



Use of cannabidiol in the treatment of compulsion eating and obesity: a systematic review

Thuany da Silva Teixeira^{1*}, Alessandra Leal de Oliveira², Mariana Carolina Braga³, Lucas Emanuel de Lima Azevedo⁴, Lara Souza Crepaldi⁵, Renata Cristina Taveira Azevedo⁶, Nathalia Galindo Cordeiro⁷, Rodrigo Siqueira de Carvalho⁸

¹ São Lucas Hospital. Travessa Frederico Pamplona, 32, Copacabana, Rio de Janeiro, Brazil.

² Vivare Clinic. Street: Victor Rensult 555, Teófilo Otoni, Minas Gerais, Brazil.

³ Sírío Libabes Hospital, Brasília, Distrito Federal, Brazil.

⁴ Dra Thaís Teles Clinic. SHIS Qi 3 Bloco i Sala 106 - Lago Sul, Brasília, Brazil.

⁵ José Nigro Hospital. Avenue Teresa Marsili, 311. Américo Brasiliense, Brazil.

⁶ Las Medical Clinic. Manhattan Office Santos - R. São Paulo, 41 - Vila Belmiro, Santos, Brazil.

⁷ Haute Clinic. Street Joaquim Floriano, 533 - 14º andar, Itaim Bibi, São Paulo, Brazil.

⁸ Dr. Rodrigo Carvalho Clinic. Avenue Antônio de goes 275 sala 603, Pina Recife, PE, Brazil.

*Corresponding author: Dr. Thuany da Silva Teixeira.
São Lucas Hospital. Travessa Frederico Pamplona, 32,
Copacabana, Rio de Janeiro, Brazil.
E-mail: dra.thuanyteixeira@gmail.com

DOI: <https://doi.org/10.54448/mdnt24404>

Received: 07-11-2024; Revised: 09-13-2024; Accepted: 09-15-2024; Published: 09-17-2024; MedNEXT-id: e24404

Editor: Dr. Mohammad Abusamak, MD FRCS MRCS.

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- Δ 9tetrahydrocannabinol, 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 is a multifactorial disease that causes serious public health problems. There are more than 2.5 billion people who are overweight or obese in the world [1], and Brazil is ranked fifth in the world. 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, high levels of negative affect, and, in particular, difficulty in managing anxiety [3]. Thus, anxiety disorders usually precede the onset of eating disorders and clinically significant anxiety persists after treatment of the eating pathology. In addition, higher levels of anxiety are associated with higher body mass index (BMI), longer duration of symptoms increased rates of compensatory behaviors, binge eating, and body dissatisfaction [4,5]. In this sense, cannabidiol (CBD) was identified 50 years ago and has effects that 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, 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-arachidonoyl-ethanolamine (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 elements of the ECS plays an important role in the development of the central nervous system (CNS), 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 modulating factors of the autonomic nervous system, the immune system, the endocrine system, the gastrointestinal tract, the reproductive system, and the 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 GABAergic and glutamatergic synapses, as well as modulators of postsynaptic transmission, interacting with other neurotransmitters, including dopamine. Endocannabinoids also participate in the modulation of the hypothalamic-pituitary-adrenal (HPA) axis and stress regulation [13]. The synthesis of cannabinoid receptor agonists and antagonists, anandamide uptake blockers, and inhibitors of endocannabinoid degradation of anandamide have opened up new treatment strategies [14].

Despite some setbacks in clinical trials related to drugs acting on the ECS, much research is still being conducted to explore and establish the therapeutic targets for cannabinoid receptor agonists and antagonists. One challenge is to develop drugs that target only cannabinoid receptors in a specific tissue,

and another is to invent drugs that selectively act on cannabinoid receptors located outside the blood-brain barrier. In addition, it is also necessary to develop suitable dosage forms with maximum efficacy and minimum adverse effects. To successfully exploit the therapeutic potential of the ECS, it is imperative to further characterize the endocannabinoid system in terms of identifying the exact cellular localization of cannabinoid receptors and their role as both "protective" and "disease-inducing" substances, depending on time-dependent changes in cannabinoid receptor expression [11,14].

In this sense, CBD may 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. Furthermore, CBD has an immunomodulatory effect that helps to slow the progression of atherosclerosis induced by high glucose levels. It may also be effective in combating ischemic disease, the most harmful complication of metabolic syndrome. However, it can only be administered as adjuvant therapy due to its low binding potency, and its inhibitory effect on cytochrome P450 enzymes should also be considered. However, it may 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 models and humans of the use of cannabidiol in anxiety and obesity.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: <http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1>. It was accessed on: 03/16/2024. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: <https://amstar.ca/>. It was accessed on: 03/16/2024.

Data Sources and Search Strategy

The literature search process was carried out from March to June 2024 and developed based on Web of Science, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The health sciences descriptors (DeCS/MeSH Terms) were used: "Bariatric surgery. Nutritional management. Metabolic deficit. Nutrients. Vitamins" (in English: Bariatric surgery.

Nutritional management. Metabolic deficit. Nutrients. Vitamins), and using the Boolean "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

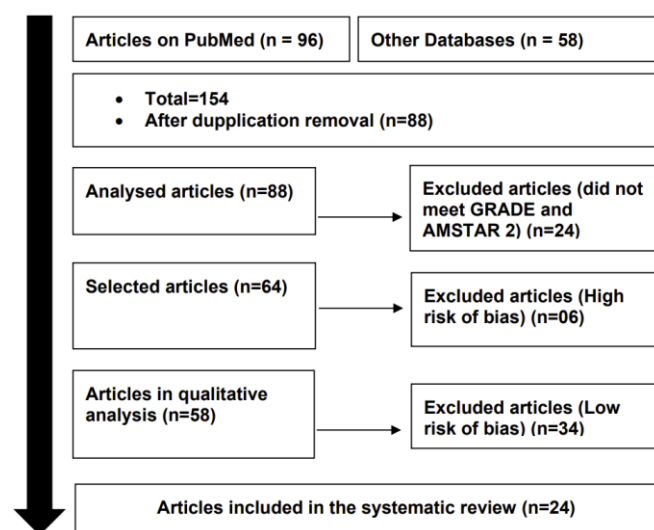
The quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. 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 by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's d test.

Results and discussion

Summary of Findings

As a corollary of the literature search system, a total of 154 articles were found that were submitted to eligibility analysis and, subsequently, 24 of the 58 final studies were selected to compose the results of this systematic review. The listed studies presented medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in study types such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with $I^2=96.8\%>50\%$. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 06 studies with a high risk of bias and 24 studies that did not meet GRADE and AMSTAR-2.

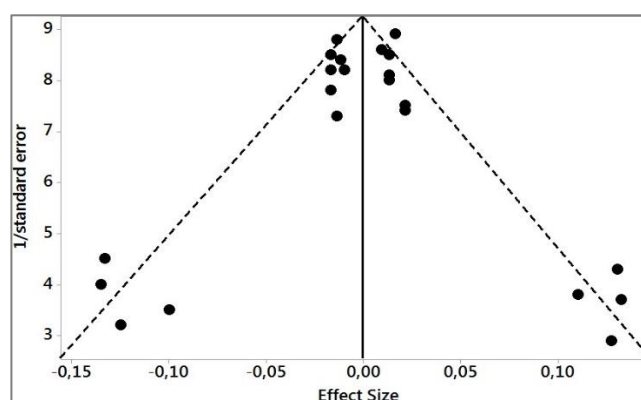
Figure 1. Flowchart showing the article selection process.



Source: Own Authorship.

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

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



Source: Own Authorship.

Main Evidences

In the context of anxiety and binge eating and the consequent increase in the incidence of obese individuals, activation of CB1 receptors improves eating by 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 important in the control of metabolism, and activates anabolic pathways, favoring energy storage [18]. In white adipocytes, activation of the CB1 receptor increases fatty acid synthesis, improves triglyceride accumulation, and reduces lipolysis, while 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 downregulated in central and peripheral tissues, as indicated by high and/or

overexpression of the CB1 receptor [13]. The exact underlying mechanisms are unclear, however, ECS are lipid mediators and their biosynthesis can be directly influenced by dietary fat intake, contributing to greater fat accumulation, increasing food intake 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 occurs predominantly through the blockade of CB1 receptors. However, recent data suggest that the ECS also controls peripheral energy metabolism. Since visceral adiposity is a major determinant of insulin resistance, it is not surprising that ECS hyperactivity favors the development of obesity-associated metabolites [13].

Emerging data suggest that a dysregulated ECS also has direct deleterious effects on insulin sensitivity and glucose metabolism independent 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 insulin-activated signaling pathways, including those required for glucose translocation through plasma membrane transporters [14].

In the liver, activation of hepatic CB1 receptors may reduce systemic insulin sensitivity independent of body weight. Indeed, mice expressing CB1 receptors exclusively in hepatocytes remain lean when fed a high-fat diet, but they develop hepatic and systemic insulin resistance, whereas mice with hepatocyte-specific CB1 receptor deletion become obese but remain insulin sensitive [13,14]. Thus, several mechanisms may underlie these findings, such as CB1 receptor activation may reduce insulin clearance by reducing hepatic expression of the insulin-degrading enzyme, resulting in increased hepatic glucose production mainly due to increased glycogenolysis [14]. Furthermore, CB1 receptor activation 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 excess CB1 receptor activity and thus be a trigger for the development of type 2 diabetes mellitus (T2DM) [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 T2DM [19,20]. Furthermore, overexpression of the

CB2 receptor in the brain induces hyperglycemia and a decreased phenotype in adult mice. However, these studies require further confirmation with improved CB2-selective ligands, particularly given the potent anti-inflammatory role of CB2 agonists reported in numerous pathological disease models [13].

In addition, 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 G-protein-mediated or non-G-protein-mediated mechanisms. These orphan receptors have been previously 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 novel mechanisms of action, and suggests novel therapeutic uses of CBD for diseases such as Alzheimer's disease, Parkinson's disease, cancer, and infertility. Furthermore, the identification of CBD as a novel inverse agonist for GPR3, GPR6, and GPR12 provides the initial chemical scaffolds upon which potent and efficacious agents that target 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 across all studies analyzed. 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 been reported only in isolated cases. To provide reliable treatment recommendations, more and larger trials with follow-up assessments, consistent outcome measures, and active comparisons are needed [18].

In addition, 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 range of disorders has exploded, although there are few clinical studies of CBD in the psychiatric literature. Thus, a 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. The retrospective chart review included monthly documentation of anxiety and sleep quality in 103 adult patients. Sleep and anxiety scores, using validated instruments, were recorded at baseline and after CBD treatment. The final sample consisted of 72 adults who presented with primary concerns of anxiety ($n = 47$) or poor sleep ($n = 25$). Anxiety scores decreased in the first month in 57 patients (79.2%) and remained decreased throughout the duration of the study. Sleep scores improved in 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 was shown to be beneficial for anxiety-related disorders [22].

Another review study described major 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 conducted 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, bipolar disorder, sleep disorders, and Parkinson's. Therefore, CBD is a useful and promising molecule that can help patients with a variety of clinical conditions. Controlled clinical trials with different neuropsychiatric populations that are currently under investigation should provide important answers in the near future and support the translation of research findings into clinical settings [8].

Despite these previous results, immersion in a controlled 3D virtual reality scenario was used to test anxiety in a sample of non-clinical volunteers ($n = 32$) pre-screened for high paranoid traits. Participants were randomized to receive oral cannabidiol (600 mg) or placebo 130 min before entering the 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, immersion in the virtual reality session provoked anxiety, as indexed by the Beck Anxiety Inventory ($p < 0.005$), and increased cortisol concentration ($p = 0.05$), heart rate ($p < 0.05$), and systolic blood pressure ($p < 0.05$). 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-trait paranoia. However, a larger sample size 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 attenuates the detrimental effects of THC, both acutely and chronically, including psychotogenic, anxiogenic, and deleterious cognitive effects. This suggests that CBD may improve the illness trajectory of individuals with early psychosis and comorbid cannabis misuse in particular [17].

Accordingly, studies show that CBD reduces anxiety via 5-HT_{1A} and cannabinoid receptor activation. In this regard, a literature review study demonstrated the anxiolytic effects of CBD before focusing on studies investigating its effects on various drug fear and memory processes. Understanding how CBD regulates emotion and emotional memory processing may lead to its use as a treatment for anxiety-related disorders and substance abuse [24].

Conclusion

Increasing evidence indicates that cannabidiol acts as an antipsychotic, anxiolytic, and neuroprotective. Some studies show weight loss in people with anxiety and binge eating, due to blocking the CB₁ receptor. Alternative strategies to combat ECS overactivity would be to develop drugs that reduce endocannabinoid levels by modulating their 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 studies with larger numbers of participants are needed.

CRedit

Author contributions: **Conceptualization** - Thuany da Silva Teixeira, Alessandra Leal de Oliveira, Mariana Carolina Braga, Lucas Emanuel de Lima Azevedo, Lara Souza Crepaldi, Renata Cristina Taveira Azevedo, Nathalia Galindo Cordeiro, Rodrigo Siqueira de Carvalho; **Data curation** - Thuany da Silva Teixeira, Alessandra Leal de Oliveira, Mariana Carolina Braga, Lucas Emanuel de Lima Azevedo, Lara Souza Crepaldi, Renata Cristina Taveira Azevedo, Nathalia Galindo Cordeiro, Rodrigo Siqueira de Carvalho; **Formal Analysis** - Thuany da Silva Teixeira, Alessandra Leal de Oliveira, Mariana Carolina Braga, Lucas Emanuel de Lima Azevedo, Lara Souza Crepaldi, Renata Cristina Taveira Azevedo, Nathalia Galindo Cordeiro, Rodrigo Siqueira de Carvalho; **Investigation** - Thuany da Silva Teixeira, Alessandra Leal de Oliveira; **Methodology** - Mariana Carolina Braga, Lucas Emanuel de Lima Azevedo, Lara Souza Crepaldi, Renata Cristina Taveira Azevedo, Nathalia Galindo Cordeiro, Rodrigo Siqueira de Carvalho; **Project administration** - Thuany da Silva Teixeira;

Supervision -Thuany da Silva Teixeira; **Writing - original draft** - Thuany da Silva Teixeira, Alessandra Leal de Oliveira, Mariana Carolina Braga, Lucas Emanuel de Lima Azevedo, Lara Souza Crepaldi, Renata Cristina Taveira Azevedo, Nathalia Galindo Cordeiro, Rodrigo Siqueira de Carvalho; **Writing-review & editing**- Thuany da Silva Teixeira, Alessandra Leal de Oliveira, Mariana Carolina Braga, Lucas Emanuel de Lima Azevedo, Lara Souza Crepaldi, Renata Cristina Taveira Azevedo, Nathalia Galindo Cordeiro, Rodrigo Siqueira de Carvalho.

Acknowledgment

Not applicable.

Ethical Approval

Not applicable.

Informed Consent

Not applicable.

Funding

Not applicable.

Data Sharing Statement

No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Peer Review Process

It was performed.

About The License©

The author(s) 2024. The text of this article is open access and licensed under a Creative Commons Attribution 4.0 International License.

References

1. WHO-World Health Organization. Available in: <https://www.who.int/topics/obesity/en/> - 62k. Accessed March 20, 2024.
2. IBGE- Instituto Brasileiro de Geografia e Estatística. Disponível em: <http://www.ibge.gov.br>>. Accessed March 20, 2024.
3. Becker KR, Plessow F, Coniglio KA, Tabri N, Franko DL, Zayas LV, germine L, Thomas JJ, Eddy KT. Global/local processing style: Explaining the relationship between trait anxiety and binge eating. *Int J Eat Disord*. 2017, Nov;50(11):1264-1272. doi: 10.1002/eat.22772.
4. Santos-Veloso MAO, Melo MISL, Cavalcanti RAN, Bezerra LS, ChavesMarkman ÂV, Lima SG. Prevalence of depression and anxiety and their association with cardiovascular risk factors in Northeast Brasil primary care patients. *Rev Assoc Med Bras* (1992). 2019, Jul 22;65(6):801-809. doi: 10.1590/1806-9282.65.6.801.
5. Guerdjikova AI, Mori N, Casuto LS, Mcelroy SL. Update on Binge Eating Disorder. *Med Clin North Am*. 2019, Jul;103(4):669-680. doi: 10.1016/j.mcna.2019.02.003.
6. Mandolini GM, Lazzaretti M, Pigoni A, Oldani L, Delvecchio G, Brambilla P. Pharmacological properties of cannabidiol in the treatment of psychiatric disorders: a critical overview. *Epidemiol Psychiatr Sci*. 2018, Aug;27(4):327-335. doi: 10.1017/S2045796018000239.
7. Fearby N, Penman S, Thanos P. Effects of Δ9-Tetrahydrocannabinol (THC) on Obesity at Different Stages of Life: A Literature Review. *Int J Environ Res Public Health*. 2022 Mar 8;19(6):3174. doi: 10.3390/ijerph19063174.
8. Crippa JA, Guimarães FS, Campos AC, Zuardi AW. Translational Investigation of the Therapeutic Potential of Cannabidiol (CBD): Toward a New Age. *Front Immunol*. 2018, Sep 21;9:2009. doi: 10.3389/fimmu.2018.02009.
9. Premoli M, Aria F, Bonini SA, Maccarinelli G, Gianoncelli A, Pina SD, Tambaro S, Memo M, Mastinu A. Cannabidiol: Recent advances and new insights for neuropsychiatric disorders treatment. *Life Sci*. 2019, May 1;224:120-127. doi: 10.1016/j.lfs.2019.03.053.
10. Elms L, Shannon S, Hughes S, Lewis N. Cannabidiol in the Treatment of PostTraumatic Stress Disorder: A Case Series. *J Altern Complement Med*. 2019, Apr;25(4):392-397. doi: 10.1089/acm.2018.0437.
11. Cavalheiro EKFF, Costa AB, Salla DH, Silva MRD, Mendes TF, Silva LED, Turatti CDR, Bitencourt RM, Rezin GT. *Cannabis sativa* as a Treatment for Obesity: From Anti- Inflammatory Indirect Support to a Promising Metabolic Re-Establishment Target. *Cannabis Cannabinoid Res*. 2022 Apr;7(2):135-151. doi: 10.1089/can.2021.0016.
12. Ben-Cnaan E, Permyakova A, Azar S, Hirsch S, Baraghithy S, Hinden L, Tam J. The Metabolic Efficacy of a Cannabidiolic Acid (CBDA) Derivative in Treating Diet- and Genetic-Induced Obesity. *Int J Mol Sci*. 2022 May 17;23(10):5610. doi:

- 10.3390/ijms23105610.
13. Gruden G, Barutta F, Kunos G, Pacher P. Role of the endocannabinoid system in diabetes and diabetic complications. *Br J Pharmacol.* 2016, Apr;173(7):1116-27. doi: 10.1111/bph.13226.
 14. Kaur R, Ambwani SR, Singh S. Endocannabinoid System: A Multi-Facet Therapeutic Target. *Curr Clin Pharmacol.* 2016, 11(2):110-7.
 15. Kleiner D, Ditrói K. The potential use of cannabidiol in the therapy of metabolic syndrome. *Orv Hetil.* 2012, Apr 1;153(13):499-504. doi: 10.1556/OH.2012.29308.
 16. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015–2016. 2017, NCHS data brief, no 288. Hyattsville, MD: National Center for Health Statistics.
 17. Hahn B. The Potential of Cannabidiol Treatment for Cannabis Users With Recent-Onset Psychosis. *Schizophr Bull.* 2018, Jan 13;44(1):46-53. doi: 10.1093/schbul/sbx105.
 18. Hoch E, Niemann D, Von Keller R, Schneider M, Friemel CM, Preuss UW, Hasan A, Pogarell O. How effective and safe is medical cannabis as a treatment of mental disorders? A systematic review. *Eur Arch Psychiatry Clin Neurosci.* 2019, Feb;269(1):87-105. doi: 10.1007/s00406-019-00984-4.
 19. Teitelbaum J. A Hemp oil, CBD, and Marijuana Primer: Powerful Pain, Insomnia, and Anxiety-relieving Tools! *Altern Ther Health Med.* 2019, Jun;25(S2):21-23.
 20. Van DIS EAM, Van VEEN SC, Hagenaaars MA, Batelaan NM, Bockting CLH, Van DEN Heuvel RM, Cuijpers P, Engelhard IM. Long-term Outcomes of Cognitive Behavioral Therapy for Anxiety-Related Disorders: A Systematic Review and Meta-analysis. *JAMA Psychiatry.* 2019, Nov 23. doi: 10.1001/jamapsychiatry.2019.3986.
 21. Laun AS, Shrader SH, Brown KJ, Song ZH. GPR3, GPR6, and GPR12 as novel molecular targets: their biological functions and interaction with cannabidiol. *Acta Pharmacol Sin.* 2019, Mar;40(3):300-308. doi: 10.1038/s41401-018-0031-9.
 22. Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in Anxiety and Sleep: A Large Case Series. *Perm J.* 2019, 23:18-041. doi: 10.7812/TPP/18-041.
 23. Hundal H, Lister R, Evans N, antley A, Englund A, Murray RM, Freeman D, Morrison PD. The effects of cannabidiol on persecutory ideation and anxiety in a high trait paranoid group. *J Psychopharmacol.* 2018, Mar;32(3):276-282. doi: 10.1177/0269881117737400.
 24. Lee JLC, Bertoglio LJ, Guimarães FS, Stevenson CW. Cannabidiol regulation of emotion and emotional memory processing: relevance for treating anxiety-related and substance abuse disorders. *Br J Pharmacol.* 2017, Oct;174(19):3242-3256. doi: 10.1111/bph.13724.