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Major approaches to cannabidiol in the treatment of binge eating and obesity: a systematic review

Laís Lopes Mascarenhas de Lacerda[1]*, Darwin dos Santos Ribeiro[2], Valdir Cerqueira de Sant'Ana Filho[1], Murilo Costa Safira Andrade[1], Joaquim Paulo Castro de Santana[1]

[1] Institute of Nutrology, Feira de Santana, Bahia, Brazil.
[2] Empresarial Thygunan, João Pessoa, Paraíba, Brazil.

*Corresponding Author: Dra. Laís Lopes Mascarenhas de Lacerda.
Institute of Nutrology, Feira de Santana, Bahia, Brazil.
E-mail: laislmlacerda@gmail.com
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Abstract

Introduction: Obesity represents a multifactorial disease that causes serious public health problems. There are more than 2.50 billion overweight and obese people in the world, and Brazil is in fifth place in the world ranking. In this context, a factor associated with eating disorders is anxiety, which affects 33.7% of the general population. In this sense, cannabidiol (CBD) was identified 50 years ago and has effects that can change mood, sensation, perception, tension, appetite, and pain. Also, CBD showed anxiolytic, antipsychotic, neuroprotective, anti-inflammatory, and antiemetic properties. **Objective:** It was to analyze, through a systematic review, the main considerations and results in animal and human models of the use of cannabidiol in anxiety and obesity. **Methods:** The model followed for the systematic review was PRISMA. The search strategy was performed in PubMed, Embase, Ovid and Cochrane Library, Web Of Science, Science Direct Journals (Elsevier), Scopus (Elsevier), and OneFile (Gale) databases. **Results:** In the context of anxiety and binge eating and the consequent increase in the incidence of obese people, the activation of CB1 receptors improves feeding, modulating the activity of hypothalamic neurons and, subsequently, the release of orexigenic and anorexigenic neuropeptides. Thus, in obesity, the endocannabinoid system (ECS) is generally down-regulated in central and peripheral tissues, as indicated by high and/or overexpression of the CB1 receptor. Therefore, CBD is beneficial for anxiety-related disorders. Thus, CBD has been shown to have anxiolytic, antipsychotic, and neuroprotective properties. **Conclusion:** Growing evidence indicates that CBD acts as an antipsychotic and anxiolytic, and several reports suggest neuroprotective effects. Furthermore, CBD attenuates the harmful effects of trans-Δ9-tetrahydrocannabinol, both acutely and chronically, including psychotogenic, anxiogenic, and deleterious cognitive effects. This suggests that CBD may improve the disease trajectory of individuals with early psychosis and cannabis misuse in particular.

Keywords: Obesity. Cannabidiol. Anxiety. Food addiction.

Introduction

Obesity represents a multifactorial disease that causes serious public health problems. There are more than 2.5 billion overweight and obese people in the world **[1]**, and Brazil is in fifth place in the world ranking. The prevalence of disordered eating behaviors increases during adolescence and young adulthood, and estimates of involvement in at least one pathological eating behavior reach 60% for adolescents and adults **[2]**.

In this context, a factor associated with eating disorders is anxiety, which affects 33.7% of the general population, the high level of negative affect, and, in particular, the difficulty in managing anxiety **[3]**. Thus, anxiety disorders often precede the onset of disordered eating, and clinically significant anxiety persists after treatment of the eating disorder. Furthermore, higher levels of anxiety are associated with higher body mass index (BMI), longer duration of symptoms, and increased rates of compensatory behaviors, binge eating, and body dissatisfaction **[4,5]**.

In this sense, cannabidiol (CBD) was identified 50 years ago and its effects can change mood, sensation, perception, tension, appetite, and pain **[6,7]**. Also, CBD has shown anxiolytic, antipsychotic, neuroprotective, anti-inflammatory, and antiemetic properties **[8,9]**. However, the growing interest in the substance as medicine was renewed in the 1990s, with the discovery of cannabinoid receptors 1 and 2 (CB1 and CB2, respectively), endogenous ligands (endocannabinoids, N-arachidonoylethanolamine (anandamide/AEA), and 2 -arachidonoyl-glycerol (2-AG)) and enzymes as part of the endocannabinoid system (ECS) in the brain **[10]**.

The correct interaction between all these ECS elements plays an important role in the central nervous system (CNS) development, synaptic plasticity, motor control, memory, cognition, stress, emotional responses, reward and motivated behavior, appetite, pain, development, and homeostasis. **[11-13]**. Outside the brain, the ECS system is one of the crucial modulators of the autonomic nervous system, the immune system, the endocrine system, the gastrointestinal tract, the reproductive system, and microcirculation **[12]**. Endocannabinoids are one of the most important systems controlling excitatory and inhibitory neurotransmission as well as neuroplasticity. They serve as retrograde signaling messengers at GABAnergic and glutamatergic synapses, as well as modulators of postsynaptic transmission, interacting with other neurotransmitters, including dopamine. Endocannabinoids also participate in hypothalamic-pituitary-adrenal (HPA) axis modulation and stress regulation **[13]**. The synthesis of cannabinoid receptor agonists and antagonists, anandamide uptake blockers, and anandamide endocannabinoid degradation inhibitors have opened up new treatment strategies **[14]**.

Despite some setbacks in clinical trials related to drugs that act on the ECS, there is still much research being done to explore and establish therapeutic targets for cannabinoid receptor agonists and antagonists. One challenge is to develop drugs that only target cannabinoid receptors in a specific tissue, and another is to invent drugs that selectively act on cannabinoid receptors located outside the bloodbrain barrier. Furthermore, the development of suitable dosage forms with maximum efficacy and minimal adverse effects is also required. To successfully explore the therapeutic potential of ECS, it is imperative to further characterize the endocannabinoid system in terms of identifying the exact cellular location of cannabinoid receptors and their role as a "protective" and "disease-inducing" substance, with time-dependent changes in expression. of cannabinoid receptors **[11,14]**.

Also, CBD can alleviate hyperphagia without the side effects of rimonabant (e.g. depression and reduced insulin sensitivity). Thus, CBD is similar to peroxisome proliferator-activated receptor gamma agonists, helping to reduce adipocyte differentiation. Also, CBD has an immunomodulatory effect that helps slow down the progression of atherosclerosis induced by high glucose levels. It may also be effective in combating ischemic diseases, the most harmful complications of metabolic syndrome. However, it can only be administered as adjunctive therapy because of its low binding potency, and its inhibitory effect on cytochrome P450 enzymes should also be considered. However, it can be beneficially used in adjuvant therapy due to its few side effects **[15]**.

Therefore, the present study aimed to analyze, through a systematic review, the main considerations and results in animal and human models of the use of cannabidiol in anxiety and obesity.

Methods

Study Design

The present study followed a concise systematic review model, following the systematic review rules - PRISMA (Transparent reporting of systematic review and meta-analysis - www.prismastatement.org/).

Search Strategy and Search Sources

The literary search process was carried out from September to November 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, addressing scientific articles from various eras to the present day. The descriptors (MeSH Terms) were used: *Obesity*. *Cannabidiol*. *Anxiety*. *Binge eating*, and using Boolean "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, accuracy, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through the analysis of the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d)

Results and Discussion

Summary of Findings

As a corollary of the literary search system, a total of 154 articles were found that were submitted to the eligibility analysis and, then, 24 of the 58 final studies were selected to compose the results of this systematic review. The listed studies showed medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in types of study such as meta-analysis, consensus, randomized clinical trial, prospective and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with X 2=96.8%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 42 studies with a high risk of bias and 24 studies that did not meet GRADE.

Figure 1. Flowchart showing the article selection process.

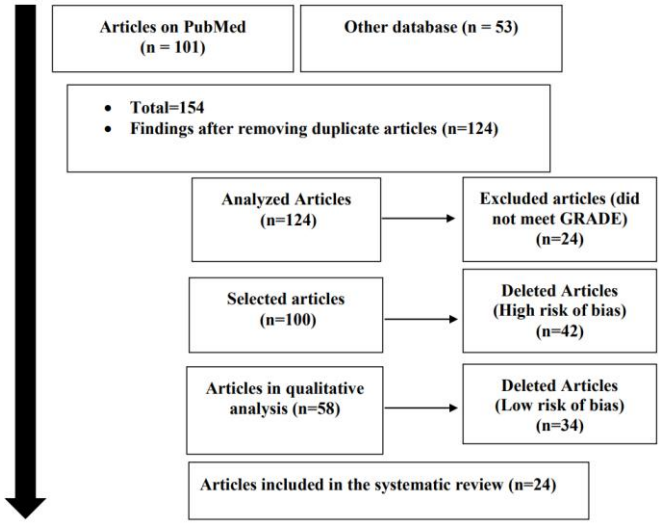
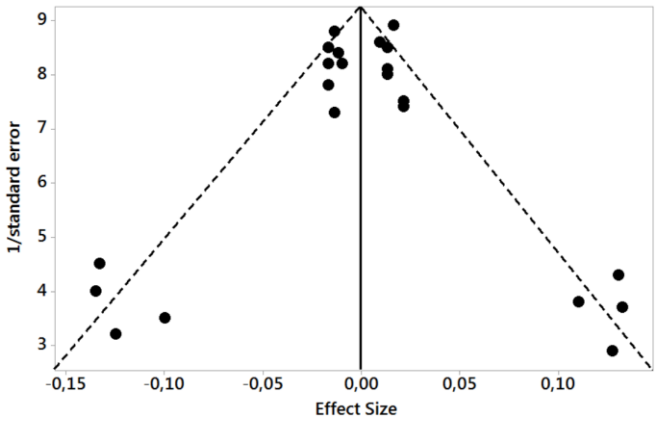


Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was indirectly determined by the inverse of the standard error (1/Standard Error). This chart had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes (lower precision) that are shown at the bottom of the chart and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=24 studies).



Source: Own authorship.

Main Evidence

In the context of anxiety and binge eating and the consequent increase in the incidence of obese people, the activation of CB1 receptors improves eating, modulating the activity of hypothalamic neurons and, subsequently, the release of orexigenic and anorexigenic neuropeptides **[11,16]**. Furthermore, CB1 receptor signaling affects reward and reinforcement circuits in the mesolimbic system, leading to a preference for highly palatable foods **[12,17]**.

Furthermore, the CB1 receptor is also present in peripheral organs that are important in controlling metabolism and activating anabolic pathways, favoring energy storage **[18]**. In white adipocytes, activation of the CB1 receptor increases fatty acid synthesis, improves triglyceride accumulation, and reduces lipolysis, whereas, in brown adipose tissue, the CB1 receptor counteracts the uncoupling of respiration from ATP production. Furthermore, the CB1 receptor enhances hepatic lipogenesis and drives defective oxidative metabolism through impaired mitochondrial oxidative phosphorylation in skeletal muscle **[18]**.

Thus, in obesity, the endocannabinoid system (ECS) is generally down-regulated in central and peripheral tissues, as indicated by high and/or overexpression of the CB1 receptor **[13]**. The exact underlying mechanisms are not clear, however, SEC are lipid mediators and their biosynthesis can be directly influenced by dietary fat intake, contributing to greater fat accumulation, increasing food intake and favoring lipogenesis, and reducing energy expenditure. in peripheral organs. Thus, both pharmacological and genetic blockade of the CB1 receptor reduces body weight in animal models of obesity.

In this sense, weight loss predominantly occurs through the blockade of CB1 receptors. However, recent data suggest that SEC also controls peripheral energy metabolism. As visceral adiposity is one of the main determinants of insulin resistance, it is not surprising

that ECS hyperactivity favors the development of metabolites associated with obesity [13].

Emerging data suggest that a dysregulated SEC also has direct deleterious effects on insulin sensitivity and glucose metabolism independently of weight gain. In adipose tissue, ECS activation increases glucose uptake to increase energy storage in the form of newly synthesized lipids, downregulates adiponectin, affecting insulin sensitivity in distant organs, and may favor local inflammation. In skeletal muscle, the CB1 receptor interferes with glucose uptake by inhibiting insulinactivated signaling pathways, including those required for the translocation of glucose across plasma membrane transporters [14].

In the liver, activation of hepatic CB1 receptors can reduce systemic insulin sensitivity regardless of body weight. Indeed, mice that express CB1 receptors exclusively on hepatocytes remain lean when fed a high-fat diet, but they develop hepatic and systemic insulin resistance, whereas mice with deletion of the hepatocyte-specific CB1 receptor become obese but remain obese. insulin sensitivity [13,14].

Thus, several mechanisms may underlie these findings, such as CB1 receptor activation may reduce insulin clearance, reducing hepatic expression of the insulin-degrading enzyme, resulting in increased hepatic glucose production mainly due to increased glycogenolysis [14]. Furthermore, activation of the CB1 receptor induces endoplasmic reticulum stress, resulting in elevated hepatic levels of long-chain ceramides, which in turn inhibit insulin signaling. These data provide strong evidence that a disturbed ECS due to conditions that lead to obesity, such as a high-fat diet, may contribute to increased fat accumulation and insulin resistance by over-activity of the CB1 receptor and thus being a trigger. for the development of type 2 diabetes mellitus (DM2) [13].

Regarding the role of CB2 receptors in the control of metabolic processes, recent studies suggest that CB2 receptors may affect inflammatory aspects of obesity and DM2 [19,20]. Furthermore, overexpression of the CB2 receptor in the brain induces hyperglycemia and a decreased phenotype in adult mice. However, these studies need further confirmation with improved selective CB2 ligands, particularly due to the potent anti-inflammatory role of CB2 agonists reported in numerous pathological disease models [13].

Furthermore, G protein-coupled receptors 3, 6, and 12 (GPR3, GPR6, and GPR12) comprise a family of closely related orphan receptors with no confirmed endogenous ligands. These receptors are constitutively active and capable of signaling through mechanisms mediated by G protein or not. These orphan receptors have previously been reported to play important roles in many normal physiological functions and are involved in a variety of pathological conditions. Although they are orphans, GPR3, GPR6, and GPR12 are phylogenetically most closely related to cannabinoid receptors. Using β-arrestin2 recruitment and cAMP accumulation assays, CBD was recently found to be an inverse agonist of GPR3, GPR6, and GPR12. This discovery highlights these orphan receptors as potential new molecular targets for CBD, providing new mechanisms of action and suggesting new therapeutic uses of CBD for diseases such as Alzheimer's disease, Parkinson's disease, cancer, and infertility. Furthermore, the identification of CBD as a new inverse agonist for GPR3, GPR6, and GPR12 provides the initial chemical scaffolds upon which potent and effective agents that act on these receptors can be developed [21].

Despite these findings, a recent 2019 study conducted a systematic review of randomized controlled trials to analyze the efficacy and safety of CBD-based medications in patients with mental disorders. Five databases were systematically searched. A total of 1629 participants were included in all analyzed studies. A narrative synthesis method was applied. Study quality was assessed using the risk of bias tool and SIGN checklists. CBD-based medications have been associated with improvements in several symptoms of mental disorders, but not with remission. Side effects have occurred, but serious adverse effects have only been mentioned in single cases. To provide reliable treatment recommendations, more and larger follow-up assessments, consistent outcome measures, and active comparisons are needed [18].

Furthermore, a recent surge in scientific publications has found clinical and preclinical evidence documenting the value of CBD in some neuropsychiatric disorders, including epilepsy, anxiety, and schizophrenia. Evidence points to a calming effect of CBD on the central nervous system. Interest in CBD as a treatment for a wide variety of disorders has exploded, although there are few clinical studies of CBD in the psychiatric literature. Thus, one study analyzed a large retrospective case series in a psychiatric clinic involving the clinical application of CBD for anxiety and sleep complaints as an adjunct to usual care. Retrospective chart review included monthly documentation of anxiety and sleep quality in 103 adult patients. Sleep and anxiety scores, using validated instruments, at baseline and after CBD treatment. The final sample consisted of 72 adults who had primary concerns of anxiety (n = 47) or lack of sleep (n = 25). Anxiety scores decreased within the first month in 57 patients (79.2%) and remained decreased for the

duration of the study. Sleep scores improved within the first month in 48 patients (66.7%) but fluctuated over time. In this chart review, CBD was well tolerated in all patients. Therefore, CBD is beneficial for anxiety-related disorders [22].

Another review study described the main advances in the development of experimental and clinical use of cannabidiol CBD in neuropsychiatry. As a result, CBD has been shown to have anxiolytic, antipsychotic, and neuroprotective properties. Furthermore, clinical and basic investigations into the effects of CBD have been carried out in the context of many other health conditions, including its potential use in epilepsy, substance abuse and dependence, schizophrenia, social phobia, post-traumatic stress, depression, and bipolarity. sleep disorders and Parkinson's. Therefore, CBD is a useful and promising molecule that can help patients with a variety of medical conditions. Controlled clinical trials with different neuropsychiatric populations that are currently under investigation should bring important answers shortly and support the translation of research findings into clinical contexts [8].

Despite these earlier results, immersion in a controlled 3D virtual reality scenario was used to test anxiety in a sample of non-clinical volunteers (n = 32) prescreened for high paranoid traits. Participants were randomized to receive oral cannabidiol (600 mg) or a placebo for 130 min before entering virtual reality. Well-validated rating scales were used to assess persecutory thinking and anxiety. Salivary cortisol concentration, heart rate, and blood pressure were measured throughout the experimental session. As a result, the immersion in the virtual reality session provoked anxiety, indexed by the Beck anxiety inventory ($p< 0.005$), and increased cortisol concentration ($p = 0.05$), heart rate ($p< 0.05$). However, CBD had no impact on any of these effects. Therefore, in contrast to previous studies, there was no evidence of any benefits of CBD on anxiety or persecutory ideation in healthy volunteers with high-grade paranoia. However, a larger sample will be needed for a definitive study [23].

However, growing evidence indicates that CBD acts as an antipsychotic and anxiolytic, and several reports suggest neuroprotective effects. Furthermore, CBD mitigates the harmful effects of THC, both acutely and chronically, including psychotogenic, anxiogenic, and deleterious cognitive effects. This suggests that CBD may improve the disease trajectory of individuals with early psychosis and comorbid cannabis misuse in particular [17].

As such, studies show that CBD reduces anxiety via 5-HT1A and cannabinoid receptor activation in that if Accordingly, a literature review study demonstrated the anxiolytic effects of CBD before focusing on studies investigating its effects on various fear processes and drug memory. Understanding how CBD regulates emotion and emotional memory processing could lead to its use as a treatment for anxiety-related disorders and substance abuse [24].

Conclusion

Growing evidence indicates that cannabidiol acts as an antipsychotic, anxiolytic, and neuroprotective. Some studies show weight reduction in people with anxiety and food compulsion, as the blockade of the CB1 receptor. Alternative strategies to combat ECS overactivity would be to develop drugs that reduce endocannabinoid levels by modulating its biosynthesis and/or degradation or to develop dietary interventions that reduce the abundance of endocannabinoid precursors. Furthermore, it is very important to develop more selective CB2 receptor agonists. Also, new randomized controlled trials with larger numbers of participants are needed.

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Ethical Approval

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Informed consent

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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