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Review article

Perspectives on the use of cannabinoids and their benefits in the treatment of chronic pain

Panorama Atual Sobre Dermatite Herpetiforme: uma revisão de literatura

Camila Brasil Barbosa[1], Isabelle Freiman Vieira Santos[1], Maria Fernanda Kezen Leite Mansur[1], Anderson Nunes Teixeira[2]

1 Medical Student, Faculdade de Medicina de Campos (FMC), Campos dos Goytacazes, RJ, Brazil.
2 Professor, Faculdade de Medicina de Campos (FMC), Campos dos Goytacazes, RJ, Brazil
Corresponding Author: Isabelle Freiman Vieira Santos
Contact: isabellefvsantos@gmail.com

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ABSTRACT

Pain is an unpleasant sensory and emotional experience associated, or similar to that associated, with actual or potential tissue damage. When it persists for more than 90 days, it is considered chronic pain (CD) and becomes a disease. The effect of cannabinoids on pain modulation improves the quality of life of patients with CD, since the management of this condition is commonly carried out using opioids, which can lead to the occurrence of dependence, withdrawal, tolerance and adverse effects. In this scenario, the present study aims to emphasizethe benefits of cannabinoid therapy in the treatment of CD, through a narrative review. As a result, it can be stated that phytocannabinoids bind to receptors of the endocannabinoid system and act as pain modulators, through analgesic action in inflammatory and hyperalgesia states, minimizing responses to harmful stimuli in behavioral and neurophysiological aspects. Aiming to treat CDs refractory to conventional treatment, the use of cannabinoids presents itself as a promising strategy, as they are capable of relieving pain and contributing to the reduction of adverse effects associated with the use of opioids, as demonstrated through studies.

RESUMO

A dor é uma experiência sensitiva e emocional desagradável associada, ou semelhante àquela associada, a uma lesão tecidual real ou potencial. Quando persiste por mais de 90 dias, é considerada uma dor crônica (DC) e se torna uma doença. O efeito dos canabinoides na modulação da dor apresenta melhoria da qualidade de vida dos pacientes com DC, visto que o manejo dessa condição é comumente realizado por opioides, que podem levar à ocorrência de dependência, abstinência, tolerância e efeitos adversos. Nesse cenário, o presente estudo visa enfatizar os benefícios da terapia com canabinoides no tratamento da DC, por meio de uma revisão narrativa. Como resultado, pode-se afirmar que os fitocanabinoides se ligam aos receptores do sistema endocanabinoide e atuam como moduladores da dor por ação analgésica em estados inflamatórios e de hiperalgesia, minimizando respostas aos estímulos nocivos em aspecto comportamental e neurofisiológico. Visando a terapêutica das DCs refratárias ao tratamento convencional, o uso dos canabinoides se apresenta como uma estratégia promissora, pois são capazes de atuar no alívio da dor e contribuir com a redução dos efeitos adversos associados ao uso de opioides conforme demonstrado em estudos.

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INTRODUCTION

As described by the International Association for the Study of Pain (IASP)[1], pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Additionally, it is characterized as a vital protective function of the human body in acute situations, capable of preventing the aggravation of a recent injury[2].

When pain persists for more than 90 days, it is considered chronic pain (CP). While acute pain is physiological, protective, and spontaneously improves when tissue injury heals, CP loses this function and becomes a disease itself, possibly independent of the causal event, without correlating in intensity with its causative agent[3]. This analysis is of great importance to obtain the most effective conduct for its treatment[4].

CP is among the Non-Communicable Chronic Diseases (NCDs) that cause the most limitations for patients and costs to healthcare systems, generating negative impacts on the individual's quality of life with serious consequences for their social and personal development[5]. Its prevalence in adults in Brazil is approximately 40%[6].

According to the World Health Organization (WHO), pharmacological treatment for CP consists of two protocols: for nociceptive and mixed chronic pain, a stepwise approach is used, including analgesics, anti-inflammatory drugs, adjuvant drugs, and opioids; for neuropathic pain, tricyclic antidepressants (TCAs) and antiepileptics are used, with opioids reserved for refractory cases[7].

Although the management of CP is commonly performed exclusively using analgesic medications, mainly opioids, long-term administration of this pharmacological class can cause numerous health problems for the patient, such as dependence, tolerance development, and withdrawal syndrome, in addition to increasing the risk of adverse effects[8].

In this context, the discovery of the endocannabinoid system (ECS) in the mid-1990s and its organic effects on pain modulation represented a source of medicinal possibilities with great potential for improving the quality of life of individuals with CP[9]. Its distribution in the peripheral and central nervous systems is broad, and among its numerous functions, this system is linked to regulatory activities affecting nociception, memory, appetite, the immune system, inflammation, the sleep-wake cycle, thermogenesis, cardiovascular function, metabolism, synaptic plasticity, as well as stress and emotion regulation[10, 11].

According to Santiago and Lima[11] (2023), the use of medicinal cannabis is historical, and its therapeutic effects result from the interaction of phytocannabinoids present in the Cannabis sativa L. plant: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which act on the endocannabinoid system, reducing nociception and the frequency of symptoms.

While THC is psychoactive, providing euphoria, antiemetic, analgesic, and hallucinogenic effects, CBD is a depressant, anticonvulsant, and anxiolytic with antipsychotic and anti-inflammatory properties[9]. Thus, CBD has the capacity to interact with endogenous receptors in the endocannabinoid system, reducing neuronal excitability, generating an analgesic effect, and being a potential compound applicable as an adjuvant in the maintenance of CP, in addition to providing therapeutic action in cases of psychosis, depression, epilepsy, and inflammation[12].

Therefore, this study aimed to highlight the possible benefits and efficacy of the therapeutic use of cannabinoids in treating chronic pain through a literature review.

MATERIAL AND METHODS

This is a narrative review regarding the efficacy of cannabinoid use for treating chronic pain. For this study, the literature review was conducted between December 2023 and January 2024, based on scientific articles using PubMed, SciELO, Lilacs, and Google Scholar databases. The keywords used

for the research were: Cannabinoids, Chronic Pain, Cannabidiol, Endocannabinoids. Inclusion criteria were full-text articles published in Portuguese, English, and Spanish, covering the years 2000 to 2024. Exclusion criteria were repeated studies and those not related to the objective of providing an overview of cannabinoid therapy's influence and implications on chronic pain. Nine studies based on pre-clinical and clinical trials were selected for developing results and discussion.

RESULTS AND DISCUSSION

Endocannabinoid System

The ECS is a neuromodulatory system that plays a crucial role in the development of the central and peripheral nervous systems, synaptic plasticity, and response to endogenous and environmental harmful stimuli. Understanding it is essential for using Cannabis sativa in treating chronic and neuropathic pain. It consists of cannabinoid receptors 1 and 2 (CB1 and CB2), endogenous ligands (endocannabinoids), and enzymes regulating endocannabinoid synthesis and degradation[13, 14].

Cannabinoid receptors are located at three distinct levels of pain processing: the periphery, the spinal cord, and the supraspinal level[15]. CB1 receptors are abundantly found in the central nervous system, responsible for most of the psychotropic effects of cannabinoids[14]. They are present in the basal ganglia, cerebellum, and hippocampus, regions that mediate effects affecting cognitive functions, pain, short-term memory, motor coordination control, hypothermia, and hyperphagia. They are also found in the spinal cord, dorsal spinal ganglia, enteric nervous system, adipocytes, endothelial cells, hepatocytes, muscle tissue, and gastrointestinal tract[16].

In contrast, CB2 receptors are mainly found in the peripheral nervous system and are more associated with immune system cells, exerting effects on inflammation and pain[13]. They relate to T cells, B cells, and activated microglial cells[17].

Besides acting on CB1 and CB2 receptors, cannabinoids can modulate pain through interaction with serotonin, opioid, acetylcholine, glycine, Gamma-aminobutyric acid (GABA) receptors, and larger endogenous pain circuits such as the endorphin/enkephalin subfamily of transient vanilloid/cation channels (TRPV) and the inflammatory system[11, 18].

Cannabinoids are divided into three types: endogenous (endocannabinoids), phytocannabinoids (derived from Cannabis sativa), and synthetic. Endocannabinoids are natural substances represented by anandamide (N-arachidonoylethanolamine) and 2-arachidonoylglycerol (2-AG). Anandamide is a partial agonist of CB1 and CB2 receptors and acts at the onset of pain, while 2-AG is a total agonist of these receptors, playing its role in pain resolution[19]. Although anandamide is a partial agonist, it has greater selectivity and affinity for CB1 than 2-AG, likely making it the primary ligand for cannabinoid receptors[18]. The ECS also includes enzymes responsible for the production, transport, and degradation of endocannabinoids: Diacylglycerol Lipase (DAGL), Fatty Acid Amide Hydrolase (FAAH), and Monoacylglycerol Lipase (MAGL)[20].

Endocannabinoids act as retrograde messengers, being produced in postsynaptic neurons and acting on presynaptic CB1 and CB2 receptors in an autocrine and paracrine manner. Unlike classic neurotransmitters synthesized and stored in synaptic vesicles, endocannabinoids are produced on demand[21]. Their synthesis is triggered by increased intracellular calcium concentration (Ca^{2+}), which occurs through neuronal depolarization or mobilization of intracellular deposits, or by direct enzymatic activation by Gq protein[22]. After synthesis, anandamide and 2-AG are transported across neuronal membranes through facilitated diffusion mediated by transporters, binding with affinity to CB1 and CB2 receptors[21]. Cannabinoid receptors are metabotropic, meaning they are coupled to G proteins. They mainly

bind to Gi proteins, although they can interact with Gs or Gq proteins occasionally[23]. CB1 receptor activation results in: 1) Inhibition of adenylyl cyclase, followed by decreased intracellular cAMP synthesis and reduced protein kinase A (PKA) activity, reducing phosphorylation of K+ channels and increasing K+ efflux from presynaptic terminals; 2) Inhibition of voltage-sensitive Ca+ channels; 3) Activation of GIRK (G protein-gated inward rectifier K+) channels, further increasing K+ efflux. This results in neuronal hyperpolarization and decreased release of excitatory neurotransmitters[23, 24]. Blocking Ca2+ channels reduces the exocytosis of glutamate and substance P, neurotransmitters involved in pain chronification[23]. In the periphery, CB1 activation controls the transduction of nociceptive stimuli[19].

CB2 receptors play an important role in immune function, inflammation, and pain modulation, especially in states of allodynia and hyperalgesia. Similar to CB1, CB2 activation promotes adenylyl cyclase inhibition, activating the MAPK cascade. In the microglia within the nervous system, these receptors explain the role of cannabinoids in modulating chronic neuropathic pain. Selective CB2 agonists suppress neuronal activity in the dorsal horn by reducing fiber activity. In the periphery, CB2 reduces the release of pro-inflammatory cytokines and algogenic factors related to pain transmission and modulation[16].

After their action, endocannabinoids undergo neuronal reuptake and are subsequently inactivated. Anandamide is converted into arachidonic acid and ethanolamine by FAAH, while 2-AG is degraded by MAGL into arachidonic acid and glycerol. This degradation process occurs both presynaptically (2-AG) and postsynaptically (anandamide), highlighting FAAH and MAGL activity regulation as crucial pharmacological targets. Cannabidiol, a phytocannabinoid present in high amounts in Cannabis sativa, inhibits FAAH and anandamide reuptake, thus maximizing its duration and action in the synaptic cleft, enhancing its analgesic effect[25].

According to Narouze[19] (2021), nociceptive stimuli trigger an increase in endocannabinoid release, resulting in pain modulation effects that can occur at peripheral, spinal, and supraspinal levels. In the periphery, endocannabinoids act on CB1 receptors in sensory afferent terminals, preventing transduction from nociceptive stimuli. On the other hand, CB2 receptors present in immune cells and keratinocytes influence endorphin release, acting on opioid receptors in primary afferent neurons, inhibiting nociception[19, 26].

At the spinal level, CB1 receptors in dorsal root ganglia and nociceptive terminals in the dorsal horn inhibit neurotransmitter release involved in pain transmission. CB2 receptors modulate central immune responses and exert antinociceptive effects[16].

At supraspinal levels, CB1 receptors inhibit ascending nociceptive transmission, especially in the thalamus and brainstem, and alter the subjective interpretation of pain by modulating neuronal activity in the amygdala and cortical areas. They also inhibit GABA release in the periaqueductal gray (PAG) and raphe nuclei, activating the descending pain inhibitory pathway[18, 19]. These mechanisms suggest that cannabinoids can suppress nociceptive transmission, confirming their analgesic action in chronic pain[13].

Phytocannabinoids in Pain Modulation

Phytocannabinoids THC and CBD, derived from Cannabis sativa, are lipophilic substances capable of crossing the blood-brain barrier and binding to receptors in the central and peripheral nervous systems, acting as pain modulators through analgesic effects, especially in inflammatory and hyperalgesia states[18].

These substances effectively minimize responses to painful stimuli both behaviorally and neurophysiologically. They inhibit wide dynamic range (WDR) neurons and nociception-specific neurons, suppress wind-up effects, and modulate thalamic and spinal neurons to control descending pain pathways[27].

THC, an analogue of endocannabinoid anandamide, is responsible for most of cannabis's pharmacological actions, such as analgesic, anti-inflammatory, antioxidant, antipruritic, bronchodilator, antispasmodic, and muscle relaxant activities, as well as psychotropic and memory effects. It acts as a partial agonist of both CB1 and CB2, with its antinociceptive action primarily mediated by CB1 through activation of supraspinal levels and serotonergic and noradrenergic descending pathways, which modulate pain[28].

THC can also act as a positive allosteric modulator of opioid receptors, suggesting their involvement in its antinociceptive effect. THC-induced analgesia is centrally mediated by the fronto-limbic positioning of cannabinoid receptors. Thus, THC can reduce discomfort from pain but not continuous intensity and hyperalgesia[28].

CBD, a non-psychoactive analogue of THC, is present in high concentrations in Cannabis sativa. Among its many activities are anticonvulsant, anxiolytic, analgesic, and anti-inflammatory actions without THC's psychotropic effect. CBD can synergistically interact with THC, improving its tolerability and safety by minimizing the occurrence of negative psychotropic effects and other adverse effects like anxiety, tachycardia, and sedation[18].

CBD's action involves numerous mechanisms that suppress neuronal excitability and pain perception[29]. With little affinity for CB1 and CB2, it acts on various targets, including non-cannabinoid G protein-coupled receptors (e.g., serotonergic receptors), ion channels (TRPV1, TRPA1, glycine receptors, and others), and PPAR. CBD also enhances anandamide effects in the ECS by inhibiting FAAH and thus its hydrolysis, and inhibiting its reuptake[19].

Impact of Cannabinoids on Chronic Pain Treatment

Knowledge of the endocannabinoid system and phytocannabinoids' potential to modulate pain has led to pre-clinical and clinical studies exploring practical applications for these substances in chronic pain treatment and their implications for patients' quality of life. Pre-clinical studies show cannabinoids' significant analgesic effects, especially in chronic inflammation and neuropathic models, by inhibiting mast cell degranulation and neutrophil migration, activating CB2 receptors, reducing inflammation, and chronic pain[30].

A recent systematic review with a meta-analysis of 17 pre-clinical studies highlights cannabinoids' role in treating chronic pain, migraines, and headaches[31]. The synergistic effect of co-administration of opioids and cannabinoids for pain relief results in a 36-fold reduction in effective morphine dose with THC compared to morphine alone[32]. An observational analysis of 1,321 patients with chronic pain (back pain, migraines, fibromyalgia, Crohn's disease, osteoarthritis, and rheumatoid arthritis) found 80% replaced opioids and benzodiazepines with medicinal cannabis, reporting fewer side effects and symptom relief. These results support previous clinical studies suggesting cannabis as an effective analgesic and a potential opioid substitute[33]. Another study reported that 53.2% of 97 chronic pain patients on opioids improved analgesia and reduced opioid use after using pure CBD for eight weeks. Since constant opioid use can lead to adverse effects like constipation, urinary retention, and respiratory depression, CBD's approach offers a perspective on reducing these medications' use, avoiding such effects[34].

Another systematic review demonstrated that cannabinoids not only improve subjective pain perception but also provide symptomatic relief, particularly for sleep disorders, appetite disturbances, and nausea. Patients reported improved focus and overall functioning[35].

A meta-analysis of 32 randomized clinical trials involving 5,174 patients discussed medicinal cannabis and cannabinoids' use in non-cancer and cancer-related chronic pain. The study showed that patients experienced over 30% pain

reduction with the substance compared to placebo, as well as improved physical functioning[36].

The importance and efficacy of cannabis in advanced cancer patients, who often struggle with conventional opioid therapy, is also noteworthy. A study with severely ill cancer patients over 24 weeks using inhaled nabiximols (synthetic cannabis-based medication) in low doses showed a 26% improvement in pain and sleep quality compared to baseline levels, highlighting cannabinoids' promising role as analgesics for cancer patients[37]. Cannabis treatment also demonstrated significant symptom relief like insomnia, anxiety, nausea, and pain in palliative care patients[38].

Among chronic pain-associated diseases, multiple sclerosis sees a high prevalence of cannabinoid use. A study investigated cannabis spray formulation use over four weeks, resulting in over 50% pain reduction in patients. Significant improvements in bladder control, muscle spasms, and spasticity were reported, frequent symptoms of the disease[39].

The use of cannabinoids is indicated for treating chronic pains of various etiologies such as migraines, neuropathic pain associated with fibromyalgia, rheumatoid arthritis, multiple sclerosis, peripheral neuropathies, and cancer-related pain refractory to conventional treatment[40]. Combining cannabinoid and opioid agents is a promising approach due to the pharmacological synergy between these substances, enhancing analgesic effects, reducing doses used, and maintaining therapeutic effects[1].

Although cannabinoid-based therapies and their studies are still recent, there is a significant positive influence of their use as adjunctive analgesic treatment in chronic pain maintenance, supported by growing clinical and pre-clinical trials. For refractory or poorly responsive CPs to conventional treatment, cannabinoid use presents a satisfactory option, capable of relieving pain and associated symptoms, improving patient quality of life, and reducing adverse effects from opioid use.

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