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THC y CBD una alternativa para el tratamiento del estrés en adultos: beneficios y controversias. Una revisión actualizada de la literatura

THC and CBD an alternative for the treatment of stress in adults: benefits and controversies: an updated literature review

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Palabras claves:
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Resumen

Introducción. El estrés es un trastorno producido por situaciones físicas o emocionales que afectan la homeostasis del cuerpo ocasionando cambios significativos en la salud. En el siglo XXI se han desarrollado terapias basadas en plantas medicinales, incluyendo aquellas que pueden tratar enfermedades del Sistema Nervioso Central. El uso de fitocannabinoides como THC y CBD han demostrado ser efectivos para reducir el estrés, pero han generado controversia debido a su uso recreativo y regulaciones. **Objetivo.** El propósito de este artículo es revisar la evidencia científica actual sobre los efectos beneficiosos y adversos del uso de THC y CBD en el tratamiento del estrés en adultos. **Metodología.** Se realizó una búsqueda y revisión bibliográfica empleando 3 palabras clave: estrés tratado con THC y CBD, stress and cannabis, treatment and stress and cannabis o marihuana empleando base de datos de alto impacto como PubMed, ScieLO, Scopus, Web of Science, Springer, Medline, Taylor & Francis, Redalyc, a través de las bases digitales de la Universidad Católica de Cuenca. **Resultados.** Varios de estos estudios que se citan en esta investigación, nos indican que estos metabolitos producen mejoras significativas en la mayoría de los pacientes. Los síntomas alcanzaron mejoras bajo el efecto de una dosificación flexible siguiendo un régimen estricto de cannabidiol y tetrahidrocannabinol. **Conclusión.** Los datos recopilados en este estudio han mostrado beneficios terapéuticos, por lo cual es crucial una investigación continua en este campo para comprender mejor los riesgos y beneficios de estos compuestos en el contexto del manejo del estrés en adultos. **Área de estudio general:** medicina. **Área de estudio específica:** uso terapéutico del cannabis medicinal. **Tipo de estudio:** Revisión bibliográfica.

Keywords:
stress treated THC and CBD, stress and cannabis, treatment, and stress.

Abstract

Introduction. Stress is a disorder caused by physical or emotional events that affect the organism's homeostasis causing significant health alterations. In the 21st century, therapies based on medicinal plants have been developed, including those that can treat diseases of the Central Nervous System. The use of phytocannabinoids such as THC and CBD

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have proven to be highly effective in reducing stress but are controversial due to their recreational use and regulations. objective. The purpose of this article is to review the existing scientific evidence on both the beneficial and harmful effects of using THC and CBD in treating stress in adults. Methodology. Literature searches and reviews were carried out using three keywords: stress treated with THC and CBD, stress and cannabis, treatment and stress, and cannabis or marijuana through high-quality databases such as PubMed, SciELO, Scopus, Web of Science, Springer, Medline , Taylor & Francis, and Redalyc, through the online databases of the Catholic University of Cuenca. Results. Several of these studies cited in this research indicate that these metabolites cause significant improvements in all patients. Symptoms achieved improvements under the effect of flexible dosing following a strict regimen of cannabidiol and tetrahydrocannabinol. Conclusion. The data collected in this study have shown therapeutic benefits, so further research in this field is crucial to better understand the risks and benefits of these compounds in adult stress management.

Introduction

Stress can be caused by a wide variety of situations, both physical and emotional, altering the homeostasis of the organism. The World Health Organization defines stress as a group of physiological reactions that prepare the organism to defend itself (1,2). In this sense, the organism will remain in a state of alert against any change that occurs, the body will stimulate a certain level of response until it reaches its objective, returning to its original state once the stimulus has ended (2). The problem arises when in certain situations such as overwork, competitive environment, social and economic pressure, the organism unconsciously detects it as a threat, which if maintained persistently will generate significant organic and functional changes causing a state of exhaustion (2).

Stress can manifest itself at any stage of life, particularly in adulthood, despite the maturity that the person may have achieved at this point. In fact, it is precisely at this stage that the number of stressors can increase, causing psychological, emotional and physiological problems, frequently associated with the search for professional and family stability. This set of factors, which are associated with greater responsibilities,

perfectionism, self-demand, fear of failure, among other aspects, generate continuous tension, progressively weakening the individual's ability to respond to these situations (3,4).

In the 21st century, several therapeutic approaches based on the use of medicinal plants have appeared with the intention of finding new alternatives for a wide range of diseases including those of the Central Nervous System (CNS) (5). In this context, plants with recognized activity on the CNS have been considered as potential treatments or as a source of phytochemicals for this type of diseases. In fact, cannabis is one of the best examples of plants with metabolites capable of affecting the functioning of the CNS, generating effects that, from the therapeutic perspective, are increasingly interesting and generating growing interest. Some studies using phytocannabinoids, mainly THC (delta-9-Tetrahydrocannabinol) and CBD (Cannabidiol), have shown the ability to reduce stress levels by activating cannabinoid receptors CB1 and CB2, jointly increasing the signaling that involves these receptors, resulting in a reduction of synaptic transmission in various parts of the central and peripheral nervous system (6). Furthermore, it is important to highlight its ability to reduce the release of inflammatory factors by immune and glial cells (7,8).

Multiple investigations and trials have revealed that the use of phytocannabinoids has contributed to the significant reduction of stress, due to the relaxing and anxiolytic properties they present. The data from such investigations have supported the great therapeutic value of these metabolites for reducing stress and improving the patient's health status, so they could constitute an attractive therapeutic option in the treatment of stress. However, the management of these metabolites has unleashed a number of controversies related to regulatory and jurisdictional aspects for therapeutic use due to their recreational psychoactive effects, distant from the promising medicinal uses mentioned above (9,10).

Methodology

A bibliographic search and review was carried out using words such as: Treatment with cannabis metabolites/stress treated with THC and CBD/Treatment of stress in adults/stress and cannabis/treatment and stress and cannabis or marijuana in English and Spanish using databases that cover recognized and high-impact indexed journals in PubMed, SciELO, Scopus, Web of Science, Springer, Google Scholar, Medline, Taylor & Francis, Redalyc, through the digital databases available at the Catholic University of Cuenca.

For a more specific search, Boolean operators were used such as: Cannabis sativa AND Cannabinoids, Tetrahydrocannabinol OR Cannabidiol, Stress AND

Tetrahydrocannabinol, Treatment AND stress AND Cannabinoids, including articles from the last ten years (2013-2023).

In this way, a total of 72 review and original articles were obtained, from which those of greatest novelty and relevance for the respective objectives set out in this study were selected. 38 works were discarded for various reasons such as: not precisely adjusting to the review topic, the use of THC and CBD for stress was not the main focus of the work, content was reiterated or some of the studies focused on the use of cannabinoids in psychiatric disorders. In addition, clinical studies were prioritized and in vitro, ex vivo and in silico studies were not considered. Thus, 31 works constitute the bibliography of this narrative review.

Results

Stress is an increasingly prevalent condition in modern society and is associated with a number of negative consequences for physical and mental health, which can have a significant impact on the quality of life of individuals. The metabolites CBD and THC present in the Cannabis sativa plant, commonly known as marijuana, have sparked growing interest for their medicinal potential (9,10). In fact, scientific evidence suggests that both CBD and THC could collaborate in stress management in adults. These active compounds are known to have psychoactive and therapeutic effects on the human body (11,12).

Although it does not produce significant psychoactive effects, CBD has been shown to have medicinal properties including analgesic, anti-inflammatory, anxiolytic, and anticonvulsant effects. In addition, its potential in the treatment of neurological disorders such as epilepsy, post-traumatic stress disorder, and multiple sclerosis has been investigated (13,14).

THC is another important metabolite responsible for the psychoactive effects associated with the consumption of this plant. It binds to cannabinoid receptors in the brain, producing feelings of euphoria, relaxation, and alterations in sensory and cognitive perception. It is important to note that both CBD and THC are metabolized by the liver through a series of enzymatic processes. These metabolic processes may vary depending on each individual and factors such as the dose administered and the route of administration (15,16). In this regard, THC administered orally has a bioavailability that ranges between 5% and 20% in controlled clinical cases; however, in some patients the bioavailability is lower due to modifications in gastric degradation (first-pass effect). CBD also has a bioavailability that ranges between 13% and 19% when administered orally (17,18).

THC is the predominant primary psychoactive component in cannabis, whose analgesic and psychoactive effect is largely due to its ability to act as a partial agonist of endogenous cannabinoid receptors type 1 (CB1) and type 2 (CB2), which are mainly found in the central nervous system and the immune system. CB1 receptors are G-protein coupled and located in different brain regions, such as the cerebellum, hippocampus, and basal ganglia (17,19). The function of CB1 agonists is to negatively regulate neurotransmission through GABAergic and glutamatergic neurons. This mechanism is believed to be responsible for the psychotropic effects of THC, which include the regulation of emotions, motor coordination, and cognition (20).

However, CBD works in a very different way, this component does not connect much or barely connects with CB1 or CB2 receptors. So, it blocks THC from binding to the CB1 receptor, which usually intensifies several effects on cells, such as changing calcium levels within them or producing antioxidant effects. Unlike THC, CBD does not cause psychoactive effects. In addition, CBD acts significantly on the 5-HT 1A serotonergic receptors, being a powerful activator, which helps CBD, even in low doses, be effective in reducing pain, anxiety and stress (21,22).

For the treatment of stress, microdosing can be beneficial due to the biphasic effects of cannabinoids. THC can help control anxiety in low doses and in high doses it could develop even more. Like CBD in low doses it can help anxiety, but one study claims it can promote awakening and in high doses it can induce drowsiness. Since CBD has an anxiolytic effect it can activate the serotonin receptor 5HT1A (23).

Over the past few decades, several studies and clinical trials have evaluated the use of CBD and THC as a possible treatment for stress, and promising results have been obtained. Several studies have shown an increase in endocannabinoid receptor signaling, slowing synaptic transmission at the level of the Central Nervous System. Some of these findings are described below:

For example, according to Li et al. (2022) (24), in a study carried out in São Paulo-Brazil, in order to determine the effects of CBD on plasma levels of cortisol (hormone associated with stress), applied to a sample of 11 volunteers between 18 and 60 years old, without any history of drug abuse or dependence. The results were very promising, indicating a very significant decrease in cortisol levels with doses of 300 and 600 mg of CBD (24).

Similarly, Appiah-Kusi et al. (2020) (25), in a study conducted in South London, aimed to find out whether CBD can help normalize stress levels in the body. A sample of 52 patients was available, of which 32 were at risk of psychosis (CHR) and 26 were healthy (HC). They were subjected to a Trier social stress test (stress induction paradigm). Half of the experimental group received 600 mg of CBD orally per day and the other half received identical placebo capsules (CHR-P) for 1 week. The results showed that the

cortisol concentration associated with stress exposure was higher in HC controls, while in patients with CHR-P, and CHR the concentration was lower (25).

For their part, Hindocha et al. (2020) (26), in a research carried out in Denver- Colorado focused on the effects of CBD through oral administration in patients with symptoms of chronic stress. A sample of 11 patients was included, under medication for 8 weeks with a flexible dose of a 25 mg CBD capsule per day, following a strict regimen. In the post-treatment evaluation and after daily monitoring, it was detected that 80% of the experimental group had a reduction in the severity of symptoms (anxiety, low mood, nightmares) after eight consecutive weeks of treatment. These results were very satisfactory, indicating that most of the patients tolerated CBD very well without any interruption in the treatment caused by the appearance of serious side effects (26).

Additionally, Childs et al. (2017) conducted a study in Chicago, United States, with the aim of determining the effectiveness of CBD in reducing stress-related effects using the Trier social stress test. A sample of 42 non-daily cannabis users aged 18 to 40, male and female, was used. In the process, the experimental group was administered an oral dose of 7.5 mg of THC and another dose of 12.5 mg. The results showed that the lower dose had a favorable effect, reducing the duration of negative emotional responses to stress. On the contrary, the higher dose produced small but significant increases in negative mood during the trial (27).

Currently, there is not enough scientific evidence to support the use of C. sativa for the treatment of stress in Ecuador. However, it is important to note that the use of cannabis for medicinal purposes must be supervised by a physician and must comply with local regulations and laws. In Ecuador, according to Ministerial Agreement 148, the use of medicinal cannabis is legal under certain conditions and must be prescribed by a licensed physician. In addition, it is important to note that cannabis consumption can have side effects and potential risks, such as increased heart rate, mood swings, decreased cognitive ability and coordination, among others (28).

Despite promising findings, several challenges need to be addressed for the effective use of CBD and THC in stress management in adults. First, although studies suggest that CBD and THC may have anxiolytic and anti-stress properties, chronic use of CBD and THC has been associated with an increased risk of cannabis dependence and abuse, especially in vulnerable individuals. This aspect should be taken into account when assessing the risks and benefits of therapeutic use (29).

Similarly, both THC and CBD may cause adverse effects such as altered perception, memory impairment, and cognitive difficulties in some individuals. Careful assessment of individual risks and benefits, as well as appropriate selection of dose and route of administration, are crucial when considering the therapeutic use of C. sativa metabolites

in stress in adults (30). It is important to note that research into cannabinoids and their therapeutic use is ongoing, and future developments may provide further insight into their efficacy and safety in treating stress. However, more scientific evidence is currently needed to support their widespread use (31).

Discussion

Stress is a condition that has a significant impact on people's health. According to the data presented, the use of phytocannabinoids present in Cannabis sativa, such as CBD and THC, are relatively effective in managing stress treatment in adults. Its action is exerted through the intervention of cannabinoid receptors (CB1 and CB2) which interact with the endocannabinoid system, thus modulating neuronal activity in brain regions involved in the stress response. Likewise, CBD influences the response of the hypothalamus-pituitary-adrenal (HPA) axis to stressful situations, limiting the release of cortisol (stress hormone) and attenuating the negative effects of stress on the body (31).

Several of these studies cited in this research indicate that these metabolites produce significant improvements in the vast majority of patients. Symptoms improved under the effect of flexible dosing, following a strict regimen of cannabidiol and tetrahydrocannabinol.

On the other hand, the manifestation of adverse effects did not have great clinical relevance that harmed the integrity and state of health. Additionally, it is relevant to consider that in those patients who received a single type of cannabinoid such as CBD, compared to those who received treatment with CBD and THC, they obtained more effective results in the reduction and improvement of symptoms, taking into account that there were no serious adverse effects that altered their state of health (31). In this sense, taking into account what was mentioned by Hindocha et al. (2020) (26), the therapeutic approach with these metabolites is safe and effective against stress, as long as there is a rigorous and strict dosage management of these.

In terms of sample size, it is worth noting that in the few studies with results favouring patients diagnosed with stress, who were subjected to oral administration of these compounds (THC and CBD), the number of participants was often quite small, which is a limitation from a statistical point of view and therefore does not yet allow these preliminary findings to be extrapolated to the entire population. For these reasons, although the results show therapeutic potential of these molecules for the treatment of stress, the aforementioned limitations generate the need to carry out new studies using more representative samples.

Conclusions

- The use of THC and CBD as treatments for stress in adults has been the subject of contemporary scientific research. Although these compounds obtained from cannabis have shown some therapeutic benefits, it is crucial to also recognize and understand their potential negative effects, especially in the context of stress management. It is essential to note that the response to these compounds can vary considerably between individuals, depending on genetic, environmental, and health factors. Before considering THC or CBD as a treatment for stress, it is imperative that individuals seek professional medical guidance and be informed about the potential risks, as well as therapeutic alternatives supported by solid scientific evidence. Continued research in this field is essential to better understand the risks and benefits of these compounds in the context of stress management in adults.

Conflict of interest

Authors must declare whether or not there is a conflict of interest in relation to the submitted article.

Authors' contribution statement

The authors contributed equally to the preparation of the article.

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