in the context of obesity, metabolic syndrome and binge eating behaviour. Future studies are strongly required to highlight the potential role of CBD in these pathologies, specifically to better understand its mechanism of action, and how factors like sex differences, route of administration and formulation might influence the therapeutic activity of CBD.

KEYWORDS
binge eating, cannabidiol, diet-induced obesity, endocannabinoids, metabolic syndrome, obesity

Abbreviations: BED, binge eating disorder; C_{max}, maximum plasma concentrations; GFAP, glial fibrillary acidic protein; GIP, gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide; HFD, high-fat diet; HOMA-IR, homeostasis model assessment of insulin resistance; IBA-1, ionized calcium-binding adaptor molecule 1; US FDA, US Food and Drug Administration; WHO, World Health Organization.

1 | INTRODUCTION

According to the World Health Organization (WHO), obesity is a chronic complex disease characterized by excessive fat deposits that can impair life and significantly influence the quality of living. The definition of obesity is based on the body mass index (BMI) for adults: a person with a BMI greater than or equal to 25 is considered overweight, while obesity is characterized by a BMI greater than or equal to 30 (WHO, 2024). Recent data from the WHO report that in 2022, 2.5 billion of adults aged 18 years and older were overweight, among which more than 890 million were obese (WHO, 2024). The prevalence of obesity has increased exponentially during the last 50 years, being now so widespread that it is possible to recognize the existence of an 'obesity pandemic' (Westbury et al., 2023).

Nowadays, obesity is considered a serious chronic disease that promotes the incidence of severe co-morbidities, including metabolic, cardiovascular, musculoskeletal, neurological and mood disorders, and certain types of cancers (Bluher, 2019; Kloock et al., 2023).

Obesity is caused by a sustained positive energy balance, in which the calories introduced by the organism significantly exceed those expended (Bluher, 2019). The aetiology of this long-term imbalance in energy homeostasis is complex and might be the result of several alterations affecting the hypothalamic control of appetite and energy expenditure, the activity of orexigenic and anorexigenic peripheral hormones and/or the gut microbiota (Bluher, 2019; Westbury et al., 2023).

The first-line intervention to prevent and treat obesity consists in lifestyle modifications, including healthy dietary habits and regular physical activity. In cases of severe obesity and failure of lifestyle interventions, bariatric surgery and pharmacotherapy are the next steps in the obesity management (Elmaleh-Sachs et al., 2023; Kloock et al., 2023). Several drugs have been developed, acting with different mechanisms: reduction in appetite, increase in energy expenditure and decrease in calorie absorption (Tak & Lee, 2021). However, the use of numerous promising medications was abandoned due to minimal weight loss achieved or some were removed from the market because of severe life-threatening effects, such as cardiovascular problems in the case of **sibutramine**, or mood disorders and suicidal ideation reported with **rimonabant** use (Kloock et al., 2023; Tak & Lee, 2021).

At present, six drugs are approved by the US Food and Drug Administration (US FDA) for chronic weight management: **orlistat**, **phentermine**–topiramate, **naltrexone**–**bupropion**, **liraglutide**, **semaglutide** and **tirzepatide** for long-term use (Elmaleh-Sachs et al., 2023).

In the last years, the use of incretin-based therapies has revolutionized the treatment of obesity, providing substantial weight loss and cardiometabolic benefits (Alhomoud et al., 2024). These compounds act as agonists of the **glucagon-like peptide 1 (GLP-1) receptor** (GLP-1R, liraglutide and semaglutide) or dual GLP-1 receptor/**glucose-dependent insulinotropic polypeptide/gastric inhibitory polypeptide (GIP) receptor** agonists (tirzepatide), resulting in enhanced glucose-dependent **insulin** secretion, decrease in glucagon release and reduction in food intake and body weight (Alhomoud et al., 2024). The efficacy of these drugs has been extensively proven, even though some concerns about their safety and tolerability exist, mostly due to mild-to-moderate gastrointestinal symptoms (such as nausea, diarrhoea or vomiting), which can be responsible for discontinuation rate in certain individuals (Ghusn & Hurtado, 2024).

Recently, beyond incretin-based medications, much interest has been directed to the potential use of **cannabidiol (CBD)**, one of the most studied phytocannabinoids isolated from *Cannabis sativa*, for the management of obesity and metabolic syndrome. Preclinical studies have demonstrated beneficial effects induced by CBD in terms of body weight and food intake regulation, glucose and lipid metabolism, neuroinflammation and behavioural disturbances associated to obesity (Bielawiec et al., 2020, 2021, 2023; Ignatowska-Jankowska et al., 2011; Rodrigues et al., 2023, 2024; Scopinho et al., 2011). Also, the ability of CBD to counteract addictive behaviours opens a new line of research, exploring CBD as a pharmacological strategy to contrast pathological eating behaviours, typically observed in bingeing-related eating disorders, suggesting potential application of CBD in these psychiatric conditions (Bi et al., 2020; Marçal et al., 2022).

The aim of the present review is to describe the potential role of CBD in the control of food intake, obesity, metabolic disorders and pathological overeating, to better elucidate whether CBD-based therapies might represent future approaches for the management of these conditions.

2 | AN OVERVIEW OF CBD

2.1 | The endocannabinoid system

The well-known ancient plant *C. sativa* has been used for religious, recreational and medical purposes for thousands of years, even though the first pharmacological experiments with cannabinoids are much more recent, being performed in 1940s and 1950s (Pertwee, 2006).

This plant contains several biologically active compounds, among which more than 100 have been identified as phytocannabinoids, because of a shared chemical structure, and they are predominantly found in the resin secreted from the trichomes of the female plants (Bonini et al., 2018; Pertwee, 2006). The phytocannabinoids represent a group of oxygenated aromatic hydrocarbon metabolites derived from *C. sativa*, possessing 21 carbon atoms, among which the most studied compounds are **Δ^9-tetrahydrocannabinol (Δ^9-THC)**, the major psychotropic component of the plant and CBD, a non-psychoactive compound (Blebea et al., 2024).

Phytocannabinoids exert their pharmacological properties interacting with the endocannabinoid system (ECS), a sophisticated signalling machinery that regulates critical physiological and behavioural functions, including mood, sleep, hunger, pain and immune system (Blebea et al., 2024; Cristino et al., 2020).

The endocannabinoid system is composed by two G-protein coupled receptors (GPCRs), known as **cannabinoid 1 (CB_1)** receptor,

mostly expressed in the brain, and **cannabinoid 2 (CB_2) receptor**, found in high concentrations in the immune system; two endogenous lipid ligands of cannabinoid receptors (CBs), named **N-arachidonoylethanolamine (anandamide)** and **2-arachidonoyl-glycerol (2-AG)**; and the enzymes responsible for biosynthesis and degradation of these ligands, which are **the N-acylphosphatidylethanolamine+ (NAPE)-specific phospholipase D-like hydrolase (NAPE-PLD)** and **fatty acid amide hydrolase (FAAH)**, implicated respectively, in the synthesis and degradation of anandamide, and the diacylglycerol lipase α and β (DAGLα and DAGLβ), and **monoacylglycerol lipase (MAGL)** involved, respectively, in the synthesis and degradation of 2-AG (Cristino et al., 2020; Zou & Kumar, 2018).

The CB_1 receptor is among the most abundant GPCRs in the brain, with high expression in the hippocampus, cortex, basal ganglia and cerebellum. It is coupled to $G_{i/o}$ proteins, reducing levels of **cAMP**, and it mostly works at presynaptic terminal of neurons to curtail the release of neurotransmitters, for example on GABAergic and glutamatergic neurons (Howlett & Abood, 2017; Leo & Abood, 2021). CB_1 receptor is often recognized as the main mediator of the psychoactive effects of *C. sativa* and of its derivatives and, consistent with its brain distribution, deals with functions like memory, cognition, anxiety and depression (Zou & Kumar, 2018). In addition, CB_1 receptors are expressed in several peripheral tissues, influencing important physiological processes like gastrointestinal motility, immunity response, energy balance, reproduction, pain and skeletal muscle energy metabolism (Galiegue et al., 1995; Howlett & Abood, 2017; Zou & Kumar, 2018).

Similar to the CB_1, the CB_2 receptor is coupled to a $G_{i/o}$ protein, but unlike the first receptor subtype, it shows only limited expression in the central nervous system (CNS), while higher levels are found in cells of the immune system (Schurman et al., 2020). Initially, the CB_2 receptor was described as a peripheral receptor with immunomodulatory functions, but nowadays, after detection of CB_2 receptors in the CNS, it gained more and more scientific interest for neurological and neuropsychiatric disorders, given its neuro-immunomodulatory properties, and influence on neuronal activity and behavioural functions (Grabon et al., 2023).

Overall, the endocannabinoid system is a very complex signalling machinery that cannot be limited to the component described above, because their modulation can influence a larger endocannabinoid-associated network, often identified as the 'endocannabinoidome', which includes components like the **peroxisome proliferator-activated receptor-α** and **-γ** (**PPARα/ NR1C1** and **PPARγ/NR1C3**), the orphan receptors, **GPR119 (GPCR 119)** and **GPR55 (GPCR55)** and the **transient receptor potential cation channel subfamily V member 1 (TRPV1)** (Cristino et al., 2020).

2.2 | Pharmacokinetics of CBD

CBD is a 21-carbon phenolic monoterpene that has been first isolated from the marijuana extract of Minnesota wild hemp and from the resin of *Cannabis indica* in 1940 (Adams et al., 1940; Jacob & Todd, 1940).

Similar to other cannabinoids, CBD shows poor oral bioavailability, mainly due to its high lipophilicity and an extensive first-pass metabolism (Mechoulam et al., 2002).

In humans, the pharmacokinetic profile of CBD has been investigated via different routes of administrations (intravenous, inhalation, oromucosal or oral) and various types of formulation and delivery systems (Millar et al., 2018; Moazen-Zadeh et al., 2024). Overall, it appears that maximum plasma concentrations (C_{max}) and area under the curve (AUC) after CBD administration are dose dependent, and T_{max} mostly ranges between 1 and 5 h (Manini et al., 2015; Sellers et al., 2013; Stott et al., 2013; Taylor et al., 2018). Evidence for a dose–response relationship between CBD administration, plasma and brain concentrations has also been observed in animal models (Hammell et al., 2016; Long et al., 2012).

In line with the lipophilicity of CBD, the presence of food can significantly influence its absorption. The consumption of a high-fat meal together with CBD dosing results in a significant increase in CBD bioavailability (AUC and C_{max}) when compared with fasting state (Crockett et al., 2020; Taylor et al., 2018). Consequently, the administration of CBD with food would be recommended to minimize the risk of poor drug availability and facilitate treatments' outcomes.

Sex may also profoundly affect the pharmacokinetic parameters of CBD. Indeed, in human studies, it appears that females report higher maximum concentrations and faster absorption rates of CBD compared with males (Knaub et al., 2019; Nadulski et al., 2005). There is also preclinical evidence in support of this. For example, repeated (28 days) oral administration of CBD results in higher AUC in female compared with male rats. Also, from days 1 to 28, the pharmacokinetic profile of CBD between sexes was completely different. In females, the C_{max} of CBD significantly increased from days 1 to 28, while in males, the T_{max} underwent a significant decrease (Child & Tallon, 2022). In addition, female rats report higher accumulation of CBD in adipose tissue, liver and muscles compared with males (Child & Tallon, 2022), and maternal CBD exposure leads to greater embryonic brain concentrations in females rather than males (Maciel et al., 2022). This different pharmacokinetic profile might be attributable to biological sex differences in the **cytochrome P450 (CYP450)** family of enzymes, responsible for the metabolism of CBD, and might suggest lower dosages of CBD required for women to achieve determined blood levels and clinical efficacy (Moazen-Zadeh et al., 2024). Therefore, sexual dimorphism in response to CBD administration is something to critically consider, and sex-dependent dosing of CBD could be extremely important, as the higher accumulation in various peripheral organs and brain, and the higher plasma concentrations in females could be associated to a divergence in the efficacy of CBD in metabolic and psychiatric disorders (Matheson et al., 2022).

Considering that CBD can inhibit several CYP450 isoforms, enzymes involved in the metabolism of the majority of pharmacotherapies, the risk of drug–drug interactions is another factor to take into account, given the widespread use of CBD-based products that can increase bioavailability of concomitantly administered drugs and exaggerate their adverse effects (Britch et al., 2021; Stollberger & Finsterer, 2023).

2.3 | Pharmacodynamics of CBD: interaction with the endocannabinoid system

The pharmacodynamic profile of CBD is very complex because of its ability to interact with several molecular targets. CBD can behave as an antagonist, agonist or inverse agonist depending on the target receptor and also act as a negative or positive allosteric modulator or affect the activity of multiple enzymes (Britch et al., 2021; Castillo-Arellano et al., 2023).

Differently from Δ^9-THC, CBD does not lead to intoxication and does not show the typical profile of a drug of abuse but displays some psychoactive properties linked to its therapeutics usefulness (Castillo-Arellano et al., 2023).

This section briefly summarizes the interaction of CBD with component of the endocannabinoid system.

2.3.1 | Interaction of CBD with CB receptors

Although CBD has a low binding affinity for CB receptors, it modulates some of their functions even at low concentrations (Pertwee, 2008). CBD is a non-competitive negative allosteric modulator of the CB_1 receptor, reducing the potency and efficacy of the CB_1 ligands 2-AG and Δ^9-THC, at concentrations lower than the CBD predicted affinity for the orthosteric binding site of the CB_1 receptor (Chung et al., 2019; Laprairie et al., 2015; Tham et al., 2019). Acting through allosteric modulation of CB_1, CBD may not produce undesirable adverse effects observed with the orthosteric ligands of this receptor, because its effect depends on the presence of endogenous ligands, such as AEA and 2-AG (Laprairie et al., 2015).

Regarding CB_2 receptors, *in vitro* studies using GTPγS binding assay have reported the ability of CBD to antagonize the CB agonist **CP55940**, displaying an inverse agonism profile at human CB_2 receptor (Thomas et al., 2007). Later, similar to CB_1 receptor, an allosteric modulation of the CB_2 receptor by CBD has been hypothesized, with high affinity at the allosteric site of the CB_2 receptor even at nanomolar concentrations, responsible for a decrease in the affinity of the orthosteric agonist CM-157 (Martinez-Pinilla et al., 2017). Recently, CBD was described as an orthosteric partial agonist of the CB_2 receptor, sharing the same binding site of the ligands CP55940 and **SR144528** (Tham et al., 2019). Therefore, the interaction of CBD with the CB_2 receptor remains somewhat controversial and not fully elucidated, but it is clear that the CB_2 receptor is necessary to mediate some of the *in vivo* actions of CBD, such as reduction in **cocaine** and sucrose self-administration (Bi et al., 2020; Galaj et al., 2020), anti-convulsant effects (Vilela et al., 2017) and reduction in body weight (Ignatowska-Jankowska et al., 2011).

2.3.2 | Interaction of CBD with other components of the endocannabinoid system

CBD can indirectly interact with the CB receptors, by increasing the levels of the endogenous ligand AEA, through inhibition of the enzyme FAAH (Bisogno et al., 2001), mechanism linked to anti-psychotic effects (Leweke et al., 2012).

Within the endocannabinoidome, CBD is also an antagonist of the GPR55, proposed as an additional CB receptor (Ryberg et al., 2007), and an agonist of the PPARγ (Puighermanal et al., 2024).

2.4 | Pharmacodynamics of CBD: Molecular targets outside endocannabinoid system

Numerous molecular targets outside the endocannabinoid system, including ion channels, receptors, transporters and enzymes, are known to interact with CBD. These targets are briefly discussed in the present section.

2.4.1 | Interaction of CBD with ion channels

CBD can modulate different ligand-gated ion channels. It stimulates **glycine receptors** (Ahrens et al., 2009) and acts as a positive allosteric modulator of **$GABA_A$ receptor**, leading to hyperpolarization and reduction in neuronal activity (Ruffolo et al., 2022). CBD can behave as a low-potency, full agonist of the TRPV1, causing the displace of capsaicin from the receptor, and its rapid desensitization (Bisogno et al., 2001; Iannotti et al., 2014). The TRPV1 appears to mediate some of the pharmacological properties of CBD, including the decrease in cocaine self-administration (Galaj et al., 2020) and anti-seizure effect (Vilela et al., 2017).

Other ion channels targeted by CBD include: the ionotropic **$5\text{-}HT_3$ receptor** and **α7 nicotinic receptors**, both inhibited by CBD (Chrestia et al., 2022; Yang et al., 2010), and several voltage-gated ion channels, including sodium and calcium channels, leading to a strong modulation of neuronal excitability by CBD (Castillo-Arellano et al., 2023).

2.4.2 | Interaction of CBD with metabotropic receptors

Multiple metabotropic receptors have been recognized as targets of CBD. The **$5\text{-}HT_{1A}$ receptor** is one of the most investigated, because CBD can activate this receptor and exert antidepressant, anxiolytic and anti-allodynic effects (Alexander et al., 2025). Furthermore, CBD might promote activation of the **adenosine A_1** (Gonca & Darici, 2015) and **A_2 receptors** (Ribeiro et al., 2012) and acts as partial agonist of the **dopamine D_2 receptor**, accounting for some of its anti-psychotic effects (Seeman, 2016).

Lastly, CBD behaves as an allosteric modulator of both **μ** and **δ opioid receptors** (Kathmann et al., 2006), and CBD is now emerging as a strong alternative for managing opioid use disorder, in particular to mitigate opioid withdrawal-related symptoms (Kudrich et al., 2022).

To summarize, the pharmacodynamic profile of CBD is extremely complex, with a variety of molecular targets identified (Britch et al., 2021; Castillo-Arellano et al., 2023).

These molecular targets may be responsible for the numerous therapeutic properties of CBD, which include the potential to manage anxiety and depression (Garcia-Gutierrez et al., 2020), epilepsy (Borowicz-Reutt et al., 2024), pain (Mlost et al., 2020), addiction (Hurd et al., 2015), schizophrenia (Schoevers et al., 2020) and neurodegeneration (Chen et al., 2023). Currently, the US FDA has approved the use of pure CBD (Epidiolex®) for the treatment of seizures associated with Lennox–Gastaut syndrome, Dravet syndrome and with tuberous sclerosis complex in patients 1 year of age or older (US FDA, 2024).

3 | SEARCH STRATEGY

For the design of this narrative review, studies performed up to year 2025 focusing on the effect of CBD on the control of food intake and on glucose and lipid metabolism in animal models of obesity or metabolic syndrome were selected, carefully reviewed and described. *In vitro* studies were included in the selection if considered relevant and appropriate for the topic.

For 'Section 6', clinical studies evaluating the effect of CBD administration on metabolic parameters were chosen and described to highlight the translational relevance of CBD, even though a limited number of works was found.

Only studies published in English were considered for inclusion. The selection of peer-reviewed publications was conducted in two electronic databases, PubMed and Scopus.

The following search terms were used in the databases: 'CBD' OR 'cannabidiol' AND 'food intake' OR 'eating behaviour' OR 'obesity' OR 'metabolic syndrome' OR 'type 2 diabetes' OR 'dyslipidaemia' OR 'maternal obesity' OR 'food reward' OR 'binge eating'.

Titles and abstracts of the articles identified were screened by the authors and selected for inclusion if they were considered relevant and appropriate for the topic. When the articles were chosen, their full text was obtained and carefully examined.

4 | THE ROLE OF CBD IN FOOD INTAKE AND BODY WEIGHT REGULATION: EFFECTS AND MOLECULAR TARGETS

4.1 | An overview of the endocannabinoid system in appetite regulation

In the CNS, the endocannabinoids act retrogradely, being produced from phospholipids at a postsynaptic level and acting at the presynaptic level, without intermediate storage in vesicles. Therefore, endocannabinoids act on demand, with a real-time response to the feeding status, playing a critical role in the regulation of appetite and energy balance (Silvestri & Di Marzo, 2013). CB_1 receptors are located in the hypothalamus, where their activation by Δ^9-THC or synthetic analogues modulates the activity of hypothalamic neurons, promotes the release of orexigenic neuropeptides and stimulates food intake (Silvestri & Di Marzo, 2013). Also, components of the endocannabinoid system are expressed in the brain reward system, mostly in the nucleus accumbens and ventral tegmental area, where endocannabinoid system activation stimulates ingestion of palatable foods, endowed with high salience and incentive values (D'Addario et al., 2014). Most of the effects of endocannabinoids on food intake and body weight regulation were initially attributed to the CB_1 receptor, a line of research that culminated into the approval of the CB_1 inverse agonist rimonabant (Acomplia, Sanofi-Aventis) for the treatment of obesity in 2006 (Cohen et al., 2024). The drug entered the European market but was never approved by the US FDA, considering several psychiatric adverse events and increased suicidality risks emerged with rimonabant use. Soon, this led the European Medicines Agency to its withdrawn from market (Sam et al., 2011).

However, the influence of the endocannabinoid system on feeding behaviour is not solely limited to mechanisms involving the central CB_1 receptor, but extend beyond, leading the research to target the peripheral CB_1 receptors (Yang et al., 2024) or to investigate other endocannabinoid system-related targets, including the CB_2 receptor (Rodriguez-Serrano & Chavez-Hernandez, 2023). In this context, the use of natural (like CBD) or synthetic cannabinoids showing negligible affinity at the CB_1 receptor, but still capable of reducing food intake, represents an interesting approach to counteract obesity without the risk of incoming into severe psychiatric adverse events. The preclinical research focused on the effect of CBD on appetite and body weight regulation, with the hypothesized underlying molecular targets and mediators are discussed in the section below.

4.2 | Preclinical studies of CBD in the control of food intake and body weight gain

Initial preclinical studies evaluating the impact of acute CBD administration on appetite control reported conflicting results.

After treatment with CBD (50 $mg \cdot kg^{-1}$, intraperitoneal [i.p.]), male rats decreased their standard food intake immediately after dosing, and for 3 days following drug administration, demonstrating the anorexigenic ability of CBD (Sofia & Knobloch, 1976). This has been replicated in another work, in which CBD, administered orally (p.o.) in satiated male rats (0.04, 0.44 and 4.40 $mg \cdot kg^{-1}$, p.o.), decreased cumulative chow intake over a period of 4 h at the highest dose tested (Farrimond et al., 2012).

Differently, no effect was observed on food intake after CBD injection (3, 10, 30 and 100 $mg \cdot kg^{-1}$, i.p.) in male mice food-deprived for 24 h (Wiley et al., 2005) or on food consumption and body weight in non-deprived mice (10 $mg \cdot kg^{-1}$, ip) (Riedel et al., 2009). The reason for such discrepancies is unclear, given that all these studies tested the efficacy of acute CBD administration, but they might rely on a potential divergent influence of CBD on standard food consumption between rodent species (rats versus mice) or on the route of administration (i.p. vs. p.o.), that would result in different peak cerebrospinal

TABLE 1 Effect of CBD on feeding behaviour and body weight in preclinical studies.

Species	Diet	CBD administration	Effect on food intake and body weight	Reference
Male Sprague–Dawley rats	Standard food intake	50 mg·kg^{-1}, i.p., acute administration	- ↓ chow intake (6 h interval) immediately after dosing and up to 3 days after administration.	Sofia and Knobloch (1976)
Male ICR mice	Standard food intake after food deprivation for 24 h	3, 10, 30 and 100 mg·kg^{-1}, i.p., acute administration	- No effect of CBD on regular chow intake in mice deprived from food for 24 h.	Wiley et al. (2005)
Male C57BL6 mice	Standard food intake	10 mg·kg^{-1}, i.p., acute administration	- No effect of CBD on body weight, food intake and water intake following acute administration.	Riedel et al. (2009)
Male Wistar rats	Standard food intake and body weight of rapidly growing rats	1. 2.5 and 5 mg·kg^{-1}, i.p., for 14 days 2. 5 mg·kg^{-1}, i.p. + pretreatment with vehicle or AM-630 (a selective CB_2 antagonist, 1 mg·kg^{-1}) for 14 days	- ↓ body weight gain with CBD administration. - Pretreatment with AM-630 prevented the ↓ in body weight gain induced by CBD. - No effect of AM-630 per se.	Ignatowska-Jankowska et al. (2011)
Male Wistar rats	Standard food intake in fed and fasted (18 h) status	1, 10 and 20 mg·kg^{-1}, i.p., acute administration	- No effect of CBD (1, 20 and 20 mg·kg^{-1}) per se on food intake in both fed and fasted (18 h) status. - CBD (20 mg·kg^{-1}) ↓ hyperphagia induced by the CB_1 agonist WIN55,212-2 (2 mg·kg^{-1}) and by the 5-HT_{1A} agonist 8-OH-DPAT (1 mg·kg^{-1}).	Scopinho et al. (2011)
Male Lister-hooded rats	Standard food intake	0.04, 0.44 and 4.40 mg·kg^{-1}, p.o., acute administration	- ↓ cumulative chow intake over a period of 4 h with CBD (4.40 mg·kg^{-1}). - No effect on meal parameters, such as latency to the first meal, or meal duration.	Farrimond et al. (2012)
Male Wistar rats	HFD and free-choice diet (standard and high-sucrose pellets)	3 mg·kg^{-1}, i.p., once daily for 3 days	- ↓ HFD intake with CBD injected once-daily for 3 days, alone or in combination with leptin (100 μg·kg^{-1}). - ↑ body weight with CBD over treatment time in rats fed a HFD. CBD ↓ leptin-induced suppression of weight gain. - In rats with a free-choice diet, CBD does not affect high sucrose intake but ↓ standard food intake. The effect on standard food intake is not observed with concomitant injection of CBD and leptin.	Wierucka-receptorybak et al. (2014)
Male Long–Evans rats; male wild type, $CB_1^{-/-}$ and $CB_2^{-/-}$ mice	Sucrose self-administration (fixed- and progressive-ratio).	20 or 40 mg·kg^{-1}, i.p., for rats; 10 or 20 mg·kg^{-1}, i.p., for mice Acute administration	- ↓ sucrose self-administration in rats (40 mg·kg^{-1}). - ↓ sucrose self-administration (20 mg·kg^{-1}) in wild-type and $CB_1^{-/-}$, but not in $CB_2^{-/-}$ mice. - The effect of CBD on sucrose self-administration is blocked by the CB_2 antagonist AM-630 (3 mg·kg^{-1}) and mimicked by the CB_2 agonist JWH133 (10 and 20 mg·kg^{-1}).	Bi et al. (2020)
Male C57BL/6J mice	HFCD	2.39 mg·kg^{-1} incorporated in the diet	- ↑ in food intake in mice fed a HFCD and supplemented with CBD, compared with mice fed only a HFCD, despite amelioration in different metabolic parameters.	Gorelick et al. (2022)
Male C57BL/6 mice	HFD	10 mg·kg^{-1} (three times a week for 5 weeks) + 5 weeks at 30 mg·kg^{-1}, oral delivery	- No effect of CBD on weight gain and average daily energy intake of mice fed a HFD compared with vehicles.	Eitan et al. (2023)
Male C57BL/6J mice	HFCD	CBD-rich extract, 5 mg·kg^{-1}, three times a week for 6 weeks, oral administration	- No effect of CBD on body weight and food intake in mice fed a HFCD compared with vehicle.	Assa-Glazer et al. (2020)

TABLE 1 (Continued)

Species	Diet	CBD administration	Effect on food intake and body weight	Reference
Male C57Bl/6J mice and Magel2^{null} mice	HFD and genetically induced obesity	EPM301 (20 or 40 mg·kg^{-1}, i.p.) for 28 days or EPM301 (20 mg·kg^{-1}) for 18 weeks	- ↓ body weight and fat mass in mice fed a HFD (40 mg·kg^{-1}). - ↓ body weight in both WT (20 and 40 mg·kg^{-1}) and Magel2^{null} mice (40 mg·kg^{-1}) but at 20 mg·kg^{-1} selectively in Magel2^{null} mice. - ↓ hyperphagia (20 and 40 mg·kg^{-1}) selectively in Magel2^{null} mice. - ↓ body weight gain in Magel2^{null} mice fed a standard diet and treated for 18 weeks.	Ben-Cnaan et al. (2022)

Abbreviations: ↓, decrease; ↑, increase; 5-HT$_{1A}$ receptor (R); CBD, cannabidiol; HFCD, high-fat–cholesterol diet; HFD, high fat diet; i.p., intraperitoneal; p.o., orally/by mouth.

fluid levels (Farrimond et al., 2012; Wiley et al., 2005). See Table 1 for comparisons of rodent species, doses and routes of administration.

At a mechanistic level, the ability of CBD to affect feeding behaviour appears to be mediated via multiple biological targets, in line with its complex pharmacodynamics, something that has been investigated by different research groups.

First, at a neuroendocrine level, preliminary *in vitro* evidence suggests that CBD might promote changes in the expression of appetite-regulating neuropeptides in the hypothalamus, the main feeding centre. Treatment of hypothalamic cells with CBD results in a lower expression of the orexigenic **neuropeptide Y (NPY)** and of proopiomelanocortin (POMC), whose anorexigenic or orexigenic effects depend on its post-transcriptional pathways, that can lead to the anorexigenic **α-melanocyte stimulating hormone (α-MSH)** or to the orexigenic **β-endorphin** (di Giacomo et al., 2020). This impact of CBD on hypothalamic feeding-regulatory circuits might rely on its ability to modulate CB receptors, which would subsequently influence the activity of first-order hypothalamic neurons (di Giacomo et al., 2020).

Indeed, despite possessing a low affinity for CB receptors, CBD can antagonize CB_1 and CB_2 agonists at low concentrations (Thomas et al., 2007). This is possibly why in a study of Scopinho et al. (2011), CBD (1, 10 and 20 mg·kg^{-1}, i.p.) did not decrease food intake per se in rats but completely blocked the hyperphagic effect induced by the CB_1 agonist **WIN55,212-2**, under both fed and fasted status. This agrees with the common interference of CBD with the behavioural effects induced by CB_1 agonists or partial agonists, such as Δ^9-THC (Murphy et al., 2017; Pertwee, 2008).

The CB_2 receptor appears particularly relevant for CBD-induced suppression of food intake. Chronically administered CBD (2.5 and 5 mg·kg^{-1}, i.p.) for 14 days slowed body weight gain of rapidly growing male rats, with a more pronounced effect at the highest dose. This effect was dependent on the CB_2 receptors, because the pretreatment with **AM-630**, a selective CB_2 antagonist, prevented the decrease in weight gain induced by CBD but was inactive when injected alone (Ignatowska-Jankowska et al., 2011). This was the first study to outline the CB_2-dependent effect of CBD on body weight.

The CB_2 receptor seems implicated not only in the homeostatic aspect of eating behaviour but contributes to the beneficial effects of CBD on non-homeostatic and reward-driven food intake. CBD suppresses oral sucrose self-administration in rats (20 and 40 mg·kg^{-1}, i.p.) and mice (10 and 20 mg·kg^{-1}, i.p.) under fixed- and progressive-ratio schedules of reinforcement, but this effect is completely reversed with pharmacological blockade (AM-630, 3 mg·kg^{-1}, CB_2 antagonist) or genetic deletion of the CB_2 receptors, whereas it is mimicked by selective CB_2 agonism (**JWH-133**, 10 and 20 mg·kg^{-1}) (Bi et al., 2020). The fact that CBD modulates palatable food intake under non-homeostatic conditions via the CB_2 receptor is potentially related to the expression of this receptor on dopaminergic neurons of the ventral tegmental area (Zhang et al., 2017) and on D_2 receptor expressing neurons of the nucleus accumbens (Aracil-Fernandez et al., 2012), and with the ability of CBD to attenuate cocaine-induced extracellular increase of **dopamine** in the nucleus accumbens (Galaj et al., 2020). Whether this CBD modulation of dopaminergic neurotransmission is relevant for pathological overeating (such as binge eating) is something that still needs to be addressed (see Section 7.2).

CBD can block the hyperphagic effect induced by the 5-HT$_{1A}$ receptor agonist **8-OH-DPAT** (Scopinho et al., 2011). In the brain, 5-HT signalling plays an important role in energy homeostasis, with high levels of 5-HT associated to a decrease in food intake and vice versa (Lam et al., 2010). 8-OH-DPAT stimulates food intake, a mechanism attributed to the agonist activity at 5-HT$_{1A}$ somatodendritic autoreceptors in the raphe nucleus, whose activation leads to a decrease in 5-HT function in the brain (Ebenezer & Surujbally, 2007). CBD acts as agonist of the 5-HT$_{1A}$ receptor, which mediates some of the *in vivo* effects of CBD, including the anxiolytic and antidepressive ones (Alexander et al., 2025). The fact that CBD reversed the effect of a 5-HT$_{1A}$ agonist on food intake is somewhat controversial, with the authors hypothesizing the possible contribution of postsynaptic 5-HT$_{1A}$ receptors, engaged by CBD instead of the somatodendritic autoreceptors (Scopinho et al., 2011). More recently, it has also been demonstrated that acute injection of CBD inhibits 5-HT neurons firing activity, while repeated low doses of CBD restore 5-HT dorsal raphe signalling, through the desensitization of 5-HT$_{1A}$ autoreceptors (De Gregorio et al., 2019).

These hypothesized mediators of the anorexigenic effects of CBD are schematically illustrated in Figure 1 and also mentioned in Table 1.

Interestingly, the influence of CBD on feeding behaviour has been investigated even in animal models of high-fat diets (HFDs) or high-sucrose diets.

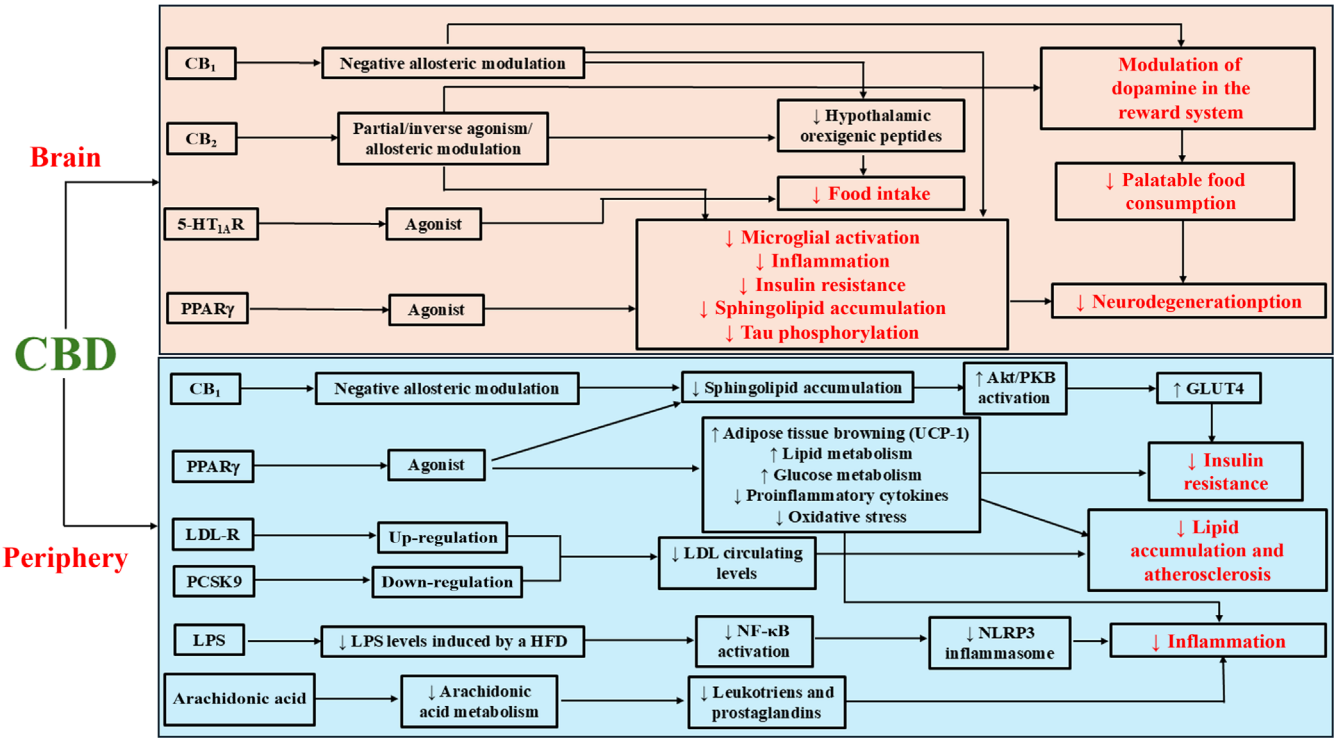

FIGURE 1 Schematic representation of the most important targets, mechanisms and outcomes of CBD in the context of appetite regulation, obesity and metabolic syndrome. This scheme illustrates some of the most important biological targets and mechanisms of CBD in obesity and metabolic syndrome that have been discussed in the present manuscript. In the brain, CBD reduces food intake through the interaction with the CB_1, CB_2 and $5\text{-}HT_{1A}$ receptor (R), which possibly results in decreased activity of hypothalamic orexigenic neuropeptides. Also, the interaction with CB receptors leads to a profound modulation of dopamine signalling in the brain reward system, that results in the reduction of palatable food intake. Targeting the PPARγ and CBs, CBD attenuates microglial activation, neuroinflammation, insulin resistance, sphingolipid accumulation and neurodegeneration. In peripheral tissues, CBD decreases insulin resistance and improve dyslipidaemia, through mechanisms that involve the negative modulation of the CB_1 receptor, which decreases sphingolipid metabolism, and stimulation of the PPARγ, which results in browning of the adipose tissue, improved glucose utilization and improvement in lipid metabolism. CBD also ameliorates dyslipidaemia, up-regulating the LDL-R and down-regulating the PCSK9, thus decreasing the circulating levels of LDL cholesterol. Finally, targeting the PPARγ and decreasing LPS levels and arachidonic acid metabolism, CBD exerts a strong anti-inflammatory activity. All these mechanisms appear interrelated and multiple targets participate in CBD-related beneficial outcomes. This supports the therapeutic potential of CBD in treating obesity and obesity-associated metabolic alterations. $5\text{-}HT_{1A}R$, $5\text{-}HT_{1A}$ receptor; AKT/PKB, protein kinase B; CB_1 receptor; CB_2 receptor; CBD, cannabidiol; CBs, cannabinoid receptors; LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptor; LPS, lipopolysaccharide; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, nucleotide-binding domain like receptor protein 3; PPARγ, peroxisome proliferator-activated receptor gamma, PCSK9, proprotein convertase subtilisin/kexin type 9; UCP-1, uncoupling protein 1.

In one study, performed in male rats accustomed to ingesting a HFD or a free-choice diet (standard and high-sucrose pellets), three once-daily injections of CBD (3 $mg{\cdot}kg^{-1}$), alone or in combination with **leptin**, decreased daily calories intake from the HFD. Paradoxically, a progressive increase in body weight in CBD-treated rats was concomitantly observed, and CBD reversed the suppression of body weight gain induced by leptin (Wierucka-Rybak et al., 2014). In rats fed the free-choice diet, no effect of CBD was observed on sucrose pellets intake, but CBD alone decreased standard food intake, fact that was not observed in CBD plus leptin-treated rats (Wierucka-Rybak et al., 2014).

Surprisingly, mice fed a high-fat–cholesterol diet (HFCD) plus CBD (2.39 $mg{\cdot}kg^{-1}$) increased their food intake compared with mice fed the high-fat–cholesterol diet alone, despite observing amelioration in multiple parameters, including glucose tolerance, inflammation and microbial dysbiosis with CBD supplementation (Gorelick et al., 2022).

Lastly, other studies revealed no effect of CBD oral delivery (10 $mg{\cdot}kg^{-1}$ three times a week for 5 weeks, followed by other 5 weeks at 30 $mg{\cdot}kg^{-1}$) on body weight gain and daily average energy intake of mice fed a HFD (Eitan et al., 2023) or of a CBD-rich extract (5 $mg{\cdot}kg^{-1}$, three times a week for 6 weeks) on body weight and food intake of mice fed a high-fat–cholesterol diet (Assa-Glazer et al., 2020). Considering these findings, it is possible that long-term administration of CBD might display different outcomes or lack of efficacy compared with acute or short-term supplementation. Alternatively, as previously proposed for standard food consumption, even for HFD, there could be a divergent susceptibility of rodent species to the effect of CBD on eating behaviour, which might explain inconsistency across research conducted in rats and mice (see Table 1 for

comparison of these studies). In this context, future investigations focused on chronic CBD administration in diet-induced obesity (DIO) rat models would be extremely important to provide more information.

Interestingly, a recent study examined the effect of the **cannabidiolic acid (CBDA)** derivative EPM301 (a CBDA-*O*-methyl ester) on diet-induced obesity and on genetically induced obesity, using a HFD model and Magel2^{null} mice. CBD is generated via decarboxylation from CBDA, which is highly instable, but EPM301 represents a more stable CBDA derivative, which allows a more consistent investigation of its behavioural and metabolic effects (Ben-Cnaan et al., 2022), and it might share a pharmacodynamic mechanism very close to that displayed by CBD. Mice fed a HFD and treated for 28 days with EPM301 (40 mg·kg^{-1}, i.p.) had a significant decrease in body weight. Similarly, at the same dosage, the reduction has also occurred in both wild type (WT) and Magel2^{null} mice fed a HFD. However, at 20 mg·kg^{-1} EPM301 selectively decreased body weight in Magel2^{null} mice. This finding could explain the specific hypophagic effect of EPM301 in this genotype, which mimics some features of the Prader–Willi syndrome, including metabolic dysregulations and obesity (Ben-Cnaan et al., 2022).

Finally, EPM301 demonstrated a preventive effect on obesity, reducing the progressive weight gain of Magel2^{null} mice fed a standard diet and treated for 18 days with the compound (Ben-Cnaan et al., 2022).

Altogether, CBD and CBDA derivatives can exert a powerful influence on feeding behaviour, reducing food intake and body weight gain. In diet-induced obesity models, CBD showed divergent effects on feeding behaviour and weight gain, despite ameliorating several metabolic parameters. Given the complex pharmacodynamics of CBD, and the multiple factors affecting its pharmacokinetics, future studies should be performed to investigate the molecular mechanisms underlying the anorectic effect of CBD, and the contribution of factors like sex differences, given that most of the studies were performed in male animals.

The results reported investigating the effect of CBD on food intake and body weight included in this section are listed in Table 1. The general influence of CBD on appetite regulation and the underlying mediators and mechanisms are also illustrated in Figure 1.

5 | THE EFFECT OF CBD ON METABOLIC PARAMETERS IN ANIMAL MODELS OF OBESITY AND METABOLIC SYNDROME

Metabolic syndrome is a highly diffuse pathological condition characterized by the presence of three or more of the following factors: high waist circumference, elevated blood triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, elevated blood pressure and high fasting glycemia (Ambroselli et al., 2023). Obesity generates a chronic inflammatory state that affects multiple organs (liver, adipose tissue, skeletal muscle, pancreatic islets and brain) and consequently energy homeostasis, favouring the onset of metabolic impairments (Saltiel & Olefsky, 2017).

CBD has demonstrated efficacy in ameliorating several metabolic alterations in animal models of diet-induced obesity and metabolic syndrome, in particular parameters related to glucose and lipids profile. The effects of CBD on these metabolic conditions are summarized in the current section. The influence of CBD on the gut microbiota in animal models of DIO or metabolic syndrome is also discussed.

5.1 | The effect of CBD on glucose homeostasis, insulin resistance and diabetes-associated neuropathology

Obesity facilitates the onset of insulin resistance, key aspect of type 2 diabetes and characterized by impairment in insulin-stimulated glucose uptake and metabolism in several organs, including liver, adipocytes, skeletal muscle and brain (Kahn et al., 2006). The endocannabinoid system is a critical regulator of glucose metabolism, with an overactive endocannabinoid system reported in the obesity status and insulin resistance, which are ameliorated by pharmacological blockade or genetic deletion of the CB_1 receptor (Jourdan et al., 2016).

As a negative allosteric modulator of the CB_1 receptor, CBD can influence the endocannabinoid system in multiple organs, improving insulin signalling and glucose utilization, commonly compromised in metabolic syndrome.

Consistent with its anti-inflammatory and immunosuppressive properties, CBD treatment (5 mg·kg^{-1}, i.p.) has been shown to decrease the incidence of diabetes, reduce serum levels of the cytokines **interferon-γ (IFN-γ)** and **tumour necrosis factor α (TNF-α)**, attenuate pancreatic beta cell disruption and leukocyte activation and restore functional capillary density in the pancreas of non-obese diabetic NOD/LtJ mice, an animal model of type 1 diabetes (Lehmann et al., 2016; Weiss et al., 2006).

Accordingly, in mice, supplementation of a high-fat–cholesterol diet with CBD (2.39 mg·kg^{-1}) decreases fasting plasma glucose and improves oral glucose tolerance compared with animals fed the high-fat–cholesterol diet only (Gorelick et al., 2022). Similarly, in rats fed a standard or HFD, CBD (10 mg·kg^{-1} for 2 weeks, ip), despite being able to reduce glucose plasma levels only in non-obese rats, decreases insulin plasma levels in HFD rats and slightly attenuates the homeostasis model assessment of insulin resistance (HOMA-IR) index (Bielawiec et al., 2020). Positive results have also been obtained with the CBDA derivative EPM301 (40 mg·kg^{-1}, ip, for 28 days), whose administration improved glucose tolerance and decreased hyperinsulinaemia in diet-induced obesity mice (Ben-Cnaan et al., 2022). Collectively, these data support that CBD can represent a promising therapeutic approach to regulate and improve glucose metabolism and insulin sensitivity under conditions of HFD, probably through the negative modulation of CB_1 receptors activity, which is known to contribute to insulin resistance and type 2 diabetes (Gruden et al., 2016). They are also in line with

TABLE 2 Effect of CBD administration on glucose and lipid metabolism parameters in animal models of diet-induced obesity (DIO) and metabolic syndrome.

Species	Model	CBD administration	Metabolic effects	Reference
Female *ob/ob* mice	Genetically induced obesity model	CBD 3 mg·kg^{-1} for 4 weeks, oral gavage	- ↓ liver triglycerides content	Silvestri et al. (2015)
Male C57BL/6J mice	HFD	CBD 5 mg·kg^{-1} for 8 weeks	- ↓ serum triglycerides and cholesterol - ↓ serum ALT - Normalization of hepatic lipid accumulation - ↓ HFD-induced hepatic inflammation (macrophage infiltration, mRNA levels of TNF-α, IL-1β and MCP-1) - ↓ NF-κB and NLRP3 inflammasome activation	Huang et al. (2019)
Male Wistar rats	HFD	CBD 10 mg·kg^{-1} for 2 weeks, i.p.	- ↓ fasting plasma glucose - ↓ plasma insulin concentration - ↓ HOMA-IR index (non-significant) - ↓ insulin resistance in the skeletal muscle - ↓ *de novo* ceramide synthesis pathway in the skeletal muscle - ↓ lipotoxicity in the skeletal muscle	Bielawiec et al. (2020)
Male C57BL/6J mice	HFCD	Cannabis extract containing 5.01 mg·mL^{-1} of CBD. Oral gavage (5 mg·kg^{-1}), every 3 days for 6 weeks.	- ↑ liver tissue - ↑ fasting glucose levels - ↓ glucose levels in the oral glucose tolerance test (non-significant) - ↑ TNF-α and iNOS gene expression in the liver	Assa-Glazer et al. (2020)
Male Wistar rats	HFD	CBD 10 mg·kg^{-1}, i.p., for 2 weeks	- ↓ lipid accumulation in white and red skeletal muscle - ↓ lipid peroxidation and inflammation in the white and red skeletal muscle	Bielawiec et al. (2021)
Male Wistar rats	HFD	CBD 10 mg·kg^{-1}, i.p., for 2 weeks	- ↓ sphingolipids accumulation in the cerebral cortex - ↓ ceramide synthesis in the cerebral cortex - ↓ insulin resistance in the cerebral cortex - ↓ tau protein phosphorylation in the cerebral cortex	Charytoniuk et al. (2021)
Male Wistar rats	HFD	CBD 10 mg·kg^{-1}, i.p., for 2 weeks	- ↓ *de novo* ceramide synthesis pathway in the heart	Charytoniuk et al. (2022)
Male C57BL/6J mice	HFCD	HFCD containing CBD (2.39 mg·kg^{-1})	- ↓ fasting glucose and blood glucose in the oral glucose tolerance test - ↓ SGOT (or AST) serum levels - ↓ TNF-α and iNOS gene expression in the liver	Gorelick et al. (2022)
Male C57Bl/6J mice	HFD	EPM301 40 mg·kg^{-1}, i.p. for 28 days	- ↑ glucose tolerance - ↓ hyperinsulinaemia - ↓ liver enzymes (ASP, ALT and ALP) - ↓ liver fat accumulation and triglycerides - ↓ serum triglycerides, total cholesterol and LDL - ↓ lipid accumulation in HepG2 cells - ↑ LDL receptor (LDLR) in HepG2 cells - ↓ PCSK9 enzyme in HepG2 cells	Ben-Cnaan et al. (2022)
Male Wistar rats	HFD	CBD 10 mg·kg^{-1}, i.p., for 2 weeks	- Improvement in sphingolipid metabolism in the adipose tissue - ↓ ceramide content in the adipose tissue - ↓ insulin resistance in the adipose tissue	Berk et al. (2022)
Male Wistar rats	HFD	CBD 10 mg·kg^{-1}, i.p., for 2 weeks	- ↓ intramuscular fatty acids accumulation in white and red skeletal muscle - ↓ *de novo* lipogenesis in white and red skeletal muscle - ↓ expression of membrane fatty acid transporters in white and red skeletal muscle	Bielawiec et al. (2023)

TABLE 2 (Continued)

Species	Model	CBD administration	Metabolic effects	Reference
Male C57BL/6 mice	HFD	Oral delivery of CBD, 10 mg·kg^{-1}, three times a week for 5 weeks, followed by 5 weeks of 30 mg·kg^{-1}	- ↑ glucose levels in the oral glucose tolerance test at 10 mg·kg^{-1} - No effect on hepatic steatosis - No effect on adipocyte sizes or inflammation In liver and adipose tissue: - ↑ expression of lipogenic genes *FASD2* and *SCD-1* - ↑ expression of lipid oxidation markers *ACOX1* and *PPAR-a* - ↑ expression of the fatty acid transporters *FATP1* and *CD36*	Eitan et al. (2023)
Male Wistar rats	HFD	CBD 10 mg·kg^{-1}, i.p., for 2 weeks	- ↑ n-3 PUFAs activity in myocardial phospholipid and triacylglycerol fractions - ↓ myocardial arachidonic acid, inflammation and redox imbalance	Sztolsztener et al. (2023)
Male C57BL/6 mice	HFD	Avidekel extract (30% CBD) three times a week, orally, 10 (5 weeks) to 30 mg·kg^{-1} (5 weeks)	- ↑ adipose tissue inflammation - ↑ liver steatosis	Eitan et al. (2024)
Male ApoE$^{-/-}$ mice	HFD	CBD, daily administered, 40 mg·kg^{-1}	- ↓ foam cells formation, total cholesterol, triglycerides and LDL - ↑ HDL - ↓ ceramide, cholesterol absorption in a macrophage foam cells model - ↑ cholesterol efflux in a macrophage foam cells model	He, Shi, Xu, and Liu (2024)
Male ApoE$^{-/-}$ mice	HFD	CBD 50 mg·kg^{-1}, oral gavage, 8 weeks	- ↓ plasma inflammatory cytokines (TNF-α and IL-1β) - ↓ plasma LPS - ↓ lipid dysregulations and levels of oxidized triglycerides induced by HFD - CBD modulates arachidonic acid metabolism	He, Shi, Wu, et al. (2024)

Abbreviations: ↓, decrease; ↑, increase; ACOX1, acyl-CoA oxidase 1; ALP, alkaline phosphatase; ALT, alanine transaminase; ASP, aspartate transaminase; CBD, cannabidiol; CD36, cluster of differentiation 36; FADS2, fatty acid desaturase 2; FATP1, fatty acid transport protein 1; HDL, high-density lipoprotein; HFCD, high-fat–cholesterol diet; HFD, high-fat diet; HOMA-IR, homeostasis model assessment-estimated insulin resistance; IL-1β, interleukin 1 beta; iNOS, inducible nitric oxide synthase; i.p., intraperitoneal; LDL, low-density lipoprotein; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein 1; NF-κB, nuclear factor kappa B; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; PCSK9, proprotein convertase subtilisin/kexin type 9; PPARα, peroxisome proliferator-activated receptor alpha; PUFA, polyunsaturated fatty acid; SCD1, stearoyl-CoA desaturase 1; SGOT, serum glutamic-oxaloacetic transaminase; TNF-α, tumour necrosis factor alpha.

clinical evidence reported in diabetic patients, as will be discussed later in the manuscript (Afshar et al., 2022).

In contrast, others found detrimental effects of oral administration of CBD (10 mg·kg^{-1} for 5 weeks followed by 30 mg·kg^{-1} for other 5 weeks, via non-invasive delivery with micropipettes) on glucose tolerance test in HFD mice (Eitan et al., 2023), and on plasma fasting glucose in mice fed a high-fat–cholesterol diet and treated orally (gavage) three times a week for 5 weeks with a CBD-enriched extract (5 mg·kg^{-1}) (Assa-Glazer et al., 2020). Therefore, more studies in rodents with standardized protocol of CBD administration would be required to contrast or to corroborate the present results obtained in terms of glycaemic control (see Table 2 for experimental details of each study).

Interestingly, the influence of CBD in regulating glucose metabolism appears to affect multiple organs. Incubation of the adipose tissue with CBD in the presence of glucose dose-dependently improves glucose uptake, anti-oxidative activity, glycolysis and glycogenesis parameters (Erukainure et al., 2022). Specifically, CBD was able to dose-dependently reverse the glucose-induced alterations in the enzymes ectonucleotidase (ENTPDase and 5′-nucleotidase), responsible for ATP degradation and the increased activity of the enzymes fructose-1,6-biphosphatase, glucose 6-phosphatase and glycogen phosphorylase, at a level comparable with the anti-diabetic drug metformin (Erukainure et al., 2022). This results in increased cellular availability of ATP and improvement in glucose-lipid metabolism, with positive outcomes for insulin resistance and obesity.

Moreover, under conditions of over-nutrition, CBD treatment (10 mg·kg^{-1} for 2 weeks, oral) can modulate adipocyte sphingolipid metabolism, reducing ceramide content, and consequently improves the sensitivity of the adipose tissue to insulin, as determined in an obese rat model (Berk et al., 2022). Ceramide is a product of the sphingolipid metabolic pathway, whose levels strongly increase in

the adipose tissue with nutrient oversupply, generated through the *de novo* ceramide synthesis pathway from saturated fatty acids. The accumulation of ceramide is detrimental for glucose utilization because it interferes with the translocation of the **glucose transporter 4 (GLUT4)**, blocking the **protein kinase B (Akt/PKB)** activation, thus reducing insulin-stimulated glucose uptake and glycogen synthesis in the adipocytes (Xia et al., 2020). In this context, treatment with CBD reduces ceramide synthesis, diminishing the expression of key enzymes part of the *de novo* pathways, increases its catabolism and restores ceramide-induced aberrations, such as the diminished activation of Akt/PKB and **glycogen synthase kinase 3β (GSK3β)** (Berk et al., 2022). This is a potential mechanism explaining the role of CBD in the prevention and/or treatment of type 2 diabetes and obesity-induced complications (see Figure 1).

Interestingly, a similar effect was replicated in the red skeletal muscle of obese rats, in which chronic CBD treatment attenuated sphingolipid accumulation and improved markers of insulin resistance and glucose metabolism (Bielawiec et al., 2020). In addition, in this experiment, the authors found an increased intramuscular expression of the CB1, TRPV1 and 5-HT_{1A} receptor as a consequence of the HFD, which was attenuated by CBD administration, that also enhanced CB2 expression (Bielawiec et al., 2020). The effects of CBD on these targets might be correlated to those on ceramide synthesis pathway, because it has been demonstrated that, under a HFD, the stimulation of CB_1 receptors by AEA facilitates ceramide accumulation, with consequent disruption of insulin signalling (Cinar et al., 2014).

These beneficial properties of CBD in peripheral tissues can be effective even for damages of the CNS, such as diabetic neuropathy, dementia or Alzheimer's disease (AD), conditions often linked to insulin resistance.

CBD is helpful for neurodegeneration induced by HFD, because treatment with CBD (10 $mg \cdot kg^{-1}$ for 14 days, i.p.) in obese rats affects sphingolipid metabolism and insulin signalling in the cerebral cortex. Under conditions of elevated fatty acids availability, CBD can decrease the content of sphingolipids and levels of proteins implicated in ceramide synthesis, improve insulin sensitivity and attenuate tau protein phosphorylation in the cerebral cortex (Charytoniuk et al., 2021). Similarly to what observed in muscles, the influence of CBD on sphingolipid metabolism and insulin signalling in the cerebral cortex was paralleled by changes in the expression of different proteins targeted by this cannabinoid. Indeed, obese CBD-treated rats displayed a decrease in the expression of GPR55 and 5-HT_{1A} receptor, while increased that of PPARγ (Charytoniuk et al., 2021). PPARγ is a nuclear receptor with a critical role in metabolism and inflammation, and CBD was demonstrated able to activate this receptor, leading to a reduction in the levels of the amyloid precursor protein, and thus of amyloid beta deposition in neurons, with consequent neuroprotection (Scuderi et al., 2014).

This, combined with the ability of CBD to improve glucose hypometabolism and memory deficits in animal models of streptozocin-induced Alzheimer's disease (de Paula Faria et al., 2022), suggests that CBD-based therapies might be evaluated for the treatment of neurodegenerative diseases linked to type 2 diabetes. The results of these studies and the outcomes on glucose regulation by CBD are summarized in Table 2 and schematically illustrated in Figure 1.

5.2 | Effect of CBD on hepatic function and inflammation, dyslipidaemia and lipid metabolism

Dyslipidaemia in metabolic syndrome is defined by elevated levels of triglycerides and low-density lipoproteins (LDLs) and by reduced levels of HDL. This lipid imbalance progressively leads to atherosclerotic plaques and impairs vascular function (Iqbal et al., 2018). Increasing evidence suggests that overactivation of the endocannabinoid system facilitates dyslipidaemia and the progression of atherosclerosis (Guillamat-Prats et al., 2019). In the liver, hepatocytes produce the endocannabinoids AEA and 2-AG, express CB receptors and feeding an obesogenic diet increases expression of the CB_1 receptor and AEA levels, which then promote *de novo* fatty acid synthesis and hepatic steatosis, effects abolished by CB_1 antagonists or genetic ablation of the CB_1 receptors (Bazwinsky-Wutschke et al., 2019; Jourdan et al., 2010).

In this context, CBD administration has been reported helpful for liver function, dyslipidaemia and lipid metabolism in multiple organs.

Silvestri et al. demonstrated that human hepatocytes cell lines exposed to oleic acid increase intracellular lipid levels, which are significantly decreased after application of CBD, resulting in enhanced lipolysis and mitochondrial activity. The lipid lowering effects of CBD were replicated in vivo in zebrafish and in the liver of *ob/ob* mice (3 $mg \cdot kg^{-1}$, oral gavage for 4 weeks) (Silvestri et al., 2015). CBD affects adipose tissue lipid metabolism, showing a reduction in lipid accumulation in CBD-treated 3T3-L1 pre-adipocytes (Silvestri et al., 2015), and the ability to decrease the lipase activity and cholesterol level, together with improved glucose uptake and anti-oxidative effects (Erukainure et al., 2022). The influence of CBD on adipose tissue metabolism is strongly dependent on the nuclear receptor PPARγ. Indeed, CBD stimulates browning of adipocytes, increasing the expression of brown fat-specific genes (including PPARγ and Uncoupling Protein 1), lipolysis and mitochondrial biogenesis, while reducing lipogenesis, with a mechanism that requires PPARγ activation (see Figure 1) (Parray & Yun, 2016).

In vivo, although CBD supplementation (2.39 $mg \cdot kg^{-1}$) did not significantly improve liver steatosis and function in a murine model of non-alcoholic fatty liver disease (NAFLD) induced by a high-fat–cholesterol diet, it partially restored the elevated serum glutamic-oxaloacetic transaminase (SGOT or aspartate aminotransferase [AST]) levels, and attenuated hepatic inflammation, lowering the expression of **TNF-α** and **inducible nitric oxide synthase (iNOS)** (Gorelick et al., 2022). The fact that CBD did not alleviate liver steatosis and function may be dependent on a non-sufficient dosage in the diet, that however was able to retain anti-inflammatory activity and to restore SGOT serum levels.

Another study revealed that oral CBD treatment (10 $mg \cdot kg^{-1}$, three times a week per 5 weeks, followed by other 5 weeks at 30 $mg \cdot kg^{-1}$) was associated to an increased transcription of lipogenic genes in the liver and adipose tissue, such as fatty acid desaturase

2 and stearoyl-CoA desaturase 1, and to increased lipid oxidation markers, including acyl-CoA oxidase 1 and PPAR-α, and of **fatty acid transporters 1 (SLC27A1)** and **CD36**, suggesting improved markers of liver and adipose tissue lipid metabolism (Eitan et al., 2023).

Interestingly, the amelioration in serum and hepatic lipid accumulation, and liver steatohepatitis induced by a HFD with CBD administration (5 mg·kg^{-1} for 8 weeks), is accompanied by a powerful anti-inflammatory activity. CBD decreased liver HFD-induced mRNA levels of pro-inflammatory mediators, such as TNF-α, **interleukin 1 β (IL-1β)**, **monocyte chemotactic protein 1 (MCP-1/CCL2)** and macrophages infiltration, as well as inhibited **nuclear factor kappa B (NF-κB)** and **nucleotide-binding domain like receptor protein 3 (NLRP3)** inflammasome activation, suggesting mechanisms by which CBD may protect against obesity-related steatohepatitis (Huang et al., 2019). Indeed, the authors proposed that CBD attenuates the activation of NF-κB induced by the endotoxin **lipopolysaccharide (LPS)** under HFD condition, which would subsequently activate the NLRP3 inflammasome, and further promotes the release of inflammatory cytokines and consequent liver injury, as illustrated in Figure 1 (Huang et al., 2019).

Evidence that CBD might represent an excellent candidate for atherosclerosis also comes from a recent study by He, Shi, Xu, & Liu, (2024), in which supplementation of a HFD with CBD (40 mg·kg^{-1}) decreased foam cells formation, total cholesterol, triglycerides and LDL, while increasing HDL levels in ApoE$^{-/-}$ mice. CBD application also decreased ceramide levels, cholesterol absorption and increases cholesterol efflux in a macrophage foam cells model, meaning that it could attenuate the progression of atherosclerosis (He, Shi, Xu, & Liu, 2024). Interestingly, the effect of CBD on foam cells seems again to require the PPARγ, because it is attenuated by a PPARγ inhibitor and by PPARγ small interfering RNA (He, Shi, Xu, & Liu, 2024). As previously anticipated, PPARγ is a crucial mediator of the influence of CBD on glucose regulation, insulin signalling, inflammation, lipid metabolism and immunity, and its activation could represent one of the main mechanisms by which CBD decreases inflammation and lipid accumulation (Khosropoor et al., 2023).

In another model of HFD in ApoE$^{-/-}$ mice, oral treatment with CBD (50 mg·kg^{-1}, oral gavage) decreased the levels of plasma inflammatory cytokines (TNF-α and IL-1β), LPS and reversed lipid dysregulations and levels of oxidized triglycerides induced by feeding the HFD. Here, it was demonstrated that CBD modulates lipid and amino acid metabolism, producing a consequent anti-inflammatory action, with a mechanism involving a negative influence on arachidonic acid metabolism, whose derivatives (principally leukotrienes and prostaglandins) are powerful proinflammatory mediators (He, Shi, Wu, et al., 2024).

Altogether, these findings point to a strong negative modulation of inflammatory pathways by CBD under conditions of HDF. This is achieved through the activation of the PPARγ, a restoration in lipid and amino acids imbalance, attenuation of LPS-induced endotoxemia and a negative regulation of the arachidonic acid metabolism, resulting in a powerful anti-inflammatory activity potentially useful for dyslipidaemia, atherosclerosis and metabolic syndrome. These proposed mechanisms are schematically represented in Figure 1.

Beyond CBD, also, the CBDA derivative EPM301 (40 mg·kg^{-1} for 28 days) restored liver function and lipid metabolism in HFD-fed mice. Treatment with this compound demonstrated a reduction of fat mass and hyperleptinaemia, hepatoprotection, improved liver function and dyslipidaemia, normalizing the obesity-induced elevation in liver enzymes, hepatic fat accumulation and triglycerides levels, as well as reduced levels of serum triglycerides, total cholesterol and LDL (Ben-Cnaan et al., 2022). Intriguingly, EPM301 can decrease lipid accumulation in HepG2 cells, up-regulate the LDL receptor (LDL-R) and down-regulate the **proprotein convertase subtilisin kexin/type 9 (PCSK9)** enzyme (Ben-Cnaan et al., 2022), whose inactivation is strongly linked to reduced risk of atherosclerotic cardiovascular diseases (Hummelgaard et al., 2023). Therefore, a positive outcome on LDL metabolism might underlie another pathway linked to the beneficial effect of CBD on dyslipidaemia (see Figure 1).

To date, detrimental effects after administration of CBD have also been reported in a few studies.

A CBD-rich extract (5 mg·kg^{-1}, three times a week for 6 weeks) enhanced liver weight and pro-inflammatory markers (TNF-α and iNOS) in the liver of mice fed a high-fat–cholesterol diet for 6 weeks, together with no effects induced by CBD on serum and hepatic lipid profiles (Assa-Glazer et al., 2020). Another study showed that an oil-based extract with high content of CBD (Avidekel, 30% CBD), orally administered three times a week (5 weeks at 10 mg·kg^{-1} followed by 5 weeks at 30 mg·kg^{-1}), even worsened diet-induced liver steatosis parameters compared with a Δ^9-THC-enriched extract (Erez, 15% Δ^9-THC) in mice fed a HFD (Eitan et al., 2024). The reason for the negative outcomes obtained by these two works compared with the others is unclear, but it might be attributed to different experimental conditions, because here, the authors administered two cannabis extracts where CBD was the main constituent, rather than pure CBD (Assa-Glazer et al., 2020; Eitan et al., 2024). Thus, the influence of other components of the extracts cannot be completely ruled out and such discrepancy needs further investigation.

Beyond liver and adipose tissue, CBD seems to improve lipid metabolism in other tissues and organs affected by high fat feeding. During obesity, increased availability of fatty acids in the diet leads to excessive storage of lipids in adipocytes and other organs, such as the liver, and in the cardiac and skeletal muscle (Samuel et al., 2010). Animal models of diet-induced obesity have demonstrated that 2 weeks administration of CBD (10 mg·kg^{-1}) in obese rats decreases the expression of fatty acid transporters, lipid accumulation, *de novo* lipogenesis and improve lipid metabolism, inflammation and oxidative status in white and red skeletal muscle (Bielawiec et al., 2021; Bielawiec et al., 2023), as well as attenuate *de novo* ceramide synthesis pathway, and the pro-inflammatory and oxidative stress states induced by lipid overload in the heart (Charytoniuk et al., 2022; Sztolsztener et al., 2023).

To summarize, CBD treatment provides beneficial effects in terms of both glucose and lipid metabolisms under conditions of high fat feeding, as proved by multiple animal models of diet-induced obesity, suggesting potential therapeutic application in metabolic syndrome. The studies using diet-induced obesity models to investigate the

metabolic effects of CBD are listed in Table 2, providing details about the experimental procedures employed. A schematic illustration reporting the principal targets of CBD, their related mechanisms and consequent outcomes in the context of food intake regulation, glucose and lipid metabolism is provided in Figure 1.

5.3 | Effects of CBD on maternal obesity

Maternal obesity does not solely cause several complications for pregnancy, but also for the long-term health of the offspring. Exposure to a suboptimal uterine environment can make the offspring more predisposed to obesity, insulin resistance, cardiovascular problems and behavioural disturbances (Denizli et al., 2022). This is a consequence of several dysregulations that occurs in the obesity status, including changes in metabolic hormones, lipid transport and accumulation, glucose metabolism, gut microbiota and to a chronic state of low-grade systemic inflammation. During pregnancy in obesity, inflammatory mediators can cross the placenta, impair its structure and function, resulting in the exposure of the foetus to an inflammatory environment that critically affects the developmental programming (Segovia et al., 2017), predisposing it to metabolic abnormalities and/or neuropsychiatric diseases (Cirulli et al., 2020; Denizli et al., 2022; Segovia et al., 2017).

Considering the beneficial effects shown by CBD in obesity and metabolic syndrome, a series of studies has been carried out to elucidate whether CBD might counteract metabolic, neuroinflammatory and behavioural impairments induced by maternal obesity in the offspring.

In the first one, it was evaluated the effects of CBD treatment (50 $mg \cdot kg^{-1}$, oral gavage, 3 weeks) starting from Postnatal Day 21, in male and female rats' offspring, whose dams were previously fed with a control or a cafeteria diet (Rodrigues et al., 2023). As expected, cafeteria diet induced obesity in dams before and during mating, gestation and lactation, generating metabolic complications, such as hyperglycaemia and hyperinsulinaemia, and increased lipid and LPS plasma levels (da Silva Rodrigues et al., 2024). It turned out that maternal diet had no influence on body weight, but the offspring born from obese mothers displayed an increase in white adipose tissue, whose deposition was attenuated by CBD treatment only in male rats (Rodrigues et al., 2023).

CBD ameliorated glucose and lipid metabolism in a sex-dependent manner. It decreased the elevated triglycerides levels in female rats with cafeteria-fed mother, while glucose metabolism parameters were more affected in males, in which CBD treatment reduced plasma insulin and improved HOMA-IR. In both sexes, CBD treatment reversed the increase in LPS plasma levels induced by maternal obesity, suggesting the ability to attenuate endotoxemia (Rodrigues et al., 2023). This is in line with other studies that evaluated the reducing effects of CBD administration on LPS levels under conditions of HFD (He, Shi, Wu, et al., 2024; Huang et al., 2019) and supports that it could be helpful for counteracting the endotoxemia due to the obesity status and that induced in the offspring as a consequence of parental obesity.

Notably, CBD treatment attenuated hypothalamic inflammation in the offspring caused by maternal obesity, decreasing gene expression of the pro-inflammatory cytokines TNF-α and **interleukin-6** (Rodrigues et al., 2023). The hypothalamus is the main feeding centre of the brain, endowed with an increased permeability to respond to metabolic signals coming from other organs. The inflammatory state associated to obesity leads to the activation of non-neural hypothalamic cells, in particular astrocytes and microglia, starting an inflammatory process that disrupts proper hypothalamic functioning and particularly the activity of the anorexigenic POMC neurons in the arcuate nucleus. This produces an aberrant regulation of energy balance, insulin and leptin resistance, overeating and the progression of obesity (Lee et al., 2020; Seong et al., 2019). The ability of CBD to counteract hypothalamic inflammation might have been the results of its interaction with the endocannabinoid system. Indeed, exposure to maternal HFD has been reported to up-regulate the hypothalamic content of the CB_1 receptors in the offspring, together with a disruption in leptin signalling (Almeida et al., 2019; Dias-Rocha et al., 2018). Therefore, the negative modulation of the hypothalamic CB_1 receptor could explain the attenuation of the neuroinflammatory process induced by maternal exposure to HFD. Moreover, CB_2 receptors and PPARγ seem implicated in CBD-induced reduction in neuroinflammation. Indeed, CB_2 receptor is strongly expressed in immune cells, including the microglia, where its stimulation generates immunosuppressive and anti-inflammatory activities (Rodrigues et al., 2024). A recent study also evidenced that CBD attenuates LPS-induced activation of the NLRP3 inflammasome complex in the microglia through mechanisms that involve both CB_2 receptors and PPARγ stimulation (Rodrigues et al., 2024), further supporting the contribution of these receptors in CBD-associated suppression of the inflammatory response.

The neuroinflammation induced by parental obesity does not only affect the hypothalamus, but extends to extra-hypothalamic regions involved in memory, cognition and social behaviour, such as the prefrontal cortex and hippocampus. In this context, CBD attenuated the increased expression of the inflammatory markers glial fibrillary acidic protein (GFAP) and ionized calcium-binding adaptor molecule 1 (IBA-1) and of the CB_1 in the prefrontal cortex and hippocampus of male and female offspring from obese mothers, in a sex- and region-dependent manner (da Silva Rodrigues et al., 2024).

The pattern of neuroinflammation observed in the offspring was paralleled by behavioural perturbations, reporting increased anxiety-like behaviours in both sexes, and a sexually dimorphic impairment in social behaviours; males revealed social memory deficits while females reported disturbed social preference. CBD was able to restore most of these behavioural disturbances probably in relation to its anti-inflammatory effect and modulation of the CB_1 expression level (Rodrigues et al., 2024). These results support that maternal exposure to an obesogenic diet has a significant impact on mental health of the children, disrupting a correct development of brain networks, favouring the onset of psychiatric disorders, such as attention deficit hyperactivity disorder, autism spectrum disorder, anxiety or depression (Cirulli et al., 2020). In this context, the modulation of the

endocannabinoid system and the attenuation in neuroinflammation by CBD appears extremely helpful to mitigate maternal obesity-induced behavioural and neurobiological alterations.

Lastly, exposure to an aversive environment during prenatal development can lead to persistent changes in the offspring, observable even during the adulthood. For this reason, the same authors have investigated perinatal maternal obesity-associated changes in metabolic, inflammatory and behavioural parameters in adult offspring (from Postnatal Day 70), to assess the persistency of these alterations even when animals reached a fully mature phenotype (Rodrigues et al., 2025).

Regarding metabolic parameters, CBD (50 mg·kg^{-1}, oral gavage, for 3 weeks) decreased plasma glucose levels in adult male and female rats from obese mothers and reduced the elevated plasma LPS levels only in females (Rodrigues et al., 2025), partially resembling what observed in the previous studies conducted in juvenile animals.

In the brain, hypothalamic inflammation was partially attenuated by CBD treatment, which resulted in a decreased expression of glial fibrillary acidic protein selectively in male rats. In the prefrontal cortex, CBD restored the increased expression levels of IBA-1 and the levels of the endocannabinoids AEA and 2-AG in male rats, probably an attempt to dampen an overactive endocannabinoid signalling. Finally, in the hippocampus, CBD lowered the expression of IBA-1 in male offspring and expression of glial fibrillary acidic protein in both male and female rats from obese dams (Rodrigues et al., 2025).

Analysing behavioural alterations, CBD decreased anxiety-like behaviour in female and male rats from cafeteria-fed mother, as determined by enhanced time spent in the open arms of the elevated plus maze, and restored proper social memory but only in male animals (Rodrigues et al., 2025).

Altogether, these works reveal that maternal obesity can generate remarkable damages in the offsprings' health, which show metabolic, neuroinflammatory and behavioural alterations. They also show a link between peripheral and CNS damages associated to maternal obesity, as peripheral inflammatory mediators can reach the hypothalamus, start a process of neuroinflammation that disrupts energy homeostasis and extend to multiple brain regions affecting critical neuronal functions. However, these aberrations can be attenuated by CBD treatment, which restores most of the impairments apparently in a sex-dependent manner, and importantly with more pronounced benefits observed with early-life interventions compared with treatment during adulthood.

Figure 2 summarizes the beneficial effects induced by CBD administration in animal models of obesity and metabolic syndrome and in the offspring born from obese dams.

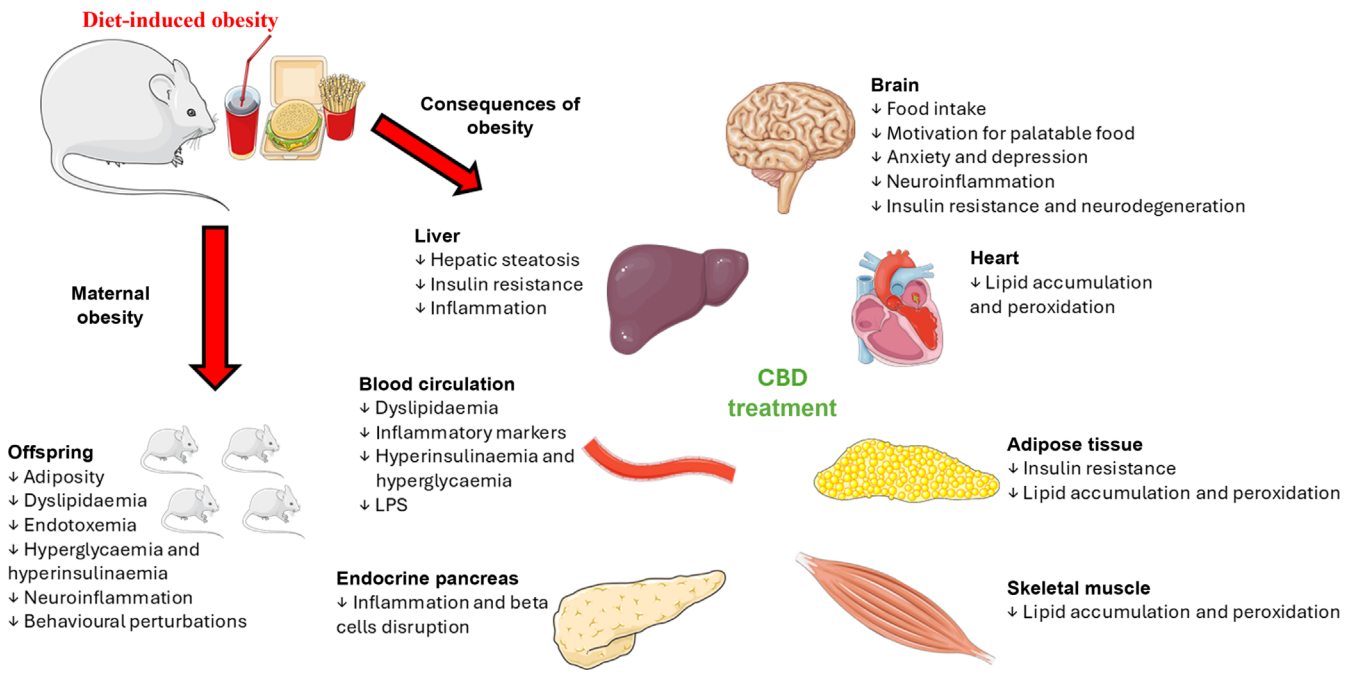

FIGURE 2 The beneficial effects induced by CBD-based interventions in animal models of diet-induced obesity (DIO). Administration of CBD in animal models has revealed positive outcomes in multiple aspects of obesity and metabolic syndrome. CBD has anorexigenic effects and decreases the motivation to consume palatable food. It also improves mood and decreases neuroinflammation and neurodegeneration. CBD affects lipid metabolism and contrasts insulin resistance in several organs. It has been demonstrated that CBD intervention can also ameliorate health damages observed in the offspring from obese dams, restoring metabolic, behavioural and neuroinflammatory parameters. CBD, cannabidiol; DIO, diet-induced obesity; LPS, lipopolysaccharide. Parts of the figure (mice and organs illustrated) were drawn with pictures generated by Servier medical art (http://smart.servier.com/). Servier medical art by Servier is licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

5.4 | CBD and the gut microbiota in animal models of metabolic syndrome

While the effects of CBD on food intake regulation, glucose and lipid metabolism and inflammation, in the context of obesity and metabolic syndrome have been more extensively investigated, surprisingly, its influence on the gut microbiota has been poorly evaluated in this research field.

The gut microbiota is a complex community of microorganisms that inhabits the gastrointestinal tract and has established a symbiotic relationship with the host individual. *Bacteroidetes* and *Firmicutes* represent the most dominant bacterial phyla populating the gut microbiota and their ratio has been usually considered a hallmark of obesity, condition supposed to increase the amount of *Firmicutes*, at expense of *Bacteroidetes*. However, this parameter has been the subject of much controversy with many studies reporting conflicting results (Magne et al., 2020).

The impact of CBD on *Bacteroidetes/Firmicutes* abundance is not well understood. A study, performed in male mice fed a high-fat–cholesterol diet to generate fatty liver disease, tested the effect of CBD supplementation in the diet (2.39 $mg \cdot kg^{-1}$) on multiple metabolic parameters, including the microbiota. high-fat–cholesterol diet increased the abundance of *Bacteroidetes* and *Deferribacteres*, with CBD being able to decrease only *Deferribacteres*. High-fat–cholesterol diet also decreased *Firmicutes*, whose amount was conversely restored by CBD supplementation, lowering the *Bacteroidetes/Firmicutes* ratio. This was associated to a general improvement in metabolic syndrome parameters with CBD supplementation (Gorelick et al., 2022). A similar outcome on *Bacteroidetes/Firmicutes* relative abundance has been reported in another study, in which a CBD-rich cannabis extract (5 $mg \cdot kg^{-1}$) was administered to mice fed a high-fat–cholesterol diet. Here, administration of the CBD extract decreased *Bacteroidetes* abundance in high-fat–cholesterol diet-fed mice, reducing the *Bacteroidetes/Firmicutes* ratio, but in this case, the general impact of CBD extract on metabolic syndrome parameters was negative (Assa-Glazer et al., 2020).

The fact that CBD decreased the *Bacteroidetes/Firmicutes* ratio contrasts with its hypothesized changes in obesity. However, it could be interpreted considering the CBD's anti-inflammatory effects and activity against metabolic LPS-associated endotoxemia. Indeed, CBD has been reported by studies previously mentioned (He, Shi, Wu, et al., 2024; Huang et al., 2019; Rodrigues et al., 2023) to attenuate the levels of LPS and the LPS-induced inflammatory cascade in animal models of HFD. LPS is a pro-inflammatory molecule produced by Gram-negative bacteria, whose main group is the phylum *Bacteroidetes* (Lukiw, 2016; Magne et al., 2020). Under an obesogenic diet, the increased gut permeability allows infiltration of the endotoxin LPS that reaches the bloodstream and starts a diffuse inflammatory response (endotoxemia) (Mohammad & Thiemermann, 2020). Therefore, a hypothesis could be that the reduction in *Bacteroidetes* abundance might possibly lead to a reduction in LPS levels and its consequent disruptive effects.

Another work (Eitan et al., 2024) reported that mice fed a HFD showed reduced richness and diversity of the microbiota, but in this case, they presented an increased abundance of *Firmicutes* compared with *Bacteroidetes*, in contrast to the previous studies (Assa-Glazer et al., 2020; Gorelick et al., 2022). Also, these parameters were not affected by oral treatment with a CBD-rich extract (Avidekel, 30% CBD, 5 weeks at 10 $mg \cdot kg^{-1}$ plus 5 weeks at 30 $mg \cdot kg^{-1}$) (Eitan et al., 2024).

Thus, information arising from animal models of metabolic syndrome regarding the influence of CBD on *Firmicutes* and *Bacteroidetes* abundance is inconclusive, considering the variability of this parameter across the studies performed, and divergent findings obtained with CBD administration.

Interestingly, in the study of Gorelick et al. (2022), the supplementation of the high-fat–cholesterol diet with CBD enhanced the levels of *Clostridia*, *Ruminococcaceae* and *Bilophila* and attenuated the increase in the genus *Mucispirillum* and in the species *Mucispirillum schaedleri*. The increase in *Ruminococcaceae* induced by CBD is particularly interesting and could explain the positive influence on metabolic parameters with the supplementation (Gorelick et al., 2022). Indeed, it could be associated to a higher production of short-chain fatty acids (Xie et al., 2022), in particular butyric acid, metabolites that have demonstrated beneficial effects on lipid and glucose metabolism, immunity and inflammation, in animal models of metabolic syndrome (Yu et al., 2025).

We are currently not aware of other works conducted in preclinical diet-induced obesity and/or metabolic syndrome models. Therefore, information regarding the ability of CBD to positively influence these conditions through the modulation of the gut microbiota is something that needs to be better explored. We believe that this research field deserves further investigation, because other animal models proved that CBD positively remodels the gut microbiota composition and contextually exerts beneficial outcomes in pathologies such as cocaine addiction (Chesworth et al., 2024), epilepsy (Gong et al., 2022) and Alzheimer's disease (Oliveira et al., 2022).

6 | HUMAN STUDIES INVESTIGATING THE EFFECT OF CBD-BASED INTERVENTIONS ON METABOLIC PARAMETERS

Despite the promising therapeutic potential of CBD in the field of obesity and metabolic syndrome, highlighted by the preclinical studies mentioned above, only a few clinical studies have been conducted so far to evaluate whether CBD might affect metabolic parameters in humans.

One of these studies demonstrated that oral twice-daily CBD treatment (200 $mg \cdot day^{-1}$, for 13 weeks) failed to achieve the expected endpoints in a randomized, double-blind, placebo-controlled, parallel-group study in participants with non-insulin-treated type 2 diabetes, being not able to affect lipids and glycaemic parameters, vascular functions and inflammatory markers when compared with placebo. However, compared with baseline, CBD decreased plasma resistin

and increased **gastric inhibitory peptide (GIP)** levels, even though these hormonal changes did not produce improvements in glycaemic parameters (Jadoon et al., 2016). Resistin is an adipose-tissue-derived polypeptide which is believed to play a causative role in inflammation, insulin resistance and obesity (Tripathi et al., 2020), while GIP is an incretin hormone secreted by endocrine k cells of the duodenum, with insulinotropic properties and with high interest in the field of obesity, considering the powerful anti-diabetic and weight-reducing activities exerted by the dual GLP-1/GIP receptor agonist tirzepatide (Sinha et al., 2023). The beneficial influence of CBD on these parameters potentially opens a new line of research that should more deeply explore the interaction of this phytocannabinoid with the physiology of peripheral metabolic hormones, such as GLP-1 and GIP, and dedicated preclinical studies should be conducted in the future.

In a second study, when healthy volunteers received CBD (45 or 90 mg) in two different oral formulations, one containing CBD encapsulated with American ginseng, *Ginkgo biloba* and organic hemp oil (TurboCBD™), which increases the absorption of CBD, and the other containing only CBD encapsulated with hemp oil, no effect on plasma insulin and glucose levels was found (Patrician et al., 2019). However, this study was conducted only in male healthy volunteers, with impossibility to explore the effect of the oral CBD administration in a pathological condition and to evaluate sex-differences in response to CBD ingestion (Patrician et al., 2019).

Differently, in a more recent study, 30 mg CBD administered right after the ingestion of a mixed macronutrients meal decreased plasmatic insulin and triglycerides concentrations in the first half-hour of the postprandial state, in individuals with a BMI of 25 $kg \cdot m^{-2}$ or higher (overweight or obese) (Abbotts et al., 2022). In the same work, it was proved that food ingestion prior to CBD administration slows the T_{max} and increases the C_{max} and AUC of CBD, compared with administration without prior food consumption (Abbotts et al., 2022). These results suggest that CBD can improve the early physiological response to food consumption of the organism, influencing insulin and triglycerides levels, and that the prior ingestion of a meal is recommended to obtain better gut absorption of CBD, reaching higher plasmatic levels and consequently, therapeutic activity.

Lastly, Afshar et al. conducted a phase I randomized, double-blind, placebo-controlled study in subjects with type 2 diabetes to investigate the effect of a sublingual spray (CBDEX1®) containing a 10:1 ratio of CBD and Δ^9-THC, on glycaemic and lipid parameters. The spray was administered twice daily (100 μg/10 μg CBD/Δ^9-THC per puff, two puffs each time) over a period of 8 weeks and led to significant improvements compared with placebo. Indeed, administration of the spray significantly decreased fasting blood glucose and haemoglobin A1C, improved the oral glucose tolerance, decreased insulin secretion and the HOMA-IR value and lowered the plasma levels of total cholesterol, triglycerides and LDL, indicating a general improvement in lipid and glucose profile in type 2 diabetic patients (Afshar et al., 2022).

It is important to note that CBD treatment was well tolerated and did not cause significant adverse effects in any of the clinical trials conducted. Different factors, including the way CBD is administered (oral versus sublingual) and dosed, the length of treatment, prior food consumption and the characteristics of the study participants, may be responsible for inconsistent results across studies. According to Afshar et al. (2022), the sublingual route of administration might be the preferred one to overcome the poor oral bioavailability of CBD, allowing to extensively avoid the first-pass metabolism, leading to a more rapid onset of action and improvement in treatment outcomes.

7 | THE INFLUENCE OF CBD ON EATING BEHAVIOUR-RELATED PATHOLOGIES: FOCUS ON PSYCHIATRIC CONDITIONS ASSOCIATED TO OBESITY AND MANAGEMENT OF EATING DISORDERS

7.1 | Can CBD alleviate behavioural disturbances associated to obesity?

The obesity status is associated to systemic inflammation and oxidative stress that affects brain functioning, resulting in neuroinflammation and behavioural disturbances (Lopresti & Drummond, 2013). CBD is known to be anti-inflammatory and anti-oxidative and to exert antidepressant, anxiolytic, neuroprotective and anti-psychotic effects (Kirkland et al., 2022; Mandolini et al., 2018; Melas et al., 2021), potentially helpful in treating psychiatric conditions often observed in obese individuals, such as mood disorders and dementia. Moreover, as discussed in Section 5.3, it was demonstrated that CBD administration could improve behavioural disturbances emerged in the offspring born from obese dams, such as anxiety-like behaviour and impairment in social behaviours, and the related neuroinflammatory status (da Silva Rodrigues et al., 2024; Rodrigues et al., 2023; Rodrigues et al., 2025). This might suggest that CBD has a potential dual role in ameliorating the obesity status, targeting both metabolic and behavioural alterations.

In a recent study by Marçal et al., the effect of acute and subchronic (8 days) treatment with CBD (30 $mg \cdot kg^{-1}$, i.p.) was evaluated on behavioural disturbances induced by feeding a high-carbohydrate diet for 12 weeks in BALB/c mice. Animals fed the high-carbohydrate diet showed compulsive-like and anxiety-like behaviours, as determined by the number of marbles buried and by the latency to eat in the marble burying and in the novelty-suppressed feeding test, respectively. Acute treatment with CBD decreased compulsive-like but not anxiety-like behaviour, while subchronic administration improved both conditions (Marçal et al., 2022). The authors did not investigate the potential neurobiological mechanisms behind the behavioural effects of CBD but hypothesized that this could be related to the neuroinflammatory actions of CBD (Marçal et al., 2022). The results of this work are consistent with previous findings evidencing antidepressant and anxiolytic effects of CBD (30 $mg \cdot kg^{-1}$, i.p., daily for 2 weeks) in streptozocin-induced diabetic rats, suggesting that CBD may be effective in managing behavioural disturbances observed in people with obesity and/or metabolic impairments (Chaves et al., 2020,

2021). Interestingly, the anxiolytic and antidepressant effects of CBD in diabetic rats were prevented by pre-treatment with the 5-HT_{1A} antagonist **WAY-100635** (Chaves et al., 2021). The 5-HT_{1A} receptor has been identified as a significant pharmacological target of CBD that appears to act as agonist of this receptor, mechanism linked to anxiolytic and anti-depressive outcomes (Alexander et al., 2025). It has also been demonstrated that the 5-HT_{1A} receptor contributes to the anorexigenic effect of CBD (Scopinho et al., 2011). Consequently, the 5-HT_{1A} receptor seems to be a key target of CBD in regulating eating behaviour and alleviating psychiatric conditions co-observed with metabolic impairments. However, this assumption is somewhat speculative and requires direct investigation in preclinical models of obesity.

Considering the evidence of improved mood with CBD administration during the obesity status, it is not possible to rule out the potential application of CBD in another condition observed in obese individuals, that is, the onset of withdrawal-like symptoms when subjects experience abstinence from palatable foods. Obese individuals undergoing restricted dietary regimens and abstaining from eating rewarding food can experience negative emotional states leading to behavioural manifestations, like anxiety and depression. These conditions are frequently responsible for subsequent relapse to palatable food intake, disruptions of dietary restraint and stress-induced overeating (Parylak et al., 2011). Pharmacological inhibition of the enzyme FAAH, which results in increased *N*-acylethanolamide tone, completely reversed the abstinence-induced anxiety-like and depressive-like behaviours in obese rats exposed to prolonged abstinence from a cafeteria diet, while concomitantly restoring neurobiological changes in the endocannabinoid system and monoamines levels in several brain regions (de Ceglia et al., 2023; de Ceglia et al., 2024). It is known that CBD has the ability to enhance the endogenous AEA signalling through the inhibition of the enzyme FAAH and CBD treatment can increase serum levels of AEA, **palmitoylethanolamide** and **oleoylethanolamide**, and improve psychotic symptoms in humans with schizophrenia (Bisogno et al., 2001; Leweke et al., 2012), revealing the clinical relevance of this pharmacological mechanism. Based on this considerations, future preclinical studies should be conducted to investigate whether CBD administration could be effective in managing anxiety and depression generated by abstinence from palatable food consumption and if the modulation of the endogenous AEA signalling exerted by CBD is the key mediator of this effect.

7.2 | Beyond obesity and metabolic syndrome: is there a role for CBD in binge eating?

7.2.1 | Binge eating, binge eating disorder (BED) and the concept of 'food addiction'

As previously anticipated, CBD does not solely influence feeding behaviour through its anorexigenic effect, but modulates the activity of the reward system, and affects the non-homeostatic aspect of eating behaviour, representing a candidate drug for bingeing-related eating disorders.

Binge eating is a central trait of many eating disorders, such as bulimia nervosa, binge-purge type of anorexia nervosa, and BED, and is characterized by eating large amounts of food within a relatively short period of time, experiencing loss of control toward eating behaviour. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision, individuals affected by BED engage in recurrent binge eating episodes, but without any form of compensatory behaviour, as observed in bulimia nervosa. These episodes are characterized by a sense of lack of control overeating, by a marked distress regarding binge eating, and they have to occur at least once a week for 3 months to fulfil the diagnostic criteria for binge eating disorder (American Psychiatric Association, 2013; Giel et al., 2022).

Binge eating and obesity share some common behavioural and neurobiological substrates with drug addiction, such as the diminished control during consumption, impaired ability to reduce the quantity and frequency of consumption and continued consumption despite negative consequences (Gearhardt et al., 2011). Extensive research has revealed the existence of overlapping neurobiological mechanisms driving both drug and food seeking (Botticelli et al., 2020; Volkow et al., 2017), and palatable foods can increase dopamine signalling in the reward system and lead to a pattern of neuronal activation in the same way that drugs of abuse do (Gearhardt et al., 2011; Kenny, 2011). Considering the similarities existing between substance use disorder and pathological overeating, the concept of 'Food Addiction' has gained more interest in the last years. This concept, based on the observation that over consumption of food resembles for some aspects substance abuse and that palatable foods can generate addictive-like brain changes, binge-like eating and withdrawal symptoms, led to the validation of the Yale Food Addiction Scale, a psychometric tool that identifies individuals suffering of addictive-like behaviours toward food (Gearhardt et al., 2009). Interestingly, there is evidence that higher 'Food Addiction' scores are correlated to the presence of BED and that they also correlate to a more severe BED-related psychopathology (Carter et al., 2019). However, the concept of 'Food Addiction' is the subject of much debate and some concern still exists about its clinical validity and use. For example, some limitations of the 'Food Addiction' model are that addictive substances in palatable foods are still undiscovered, there is not a convincing demonstration of what neurobiological changes are associated to 'Food Addiction' and translation of data from intermittent-access animal models to humans is challenging, as discussed in Fletcher and Kenny (2018). Therefore, the interpretation, clinical validity and the use of the term 'Food Addiction' is something that still needs a better understanding and is not completely accepted by the totality of the scientific community.

7.2.2 | CBD and its potential role in binge eating

The endocannabinoid system, through the modulation of the release of various neurotransmitters (e.g. **GABA**, **glutamate** and dopamine), has been hypothesized as a common mediator and potential target in

drug addiction, pathological overeating (D'Addario et al., 2014) and in the management of diet-induced obesity (de Ceglia et al., 2025). In this context, there are studies that support a role for CBD in the treatment of these conditions.

Differently from Δ^9-THC, CBD has a low psychotropic nature, does not display hedonic properties and does not generate drug seeking, not behaving as an addictive substance (Hurd et al., 2015). However, preclinical and clinical studies of addiction have revealed the ability of CBD to ameliorate the behavioural manifestations typical of substance use disorder, such as opioid-withdrawal symptoms (Kudrich et al., 2022), addictive behaviours induced by cocaine and methamphetamine (Hay et al., 2018; Lujan et al., 2018) and alcohol consumption (Viudez-Martinez et al., 2018), via mechanisms involving the receptors CB_1, CB_2, TRPV1 and 5-HT_{1A} (Galaj & Xi, 2020).

Based on these findings, Bi et al. conducted a study to determine whether administering CBD could reduce sucrose self-administration, as it previously did with alcohol, cocaine and methamphetamine (Hay et al., 2018; Lujan et al., 2018; Viudez-Martinez et al., 2018). The authors found that systemic CBD administration dose-dependently decreased sucrose self-administration in mice and rats under fixed- and progressive-ratio schedules of reinforcements. CBD was able to decrease sucrose self-administration in WT and $CB_1^{-/-}$ mice but not in $CB_2^{-/-}$. This effect was enhanced by pretreatment with the CB_1 antagonist **AM251**, blocked by the CB_2 antagonist AM-630 and mimicked by the CB2 agonist JHW133 (Bi et al., 2020). Therefore, it was assumed that CBD attenuates the motivation to consume sucrose through a mechanism involving CB_1 inhibition and CB_2 stimulation. Given its crucial role in CBD capacity to reduce sucrose reward (Bi et al., 2020) and food intake (Ignatowska-Jankowska et al., 2011), the CB_2 receptor may contribute to the potential benefits of CBD in treating binge eating behaviour.

The CB_2 receptor has been demonstrated implicated in the modulation of dopamine signalling in the mesolimbic system, with relevance to drug addiction. CB_2 receptor is expressed on ventral tegmental area dopaminergic neurons and on terminals of dopamine neurons in the nucleus accumbens, it is up-regulated by cocaine self-administration and its stimulation attenuates ventral tegmental area dopamine neurons firing and release in the nucleus accumbens and dopamine-related behaviours (Aracil-Fernandez et al., 2012; Zhang et al., 2014, 2015, 2017). Considering that he CB_2 receptor appears a critical mediator of CBD influence on drug and food reward and that systemic injection of CBD significantly attenuated the cocaine-evoked increase in extracellular dopamine in the nucleus accumbens (Galaj et al., 2020), it is conceivable that CBD could dampen the activation of the reward system even in response to palatable food, revealing therapeutic potential for the treatment of binge eating. Additionally, a recent study found that pharmacological activation of the CB_2 receptors effectively reduces binge-like eating in mice (Rodríguez-Serrano & Chávez-Hernández, 2025) and a non-synonymous polymorphism of the *CNR2* gene has been linked to diet-induced obesity in a human population (Ishiguro et al., 2010).

Another molecular target of CBD recently identified is the **orexin 1 (OX_1) receptor**, discovery that may further increase the clinical significance of CBD for the management of drug addiction, obesity and diet-induced obesity.

CBD selectively binds to the OX_1 receptor, displacing orexin-A from its binding and behaving as an antagonist of this receptor (Vitale et al., 2021). This pharmacodynamic property of CBD could represent a potential mechanism underlying CBD effects on pathological overeating, because the OX_1 receptor signalling strongly promotes seeking of palatable foods, while pharmacological blockade of the OX_1 receptor prevents binge-like eating in a well-characterized animal model of binge eating (Piccoli et al., 2012; Steiner et al., 2024). Thus, whether this established interaction of CBD with the OX_1 receptor is clinically meaningful for the treatment of binge eating behaviour should be the subject of future research.

Figure 3 summarizes all proposed pharmacological targets of CBD that have been hypothesized in this review to be responsible for its anorexigenic effect, ability to decrease the motivation to consume palatable food and the amelioration in behavioural disturbances arising from the consumption of HFD.

8 | FUTURE DIRECTIONS AND CONCLUDING REMARKS

8.1 | Limitations of the current research and future directions

The evidence that CBD might represent a useful approach to prevent and/or treat conditions such as obesity, metabolic syndrome and binge eating is promising and deserves further investigation. However, there are limitations that it is important to highlight and that should be considered the fundamental bases orienting innovative and future studies.

First, the pharmacokinetics of CBD still represents a big issue in its clinical usefulness. The lipophilic nature of CBD clearly limits the drug bioavailability, but there are strategies potentially helpful to counteract the intense first-pass metabolism. Indeed, administration of CBD with food rather than in a fasted state is recommended to promote more bioavailability. Also, the sublingual route of administration proved to be the preferred one to achieve better pharmacokinetic and pharmacodynamic outcomes. It is important to state that, given the high interest in CBD pharmacology, research is being conducted to formulate innovative delivery systems to overcome the current issues regarding CBD administration.

Second, the preclinical studies discussed in this review have been conducted almost exclusively in male animals. Research on female rodents in the context of food intake, metabolic syndrome and diet-induced obesity focused on CBD effects is lacking, and this represents a critical gap that needs to be filled to highlight a potential sexual dimorphism in response to CBD administration. This is extremely important given that differences in the pharmacokinetic profile of CBD have been reported between male and female rodents and humans.

Third, despite many biological targets have been highlighted as mediators of CBD anorectic effects, impact on glucose and lipid

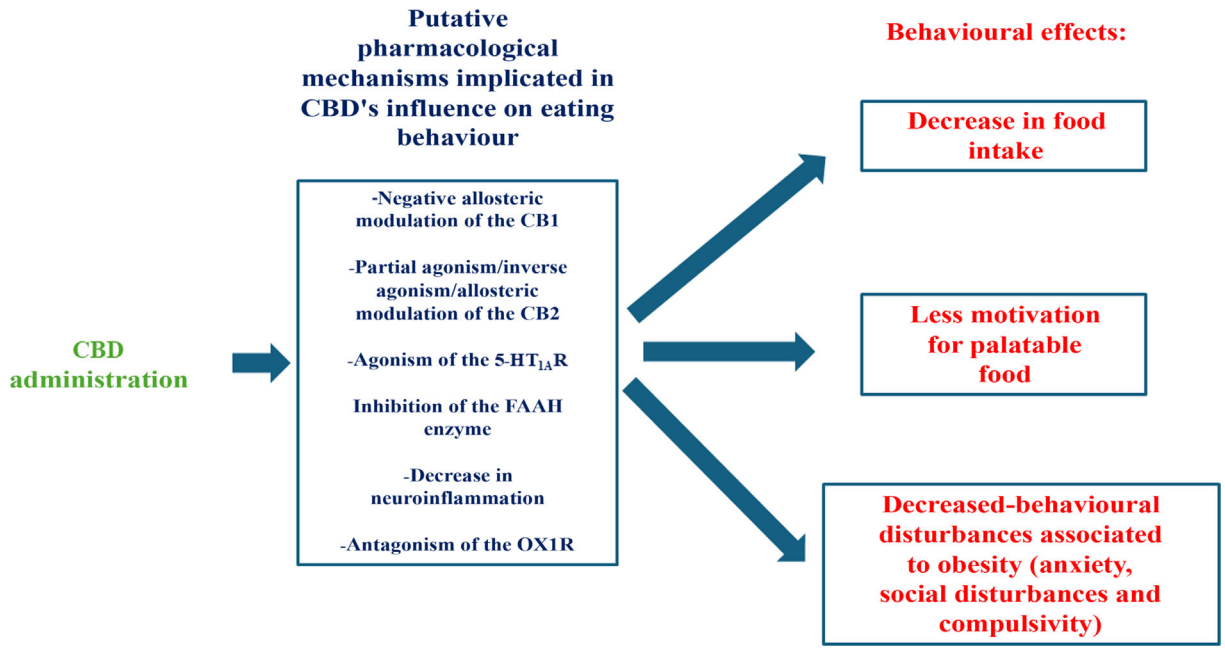

FIGURE 3 Effect of CBD administration on food intake and eating behaviour-related psychopathologies. Animal models revealed that the administration of CBD leads to anorexigenic effects and to a decrease in the motivation to consume palatable food. Also, CBD can improve behavioural disturbances arising from the ingestion of palatable foods and frequently observed in obese individuals. These effects might underlie a potential role for CBD in the treatment of obesity and binge eating behaviour. CBD appears to influence food intake via negative allosteric modulation of the CB_1, and through the modulation of the CB_2 receptor, whose interaction with CBD is still not completely understood. CBD has been reported to act as a partial agonist, inverse agonis, or to allosterically modulate the activity of CB_2, and antagonists of the CB_2 receptors block the anorexigenic effect of CBD. Also, CBD can inhibit the enzyme FAAH, increasing the levels of AEA; act as agonist of the 5-HT_{1A} receptor (R); and exert strong anti-inflammatory properties, counteracting neuroinflammation, mechanisms linked to amelioration in behavioural disturbances observed in obesity. Recent findings additionally suggest that CBD can antagonize the OX_1R, pharmacological activity that could have strong relevance for motivated behaviours. 5-HT_{1A} receptor; AEA, anandamide; CB_1, cannabinoid receptor type 1; CB_2, cannabinoid receptor type 2; CBD, cannabidiol; FAAH, fatty acid amide hydrolase: OX_1R, orexin 1 receptor.

metabolism and inflammation, the influence of CBD on important physiological mechanisms implicated in obesity is not clear. For example, to the best of our knowledge, there is no evidence of investigations focused on the effect of CBD on incretin hormones physiology. However, in the clinical study of Jadoon et al. (2016) in type 2 diabetic patients, treatment with CBD led to an increase in GIP levels compared with the baseline. Given the current interest in the hormones GIP and GLP in obesity, and the pharmacological relevance of the agonists of their receptors, future preclinical research should investigate the impact of CBD on GIP/GLP-1 levels, to unveil a potential incretin-sensitizing effect of this cannabinoid.

Fourth, there is not a clear understanding of the hypothalamic mediators of CBD anorectic properties. To date, it seems that CBD can lower the expression of orexigenic neuropeptides in the hypothalamus, as reported in an in vitro study (di Giacomo et al., 2020), but these data are preliminary and more investigation is required. CBD interacts with CB receptors and other targets in the brain to reduce food intake, but the exact hypothalamic mechanisms underlying these effects are still not clear.

Fifth, most of the studies here presented have reported beneficial influences of CBD on food intake and metabolic parameters, but there are also negative outcomes obtained in some works. It is important to critically analyse inconsistency across studies, focusing on the experimental approaches, such as the use of different animal models or species, or differences in CBD formulations. For example, in some works, they used pure CBD, while others tested CBD-rich cannabis extracts. The contribution of other components in the extracts to the outcomes reported on metabolism cannot be completely ruled out. Contextually, the use of pure CBD should be preferred, when possible, to have more precise evaluation of its biological activity and to exclude potential confounding factors.

Lastly, there is no evidence of the effect of CBD on a well-characterized animal model of eating disorders (such as those used to mimic anorexia nervosa or BED) so far. This is something that should be investigated in the nearby future, given the promising potential of CBD in this field, as demonstrated by its ability to modulate the brain reward system and to reduce the non-homeostatic consumption of palatable food.

8.2 | Conclusions

CBD is the most abundant phytocannabinoids of the *C. sativa* plant and is nowadays the subject of great interest in the biomedical

research. Preclinical studies have investigated the effect of CBD in the context of eating behaviour, showing that it might reduce the consumption of food with mechanisms involving the CB_1, CB_2 and the $5\text{-}HT_{1A}$ receptor. In diet-induced obesity models, CBD treatment exerted anorexigenic effects, improved metabolic impairments, such as insulin resistance, dyslipidaemia and liver steatosis, typical of metabolic syndrome, while showing anti-inflammatory and anti-oxidative properties. CBD also ameliorates psychiatric symptoms and neuroinflammation induced by the obesity status. These beneficial effects are accompanied by a relatively high safety profile that could encourage further clinical investigations in the treatment of obesity.

Nowadays, CBD-based products are very popular in the marketplace and are widely available in different forms, and the US FDA has expressed concerns about the proliferation of CBD products that claim to be useful for medical purposes but are not approved by the FDA (US FDA, 2024).

To validate the use of these products in obesity and metabolic syndrome, further preclinical and clinical studies will be strongly necessary.

It is of high interest that CBD, despite not possessing a psychotropic nature and not behaving as a drug of abuse like Δ^9-THC, can strongly modulate the activity of the reward system and showed positive outcomes in the field of drug addiction, for example, in attenuating opioid-withdrawal related symptoms. Emerging evidence supports the idea that the anti-addictive properties of CBD could be translated to pathological overeating, given the existence of similarities between drugs of abuse and palatable food. Therefore, CBD-based interventions need future investigation in well-characterized animal models of binge eating.

8.3 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24 (Alexander, Christopoulos, et al., 2023; Alexander, Cidlowski, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Amarosi, et al., 2023a; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Annett, et al., 2023b; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Beuve, et al., 2023c; Alexander, Kelly, et al., 2023; Alexander, Mathie, et al., 2023).

AUTHOR CONTRIBUTIONS

L. Botticelli: Conceptualization; writing—original draft; writing—review and editing; visualization. **E. Micioni Di Bonaventura:** Conceptualization; writing—original draft; writing—review and editing; visualization. **G. Einaudi:** Conceptualization; writing—original draft; writing—review and editing; visualization. **G. Provensi:** Writing—review and editing; supervision; visualization. **A. Costa:** Writing—review and editing; supervision; visualization. **C. D'Addario:** Writing—review and editing; supervision; visualization. **C. Cifani:** Writing—review and editing; supervision; visualization. **M. V. Micioni Di Bonaventura:** Writing—review and editing; supervision; visualization. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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