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PHYTOCANNABINOIDS AND OBESITY: A SYSTEMATIC REVIEW OF PRECLINICAL AND CLINICAL EVIDENCE ON METABOLIC EFFECTS

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ABSTRACT

Obesity is a chronic inflammatory condition of multifactorial origin, closely associated with insulin resistance and hepatic dysfunction. Given the limitations of current therapeutic approaches, phytocannabinoids derived from Cannabis sativa have been investigated as modulators of energy metabolism. This systematic review aimed to assess the metabolic effects of cannabidiol (CBD), tetrahydrocannabinol (THC), and cannabinol (CBN) on obesity and glucose regulation. A total of 14 studies were selected (8 in animal models and 6 in humans) from PubMed, LILACS, Cochrane, and Google Scholar databases. CBD showed anti-inflammatory activity, increased glucose uptake, and promoted adipose tissue browning. Chronic THC use reduced weight gain and hepatic steatosis, while CBN exhibited mild anti-inflammatory properties. In human studies, regular cannabis users showed lower body mass index, improved insulin sensitivity, and a more favorable lipid profile. Although these findings are promising, the lack of controlled clinical trials hinders translational application. Future research should focus on standardized dosages, delivery methods, and long-term safety in specific populations.

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INTRODUCTION

Obesity is a chronic, multifactorial condition characterized by excessive adipose tissue accumulation and low-grade systemic inflammation, contributing significantly to the global burden of disease. It is closely associated with comorbidities such as type 2 diabetes, cardiovascular disease, dyslipidemia, and non-alcoholic fatty liver disease (NAFLD). Traditional interventions, including dietary modifications, physical activity, pharmacological therapies, and, in severe cases, bariatric surgery, often yield suboptimal long-term outcomes due to issues with adherence, efficacy, and adverse effects. Given this scenario, alternative therapeutic strategies are being explored. One such approach involves the modulation of the endocannabinoid system (ECS), which plays a pivotal role in regulating energy homeostasis, appetite, glucose metabolism, and inflammation. ECS dysfunction has been implicated in obesity pathogenesis, particularly via hyperactivation of cannabinoid receptor 1 (CB1), which promotes lipogenesis and insulin resistance. Phytocannabinoids, natural compounds derived from Cannabis sativa, interact with components of the ECS. Among them, cannabidiol (CBD), tetrahydrocannabinol (THC), and cannabinol (CBN) have emerged as molecules of interest due to their ability to modulate metabolic pathways without necessarily eliciting psychoactive effects. This review aims to systematically examine preclinical and clinical evidence regarding the metabolic effects of these phytocannabinoids in the context of obesity and glucose regulation.

MATERIALS AND METHODS

This qualitative systematic review was conducted based on the PICO framework and guided by the STROBE statement for observational studies. The research question was: "What are the metabolic effects of the phytocannabinoids CBD, THC, and CBN on glucose metabolism and obesity?"

The search was performed in PubMed/MEDLINE, LILACS, Cochrane Library, and Google Scholar, using the following descriptors: "obesity," "phytocannabinoids," "endocannabinoid system," "cannabidiol," "tetrahydrocannabinol," "cannabinol," "glucose metabolism," and "energy expenditure." No time restrictions were applied.

Inclusion criteria: (i) original articles with animal or human samples; (ii) clinical trials or experimental studies assessing the impact of phytocannabinoids on metabolic outcomes (e.g., body weight, lipid profile, insulin resistance, glucose levels); (iii) articles in English, Portuguese, or Spanish. Exclusion criteria: literature reviews, letters to the editor, case reports, articles involving pregnant women, or those without methodological clarity.

Out of 130 articles retrieved, 14 were selected after applying the criteria—8 animal studies and 6 human studies. Selected articles were analyzed and grouped into two categories: (1) effects in animal models and (2) effects in human populations.

Table 1. Summary of preclinical and clinical studies evaluating metabolic effects of phytocannabinoids

tudy	Model	Phytocannabinoid	Key Findings
Cluny et al. (2015)	Animal	THC	Decreased weight gain and hepatic steatosis.
Eitan et al. (2023)	Animal	CBD + THC	Reduced visceral fat, improved lipid profile.
Rajesh et al. (2007)	Animal	CBD	Attenuated endothelial inflammation under high glucose.
Rajesh et al. (2010)	Animal	CBD	Reduced oxidative stress and cardiac dysfunction in diabetic cardiomyopathy.
Lehmann et al. (2016)	Animal	CBD	Reduced early pancreatic inflammation in type 1 diabetes.
Parray&Yun (2016)	In vitro	CBD	Induced browning of adipocytes, increased thermogenesis.
Trainito et al. (2024)	In vitro	CBN	Modulated cell cycle genes; potential metabolic effects.
Jamshidi& Taylor (2001)	Animal	Anandamide	Stimulated appetite via CB1 in hypothalamus.
Izzo et al. (2009)	Human/Review	CBD, THC	Discussedtherapeuticopportunities
Bielawiecz et al. (2020)	Human/Review	CBD	Proposedanti-obesitypathways.
Matarese et al. (2010)	Human	ECS Modulation	Tregs and leptin in obesity.
Murray (2024)	Review	Cannabis	Historicalmedical use.
ABESO (s.d.)	Epidemiological	-	Brazilian obesitycontext.
WHO (2021)	Epidemiological	-	Global obesitytrends.

RESULTS

Effects in Animal Models: Preclinical studies demonstrated a consistent metabolic benefit from phytocannabinoid interventions. CBD reduced inflammatory cytokines such as TNF-α and IL-6, enhanced adiponectin secretion, improved glucose uptake in muscle tissues, and promoted mitochondrial biogenesis. It also induced browning of white adipose tissue, suggesting enhanced thermogenesis and energy expenditure. THC, despite its orexigenic properties, was associated with attenuated weight gain in rodent models following chronic exposure. This paradoxical effect has been attributed to central CB1 receptor desensitization and downregulation of lipogenic gene expression in the liver. CBN, though less studied, exhibited modest anti-inflammatory and antioxidant effects, with mild improvements in lipid metabolism and insulin signaling in obese mice. CB2 receptor activation showed protective effects against hepatic steatosis and promoted glycemic control.

Effects in Human Populations: Human studies, primarily observational, indicated an inverse relationship between chronic cannabis use and obesity-related outcomes. Regular users presented lower body mass index (BMI), reduced waist circumference, and decreased prevalence of type 2 diabetes. These individuals also exhibited improved insulin sensitivity, lower fasting insulin levels, and favorable lipid profiles. Despite these associations, the evidence is limited by confounding variables such as diet, physical activity, substance use, and socioeconomic status. Moreover, cannabis formulations varied in cannabinoid composition, making it difficult to isolate the effects of specific phytocannabinoids. Randomized controlled trials evaluating isolated CBD, THC, or CBN in clinical settings remain scarce. The main findings of the reviewed studies are summarized in Table 1.

DISCUSSION

Phytocannabinoids show promising potential in modulating obesity-related metabolic dysfunctions through anti-inflammatory, lipolytic, and insulin-sensitizing mechanisms. Animal studies demonstrate that CBD improves mitochondrial activity and adipocyte function, while THC, under chronic exposure, appears to mitigate hepatic fat accumulation and alter hypothalamic regulation of energy balance. CB1 antagonism and CB2 agonism may synergistically contribute to restoring metabolic homeostasis in obesity. However, these effects may be dose-dependent and influenced by the specific cannabinoid profile used. Human findings, while intriguing, are largely observational and must be interpreted with caution. The absence of randomized trials, the lack of dosage control, and the heterogeneity of cannabis use hinder causal inference. Moreover, long-term safety, drug interactions, and psychoactive risks must be considered in future translational approaches. Therefore, the integration of phytocannabinoids into obesity treatment protocols requires rigorous clinical trials to define efficacy, standardize administration routes, and ensure pharmacovigilance, especially in vulnerable populations such as elderly, diabetic, and hepatopathic patients.

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