



## The diverse use of cannabis derivatives in the treatment of chronic pain

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### Abstract

#### Introduction

Chronic pain is a pathology that affects thousands of people annually, resulting from different factors and having different etiologies. Several treatments are available today for it, but some cases are still refractory.

#### Objective

This article seeks to highlight the impacts of using cannabis derivatives as an alternative in the treatment of chronic pain.

#### Methodology

This is a bibliographic review that used the PubMed and Scopus databases to search for and select articles on the use of cannabis derivatives in the treatment of chronic pain. Only clinical trials, cohort studies, case-control studies, and case reports were selected.

#### Results

336 articles were found, after applying the inclusion and exclusion criteria, 7 articles were selected to be analyzed, of which 3 used vaporized formulations, 3 used compounds for oral ingestion and 1 analyzed topical use.

#### Conclusion

Good efficiency was observed in the use of cannabis derivatives in the treatment of chronic pain, especially compounds rich in delta-9-tetrahydrocannabinol (THC).



## Introduction

Pain is an unpleasant sensory or emotional experience that is associated with a real or potential injury (1). It is not a simple phenomenon, it involves several mechanisms and systems, from physiological changes to psychosomatic effects (2).

Regarding the classification of pain and its types, it is studied in terms of its pathophysiological mechanism, being subdivided into somatic or visceral nociceptive, central or peripheral neuropathic and those of psychogenic origin. Another way to classify it is according to its duration, being divided into chronic or acute (3,4).

Epidemiological studies indicate a prevalence of chronic pain of around 1-2%, while neuropathic pain is linked to a prevalence of 6.9-10% (2,4). Other aspects related to the prevalence of chronic pain that can be observed are the higher incidence in females (69%) compared to males (52.2%) (4,5). Furthermore, it is noted that the main cause of chronic pain is headache, followed by low back pain and pain in the lower limbs (5).

Currently, the lines of treatment for pain are very broad, covering both medicinal and non-medical routes. Regarding medication routes, drugs such as opioids, anti-inflammatories, muscle relaxants, anticonvulsants and antidepressants are the main ones. In the non-drug route, alternatives such as thermotherapy, nerve blocks, massages, acupuncture, cutaneous electrical stimulation and spinal electrodes are the most studied (1,3,6,7).

The clinical application of cannabis derivatives dates back to ancient times, with reports from China in 2737 BC showing their use for purposes such as muscle relaxant, anticonvulsant, analgesic, sedative and several others<sup>6</sup>. The introduction of the substance to the West dates back to the mid-19th century, with the application of extracts such as hypnotics and anticonvulsants (8).

With the ability to isolate substances derived from cannabis, as well as delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD) and other phytocannabinoids (CF), it was possible to identify the physiological effects of these substances (1,6). Two types of receptors were determined which have affinity with cannabis derivatives, named CB1 and CB2. CB1 receptors are located in the central nervous system (CNS) and are closely associated with cognitive functions, pain and memory pathways. CB2 receptors are located in other organs, such as the peripheral system, spleen, tonsils and are closely associated with the immune system (1,6).

Therefore, given the growing number of studies on this topic, the present study seeks to highlight the impacts of using cannabis derivatives as an alternative in the treatment of chronic pain.

## Methods

### Eligibility and exclusion criteria

Studies that had as their main objective the analysis of the use of cannabis derivatives in the treatment of chronic pain were included in this review. Furthermore, the following study designs were selected: clinical trials, cohort studies, case-control studies and case reports. The selection included articles published in the English language between 2019 and 2024

Conference abstracts, reviews, notes to the editor and any other study that did not meet the eligibility criteria listed above were excluded. Furthermore, studies that did not analyze the use of cannabis derivatives for the treatment of chronic pain were excluded.

### Databases

Between 03/22/2024 and 03/24/2024, the PubMed and Scopus databases were consulted and articles were selected.

### Search and selection strategy

The search terms used were "pain", "pathophysiology", "cannabis", "medical cannabis", "cannabidiol" and "THC". These terms were organized along with Boolean operators as follows: (((((pain) AND (pathophysiology)) AND (cannabis)) OR (medical cannabis)) OR (cannabidiol)) OR (THC).

In the Scopus database, organizing the search terms along with Boolean operators, the following search phrase was used: TITLE-ABS-KEY (pain AND pathophysiology AND cannabis OR medical AND cannabis OR cannabidiol OR thc ) AND PUBYEAR > 2018 AND PUBYEAR < 2025 AND ( LIMIT-TO ( DOCTYPE , "ar" ) ). We chose to select the "article" filter for document types.

In the PubMed database, the following search phrase was used: (((((pain[Title/Abstract]) AND (pathophysiology[Title/Abstract])) AND (cannabis[Title/Abstract])) OR (medical cannabis [Title/Abstract])) OR (cannabidiol[Title/Abstract])) OR (THC[Title/Abstract]). Furthermore, the filters "publication year" 2019 – 2024 and "article type" Clinical trial and Randomized controlled trials were selected.

The search and selection was carried out in two stages, the first being the selection by reading the titles and summaries of the articles found. The second one consisted of the full reading of the studies selected in the first stage.

### Data collection

Data from each selected study were collected and tabulated.



The data tabulated were: first author, title, country of origin, type of study, methodology and results.

## Results

In the systematic literature search, a total of 336 articles were found, of which, after reading the titles and abstracts,

319 articles were excluded according to the inclusion and exclusion criteria of this review. After reading the text in full, 10 articles were excluded, one of them due to not being in English and the other 9 by applying the inclusion and exclusion criteria. In the end, 7 articles were selected to be analyzed. In line with the PRISMA methodology for reviews, Figure 1 was created to illustrate the flowchart of the search and selection of articles.

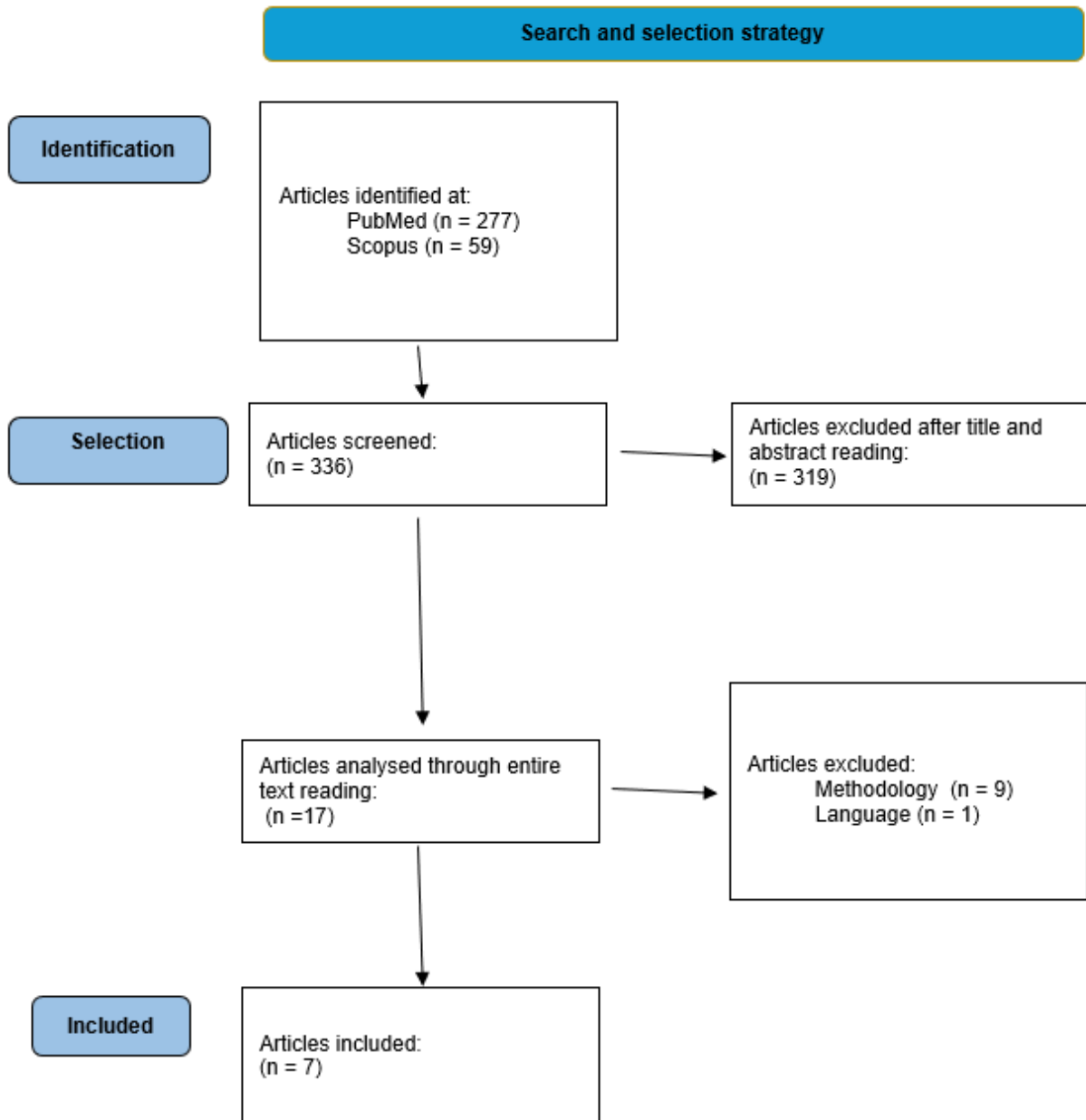




Table 1 contains information on the seven selected articles, namely: author, title, country of origin, type of study, methodology and results.

**Table 1.** Extraction of data from selected articles (author, title, country of origin, type of study, methodology and results)

First author	Title	Country	Study type	Methodology	Results
Abrams DJ, 2020	Effects of inhaled cannabis for pain in adults with sickle cell disease: A randomized clinical trial	United States of America	Randomized double-blind clinical trial	Composition: vaporized CBD + THC. Program: two hospitalizations with a minimum interval of 30 days between them; each hospitalization lasted 5 days and 4 nights; patients were subjected to cannabis inhalation three times a day (8 AM, 2 PM and 8 PM); the medications they were already using for pain were not discontinued during hospitalizations and during the research period; To analyze pain improvement, the visual analogue pain scale (VAS) was used, which was applied at admission and two hours after morning inhalation.	23 patients completed the research protocol. There was no statistical relevance observed in the inhalation of cannabis VS placebo in terms of pain perception, on day 1 it was -5.3 (8.1) (P = .51), on day 2 it was -10.9 (7.0) (P = .12), on day 3 it was -16.5 (9.2) (P = .07), on day 4 it was -8.9 (6.7) (P = .19), and on day 5 it was -8.2 (8.1) (P = .32). There was a statistical improvement in the patients' mood (day 1: 0.96 [0.59]; day 5: -1.4 [0.6]; P = .02). There was no statistical significance regarding the reduction in opioid use (2.05 [0.21] vs 2.09 [0.22]; P = .20).
Almog S, 2020	The pharmacokinetics, efficacy, and safety of a novel selective-dose cannabis inhaler in patients with chronic pain: A randomized, double-blinded, placebo-controlled trial	Israel	Randomized double-blind clinical trial	Composition: THC vaporized using the Syge Inhaler device. Program: each patient participated in three visits to the clinic, with a time interval of at least two days. At visits, only one inhalation with a dose of 0.5 mg or 1.0 mg of THC or placebo was administered in random order. Medications that patients were already using to control pain were not discontinued. To evaluate the response to pain, the visual analogue pain scale was used at a time interval of 5, 15, 30, 60, 90, 120 and 150 minutes after inhalation.	24 patients completed the research protocol. Of these, 23 participated in the placebo group, 22 in the 0.5 mg/inhalation group and 24 in the 1 mg/inhalation group. A statistically relevant drop in VAS was observed after 15 minutes of inhalation, with a peak at 120 minutes. The reduction in VAS was greater in the group that inhaled 1.0 mg compared to the group that inhaled 0.5 mg (RM-ANOVA, p = .0015 [95% CI, 0.53;2.23], p = .0058 [95% CI, 0.35;2.08], respectively). The average reduction in VAS was 1.95 points in the 0.5 mg group and 2.95 points in the 1.0 mg group.
Bebee B, 2021	The CANBACK trial: a randomised, controlled clinical trial of oral cannabidiol for people presenting to the emergency department with acute low back pain	Australia	Randomized double-blind clinical trial	Composition: CBD taken orally in a single dose. Program: patients with acute low back pain (patients already hospitalized and emergency room patients) received the service's standard treatment for acute low back pain (paracetamol 1g orally and ibuprofen 400 mg orally) and then received placebo or the intervention (CBD 400 mg orally). To evaluate the response to pain, a verbal numerical scale from 0 (absence of pain) to 10 (worst pain of life) was used at time intervals of 0, 30, 60, 90 and 120 minutes after the intervention. The primary outcome analyzed was the response at 120 minutes.	100 patients completed the research protocol, 50 of whom participated in the placebo group and 50 in the intervention group. No statistically relevant difference in pain response was observed in the intervention group relative to the placebo group [(6.2 points; 95% CI, 5.5–6.9 points in the intervention group) (5.8 points; 95% CI, 5.1–6.6 points in the placebo group) (absolute difference, -0.3 points; 95% CI, -1.3 to 0.6 points)].
Chaves C, 2020	Ingestion of a THC-Rich Cannabis Oil in People with Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial	Brazil	Randomized double-blind clinical trial	Composition: THC + CBD orally at a concentration of 48/1. Program: patients with fibromyalgia or widespread chronic pain were stratified into two groups, one placebo and one intervention. In the intervention group, patients received 30 ml of a solution containing THC (24.4 mg/ml), CBD (0.51 mg/ml) and other cannabinoids. At the beginning of the program, each participant received 30 ml of the solution, being instructed to receive one dose per day (approximately 1.2 mg of THC and 0.02 mg of CBD) sublingually. For eight weeks, every ten days, patients were evaluated; In these meetings, they were instructed to increase one dose per meeting, in addition to completing the Fibromyalgia Impact Questionnaire (FIQ).	18 patients completed the research protocol, 9 from the placebo group and 9 from the intervention group. After the eight weeks of intervention, a statistically significant difference (p < 0.005) was observed in the FIQ score between the placebo and intervention groups. In relation to pain, one of the variables of the FIQ questionnaire, a reduction of 4.53 points was observed in the intervention group (p = 0.011), while in the placebo group the reduction was not statistically significant, being 1 point (p = 0.235)
van de Donk T, 2019	An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia	Netherlands	Randomized double-blind clinical trial	Composition: CBD + THC vaporized. The combination of these substances varied, with three possibilities: Bedrocan (22% THC + 1% CBD), Bediol (6.3% THC + 8% CBD) or Bedrolite (9% CBD + ~1% THC). Program: patients with fibromyalgia underwent the intervention program. Five sessions were carried out, and in each of them, patients could receive one of the three compounds above or the placebo. There were two tests to evaluate the response to pain. The first test was the pressure pain test, being applied at 0, 12, 22, 32, 42, 62, 92, 122, 152 and 182 minutes after inhalation. The second test was the electrical pain test, being applied at 0, 10, 20, 30, 40, 60, 90, 120, 150 and 180 minutes after inhalation..	20 patients completed the research protocol. Regarding the electricity pain test, none of the three cannabinoid formulations were superior to placebo (intervention vs placebo (Bedrocan p = 0.383) (Bediol p = 0.825) (Bedrolite p = 0.954)). In relation to pressure pain tests, a greater pain tolerance was observed in two cannabinoid compounds, and in the one where the concentration of both THC and CBD was higher, tolerance was also greater (intervention vs placebo (Bedrocan p = 0.006) (Bediol p < 0.001) (Bedrolite p = 0.095)).
Palmieri B, 2019	Spontaneous, anecdotal, retrospective, open-label study on the efficacy, safety and tolerability of cannabis galenic preparation (Bedrocan)	Italy	Observational study	Composition: Bedrocan (22% THC + <1% CBD). Program: patients with persistent, severe or chronic symptoms who were admitted to the "Second Opinion Medical Consulting Network" program. Patients were given 5 g of Bedrocan diluted in 50 ml of olive oil; in the first three months, they were instructed to ingest twice a day, with a maximum of 0.5-1 ml/day in the first three months and subsequently reducing to 0.5 ml/day after the 12th week. The response to pain was assessed using a questionnaire on the patients' quality of life.	20 patients completed the research protocol. There was a satisfactory and statistically relevant response to the use of sublingual Bedrocan (p < 0.03)
Xu DH, 2020	The Effectiveness of Topical Cannabidiol Oil in Symptomatic Relief of Peripheral Neuropathy of the Lower Extremities	United States of America	Randomized double-blind clinical trial	Composition: Theramu Relieve (250 mg of CBD in 3 fl. oz). Program: Patients with symptomatic peripheral neuropathy were divided into two groups, a placebo group and an intervention group. The program lasted 4 weeks. The intervention group received Theramu Relieve CBD cream, which contains 250 mg of CBD in the 3 fl tube. oz (~90 mL), being instructed to apply the cream up to a maximum of four times a day in the area of pain. Pain response assessment was performed using the Neuropathic Pain Scale in weeks two and four.	26 patients completed the research protocol. Pain reduction was observed in the following subtypes of EDN: intense pain, acute pain, cold pain and itching. A greater reduction in severe pain (p = 0.009), acute pain (p < 0.001) and itching (p = 0.001) was observed.



## Discussion

It was observed that the use of cannabis derivatives in the treatment of chronic pain is an effective and safe alternative. Furthermore, compounds rich in THC are the best when it comes to responding to chronic pain.

Current research on the use of cannabis derivatives in the medical field uses CBD and THC formulations to be administered orally (16). However, it was noted that a current trend is the use of this class of medication in the most diverse presentations available, such as vaporizers and topicals (9,10,13).

It was observed that when administration is via inhalation, THC may be the main compound associated with analgesia (10,13), in line with what has been observed in the literature, where several studies relate the inhalation route as a promising route of drug administration, having several pros and cons (17). Furthermore, it is established in current literature that CB1 receptors are the main ones linked to pain modulation in the endocannabinoid system, and these receptors have a great affinity for THC (7,18).

The study of the use of cannabis derivatives in the treatment of acute pain is an emerging issue along with its use in the treatment of chronic pain. A recent meta-analysis showed that there is no statistical relevance of the use of these medications in relation to the use of non-steroidal anti-inflammatory drugs (NSAIDs) already well established in clinical practice (19,20). This data was corroborated by what was evidenced in the present study (10,14).

In the articles analyzed here, a constant was observed: the higher the concentration of THC in relation to that of CBD, the better the response to pain. This reality was also elucidated by a recent systematic review (21), as well as a lower frequency of adverse events, which are more benign.

The use of a CBD-based ointment was observed in the treatment of chronic neuropathic pain (15), showing an improvement in the pain condition. This form of administration, to date, is the only one found in the literature, and may be a new alternative for this type of pain, especially in cases refractory to already structured drug treatment.

## Conclusion

The use of cannabis derivatives in the treatment of chronic pain has proven to be effective in the most diverse forms of administration. It is noted that the effectiveness of this class of medications is not perfect and is susceptible to several variables that are increasingly being clarified through research.

It is evident that several advances have already been made in the research of these medications, it has been observed

that delta-9-tetrahydrocannabinol is as effective - and sometimes superior - as cannabidiol in the treatment of chronic pain. However, the reasons for the divergence observed in some studies still lack physiological explanations and the pharmacokinetics of cannabis derivatives.

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