International Journal of Orthopaedics Research
www.orthopaedicsjournal.in
E-ISSN: 2663-0923, P-ISSN: 2663-0915
Received: 13-11-2022, Accepted: 30-11-2022, Published: 16-12-2022
Volume 4, Issue 2, 2022, Page No. 83-88

Topical cannabinoids for the management of musculoskeletal pain: Understanding and review

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Abstract
Musculoskeletal pain is a common healthcare burden, and is often managed with oral pain relief medications. When used recurrently or long-term, such medications can present adverse effects and tolerability concerns. Recent research on the endocannabinoid system and cannabinoid receptors has opened a new avenue in pain management. Cannabinoids such as Cannabidiol (CBD) and others from the leaf extract of *Cannabis sativa*, can be administered as topical oils, creams and gels, and be a useful alternative and adjunct in the management of chronic musculoskeletal pain. Cannabinoids act via multiple receptors and pathways to reduce pain transmission and perception. Early pre-clinical and clinical evidence has shown the efficacy, safety and tolerability of topical cannabinoids in arthritis pain, back pain, myofascial, and neuropathic pain. Larger and a greater number of clinical studies as well as real-world evidence can add further insights.

Keywords: musculoskeletal pain, cannabinoids, cannabidiol (CBD), topical, cannabis

Introduction
Musculoskeletal pain is a significant health care burden that compromises quality of life. There is a gamut of anti-inflammatory and analgesic pain relief agents available. These include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids and gabapentinoids. These oral medications for chronic musculoskeletal pain while effective, rarely prove to be a practical long-term or recurrent option due to issues of adverse effects and tolerability. Topical medication represents an effective, safer, and well tolerated option especially for recurrent and prolonged use. The currently available topical pain relief armamentarium mainly includes NSAIDs, and counterirritants. These act at the peripheral site of injury to reduce inflammation and aid local pain relief.

Understanding Cannabinoids
Cannabinoids are a class of compounds found in the *Cannabis sativa* plant. That is why they are also called phytocannabinoids. The word "marijuana" refers to the species of *Cannabis sativa* that contain substantial amounts of tetrahydrocannabinol (THC), that is responsible for psychoactive effects and an altered stimulated mental state. However, strains of *Cannabis sativa*, like Hemp that are cultivated for medicinal and industrial purpose, though rich in cannabinoids mainly Cannabidiol (CBD) as well as others like Cannabinol (CBN), Cannabigerol (CBG) and more than 100 other cannabinoids, have low quantity of THC (usually less than 0.3%) [1]. *Cannabis sativa* leaf extract also contains substances called terpenes that potentiate the effect of cannabinoids. Thus, cannabinoids can be an effective addition to the armamentarium of pain relief medications.

Mechanism of Action
The endocannabinoid system (ECS) is a widespread neuromodulatory system in our body that plays important roles in central nervous system (CNS) function, nerve and synaptic transmission, and the response to endogenous and environmental insults [2]. The ECS is comprised of cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and the enzymes that synthesize and degrade the endocannabinoids. The best studied endogenous cannabinoids are 2-arachidonoyl glycerol (2-AG) and arachidonoyl ethanolamide (anandamide-ANA).
Cannabinoids act on multiple levels of pain transmission and are a unique class of medicines for pain relief. The mechanisms of the analgesic effect of cannabinoids include desensitization of peripheral nociceptive receptors, inhibition of the release of neurotransmitters and neuropeptides from presynaptic nerve endings, modulation of postsynaptic neuron excitability, inhibition of ascending nociceptive pain transmission, activation of descending

inhibitory pain pathways, reduction of neural inflammation, and reduction in emotional and cognitive manifestations of pain [3, 4].

Cannabinoids (exogenous phytocannabinoids or endogenous cannabinoids) exert their action through multiple receptors (Table 1) [5-7]. These are mainly the G protein-coupled cannabinoid receptors CB1 and CB2. Other important G protein-coupled receptors involved include GPR55 proposed to be classified as CB3, GPR18 and GPR119. The nociceptive transient receptor potential cation channels mainly TRPV1 (as well as TRPV2 and 3), are also an important target. Other pathways of the action of cannabinoids are through peroxisome proliferator-activated receptor (PPARα and PPARγ) agonism, ion channels with the serotonin 5-HT_{1A} receptor, opioid receptors, intracellular calcium release, and inhibition of adenosine uptake.

Phytocannabinoids modulate the endogenous cannabinoids of the endocannabinoid system (ECS), by inhibiting the enzymatic degradation of AEA and 2-AG [8]. Terpenes present along with cannabinoids in the leaf extract have anti-inflammatory and antioxidant properties, and also mimic some of the action of cannabinoids. When administered as an extract with different cannabinoids like CBD, CBG, CBN and several others, along with terpenes, the overall action is amplified in a synergistic manner, described as the 'entourage effect' [9].

Table 1: Cannabinoid Receptors [5-7]

Receptor	Location
CB_1	Mainly Brain and other parts of Central Nervous System. Others – Muscle, Endocrine glands and Abdominal organs
CB_2	Immune system (White Blood Cells, Tonsils, Spleen), Brain, Peripheral Nerves, Digestive tract.
TRPV (1, 2, 3)	Skin, Muscle, Bone, Liver, Kidney, Bladder, Digestive tract, Brain, Fat cells and Reproductive organs
GPR55	Brain, Bone, Immune system, Digestive tract (intestines), Bladder and Reproductive Organs.
GPR18	Bone Marrow, Immune System, Reproductive System
GPR119	Digestive tract, Pancreas

CB - cannabinoid receptors; GPR- G protein-coupled receptors TRPV- transient receptor potential cation channel

Cannabinoids are lipophilic compounds and are rich in the leaf extract of *Cannabis sativa* plant from which they are commonly derived. Enteric bioavailability is low, due to the hydrophobic nature of CBD and first-pass metabolism. As topical formulations, their lipophilic nature and delivery in a suitable carrier vehicle, allows penetration through skin pores and sebum, and binding to different cannabinoid receptors present in skin, muscles and joints. This leads to the local pain modulating action of topical cannabinoids at the site of application, without significant systemic absorption.

Animal studies with plasma data have shown transdermal penetration of cannabinoids with reduction in inflammation, pain-related behaviors, joint swelling, limb posture scores for spontaneous pain, immune cell infiltration and thickening of the synovial membrane in a dose-dependent manner, in a rat model of arthritis.[10] CBD shows better penetration than THC (by 10 times) and CBN. Suitable carriers like ethanol and oils can further enhance topical penetration.

Cannabis seed oil serves as an effective vehicle for delivering cannabinoids [11]. In a topical preparation, the seed oil helps to increase the penetration of cannabinoids from the leaf extract. The seed oil is rich in 3 poly unsaturated fatty acids (PUFAs): linoleic acid, alpha-linolenic acid, and gamma-linolenic acid with a favourable ratio of omega-6 (linoleic acid) to omega-3 (alpha-linolenic acid) fatty acids of 2:1 to 3:1 [12]. It is also rich in antioxidants like tocopherols, polyphenols and flavonoids, along with important minerals [13]. Therefore, the seed oil exerts an anti-inflammatory and anti-oxidant action adding to the benefit derived from cannabinoids for chronic musculoskeletal pain and inflammation. Cannabis leaf extract containing cannabinoids formulated in seed oil are available for topical application and pain relief, in many countries including India (Oreka+™). Other topical cannabinoid preparations like gels, creams, and transdermal patches have also been globally developed [14].

Regulatory and Legal aspects

The legal and regulatory aspects related to cannabinoids vary from country to country, however the medical use and benefits of cannabinoids are now widely accepted. In India, as per the Narcotic Drugs and Psychotropic Substances (NDPS) Act, trade and consumption of marijuana or use of the *Cannabis sativa* fruiting flowers and buds, is illegal. However, the law does not restrict the medicinal use of seeds and leaves of the plant [15]. Cannabis leaf extract in seed oil as topical use for medicinal purpose and pain relief has received Indian regulatory approval. Few states in India have even legalized *Cannabis sativa* /Hemp cultivation.

Scientific and Clinical evidence

A review of the scientific evidence for cannabinoids in pain management was conducted with relevant study publications from PubMed and Google Scholar data bases, as well as from web updates of associated clinical societies and foundations.

Cannabinoid receptors present a therapeutic target for managing musculoskeletal pains especially due to arthritis. Scientific evidence of the same was seen in a study with 32 osteoarthritis (OA) and 13 rheumatoid arthritis (RA)

patients undergoing total knee arthroplasty [16]. Results showed that CB1 and CB2 protein and RNA were present in the synovia of OA and RA patients. The endocannabinoids anandamide (AEA) and 2-arachidonyl glycerol (2-AG) were identified in the synovial fluid of OA and RA patients, but not normal volunteers. This data predicted that the cannabinoid receptor system present in the synovium may be an important therapeutic target for the treatment of pain and inflammation associated with OA and RA. Similarly, another study showed that chondrocytes from joints in patients with symptomatic OA were shown to express a wide range of cannabinoid receptors including cannabinoid receptors 1 and 2 (CB1 and CB2), G-protein-coupled receptors (GPR55) and peroxisome proliferator-activated receptors alpha and gamma (PPARα and PPARγ), even in degenerate tissues, demonstrating that these cells could respond to cannabinoids [17].

Though there is still a lack of high-quality evidence for medical cannabis in the core orthopaedic areas, the best available evidence suggests cannabis can be effective for managing arthritis pain, and back pain. This was based on a review of 118 studies with cannabinoids and general musculoskeletal pain that showed effectiveness in 72% [18]. Another review of the evidence and current guideline recommendations for use of cannabinoids in chronic, non-cancer musculoskeletal pain demonstrated a statistically significant reduction in chronic pain conditions with cannabinoids, compared with placebo, suggesting that cannabinoids may be considered as an adjunctive therapy in pain [19]. In a metanalysis, participants of the 49 included studies reported that medical cannabis use helped them to reduce chronic musculoskeletal pain with only minor adverse effects, and some also reported improved psychological well-being [20].

The Arthritis Foundation conducted a survey in 2019 in 2600 patients living with arthritis for over 10 years as industry reports show that people who buy CBD, cite arthritis and/or pain from arthritis as one of the most common reasons for purchasing CBD [21]. The survey gave insights into the usage and benefits of cannabinoids, for chronic musculoskeletal pain (Table 2). It was seen that CBD topical formulations are used by more than half the arthritis population surveyed, and the majority of the population reported relief from pain and symptoms of arthritis.

Table 2: Insights from Arthritis Foundation survey in 2019 in 2600 patients living with arthritis for over 10 years. [21]

Data Insight	Percentage Patients
Currently using CBD, used in past or considering using it.	79%
Daily use in those currently using CBD	63%
CBD as topical formulations for application	55%
Liquid CBD forms	62%
Currently using for managing arthritis symptoms	87%
Perceived pain relief	94%
Perceived improvement in physical function	67%
Perceived relief from morning stiffness	30%

In another exploratory cross-section study in 2020, a novel anonymous questionnaire was created to evaluate perceived efficacy of cannabidiol for the treatment of arthritis in 428 patients [22]. CBD use was associated with improvements in pain (83%) and physical function (66%), with the osteoarthritis group having greater percentage reduction ($P=0.020$) and point reduction ($P<0.001$) in pain compared to rheumatoid arthritis and other autoimmune arthritis. The majority (60.5%) reported a reduction or cessation of other medications after CBD use including anti-inflammatories (49%), paracetamol (36%), and opioids (27.5%).

There are still more studies needed on the use of topical cannabinoids in musculoskeletal pain. Topical Cannabidiol (CBD) has shown promise in reducing pain and inflammation in pre-clinical models. A study examined efficacy of transdermal CBD gel (0.6-6.2 mg/day doses) for reduction in inflammation and pain, and assessing adverse effects in a rat complete Freund's adjuvant-induced monoarthritic knee joint model [23]. Transdermal CBD gel significantly reduced joint swelling, limb posture scores as a rating of spontaneous pain, immune cell infiltration, and thickening of the synovial membrane in a dose-dependent manner. Paw withdrawal latency (PWL) in response to noxious heat stimulation that determined nociceptive sensitization, and exploratory behaviour that ascertained animal's activity level, recovered to near baseline level. Immunohistochemical analysis of spinal cord and dorsal root ganglia revealed dose-dependent reductions of pro-inflammatory biomarkers. Exploratory behaviour was not altered by CBD indicating limited effect on higher brain function. This preclinical study suggested that topical CBD application has therapeutic potential for relief of arthritis pain-related behaviours and inflammation without evident adverse effects.

Similarly, another study in Wistar rats with induced osteoarthritis showed that topical CBD (100-300ug) dose dependently and significantly increased withdrawal threshold and weight bearing, reduced acute transient joint inflammation, and prevented development of MIA (sodium monoiodoacetate intra-articular injection) induced joint pain later. Topical local administration of CBD was found to block OA pain and was also neuroprotective.[24]

A meta-analysis of 46 studies (6 human - 1 randomized controlled trial and 5 case studies/series, and 40 animal) reported no adverse events to topical cannabinoids with preliminary evidence of decreased pain ratings, and prolonged analgesic response in peripheral cannabinoid groups compared with controls [25].

A clinical study evaluated the efficacy and safety of a topical CBD gel for osteoarthritis (OA) knee pain in 320 human adults aged 41-78 years [26]. Patients met ACR criteria for OA of the knee and underwent a 1-week washout to stop current anti-inflammatory agents/other analgesics (except paracetamol) followed by a 7 to 10-day baseline period capturing daily worst pain ratings using a 0 to 10 numeric rating scale. The study was a randomized, double-blind, placebo-controlled, multiple-dose study with 250/500mg CBD gel twice daily application, for 12 weeks. The primary efficacy endpoint was the change from baseline in the weekly mean of the 24-hour average worst pain score at Week 12. The secondary endpoint was the responder analysis, defined as average weekly improvement in worst pain score of > 30% and decrease in WOMAC physical function sub scale of at least 20% at last observation. (Figure 1)

The average baseline mean worst knee pain score in this study was 6.9. Week 12 mean reduction from baseline in average worst knee pain score was -2.64 for CBD gel 250 mg/day (n= 106), -2.83 for CBD gel 500 mg/day (n = 105) and -2.37 for placebo (n =103). Patients using CBD gel significantly outperformed placebo for the responder analysis (52.7% vs 34.1%, p = 0.016). Men treated with CBD gel had significantly greater reductions from baseline in average worst knee pain scores than placebo-treated men. (-2.68 vs -1.70, p= 0.049) and greater performance in the responder analysis (60% vs 26.7%, p = 0.003), as compared to men who received placebo. Patients with the least amount of variability in baseline pain scores had greater performance in the responder analysis in both the 250 mg/day and 500 mg/day CBD gel as compared to placebo. There were 2 treatment emergent adverse events: application site dryness (3.8% vs 0.9%) and headache (3.3% vs 1.9%).

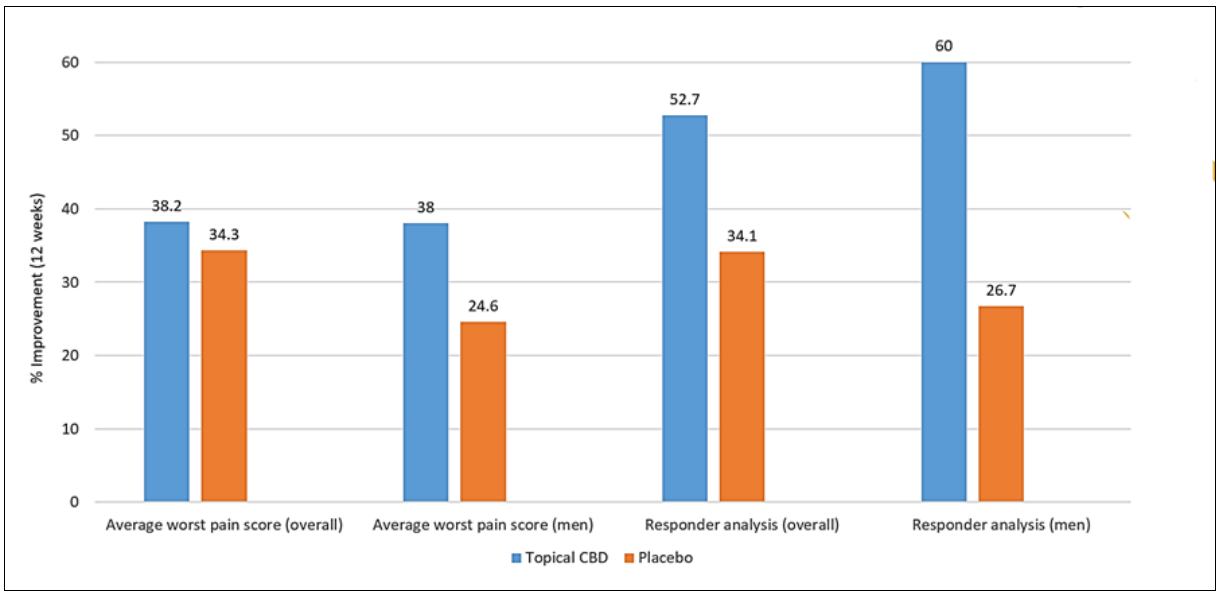

Fig 1: Improvement in Arthritis symptoms with Topical CBD [25]

Primary end point: Improvement in the weekly mean of the 24-hour average worst pain score.

Secondary end point (responder analysis) - average weekly improvement in worst pain score of > 30% and decrease in Western Ontario and McMaster Universities Osteoarthritis Index **(**WOMAC) physical function sub scale of at least 20% at last observation.

A recent phase 1 and 2 study was carried out with a topical preparation of CBD with shea butter in arthritis [27]. In phase 1, skin test was completed with 10 healthy participants monitored for 1 week after twice-daily application of 1 mL of topical CBD (6.2 mg/mL) with shea butter. After no adverse events were identified, a phase 2, double-blinded, randomized controlled trial with 18 participants with symptomatic thumb basal joint arthritis were randomized to 2 weeks of twice-daily treatment with CBD (6.2 mg/mL CBD with shea butter) or shea butter alone, followed by a 1-week washout period and crossover for 2 weeks. Cannabidiol treatment resulted in improvements from baseline ($P \leq 0.05$) among patient-reported outcome measures, including Visual Analog Scale pain (VAS); Disabilities of the Arm, Shoulder, and Hand score (DASH); and Single Assessment Numeric Evaluation score (SANE), compared to the control arm, with no adverse events reported. The study showed significant improvements with topical CBD treatment in thumb basal joint arthritis-related pain and disability. (Figure 2).

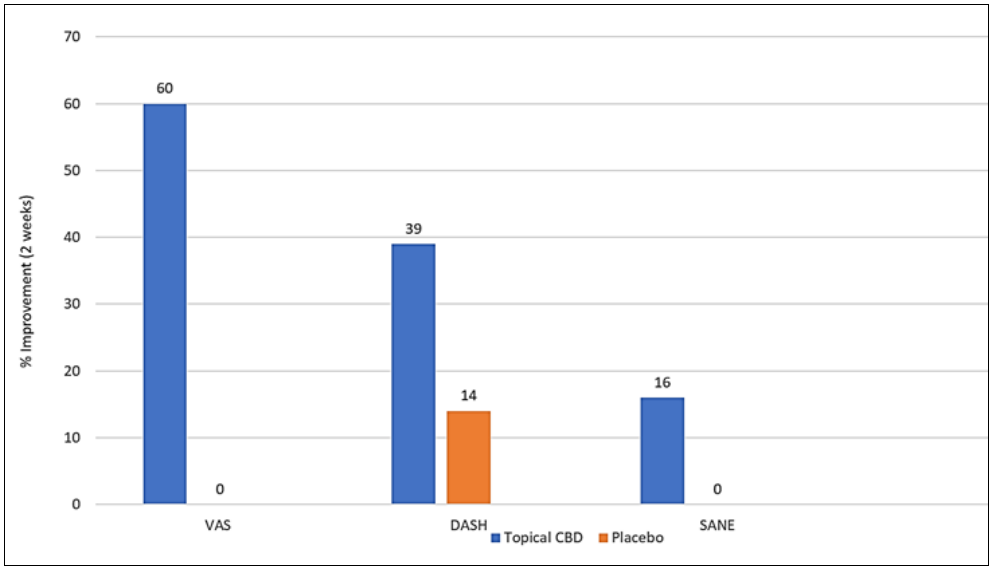

Fig 2: Effect of Topical CBD in Thumb Arthritis [24]

VAS - Visual Analog Scale (Pain); DASH - Disabilities of the Arm, Shoulder, and Hand score; SANE - Single Assessment Numeric Evaluation score.

In a cross-sectional, anonymous electronic, voluntary survey developed to assess the use of topical cannabis amongst adults in Canada, cannabis was used topically at least once by 24.3% of respondents who started the survey [28]. The commonest form of topical cannabis were creams (26.2%), and in 30% of cases it was used and found most effective for joint stiffness, tendonitis or muscle soreness, the others being dermatological conditions and headaches.

A study evaluated the myorelaxant effect of topical CBD applied for 2 weeks twice daily, in 60 patients with myofascial pain [29]. The masseter muscle activity measured with surface electromyography (sEMG) decreased by 11% and 12.6% in right and left masseter respectively in the CBD group as compared to 0.23% and 3.3% in the placebo group. VAS (Visual Analog Scale) pain intensity was significantly decreased in topical CBD group (70.2%, vs 9.81% in placebo group), suggesting that topical CBD application maybe useful in patients with myofascial pain.

In a placebo controlled clinical study, 29 patients with symptomatic peripheral neuropathy were treated with topical CBD oil containing 250 mg CBD/3 fl. Oz [30]. After 4 weeks, the placebo group was allowed to crossover into the treatment group. The Neuropathic Pain Scale (NPS) that was administered biweekly to assess the mean change from baseline to the end of the treatment period, showed a statistically significant reduction in intense pain, sharp pain, cold and itchy sensations in the CBD group when compared to the placebo group. No adverse events were reported in this study. The study though small, suggested that the transdermal application of CBD oil can achieve significant improvement in pain and other disturbing sensations in patients with peripheral neuropathy, and may provide a more effective and well tolerated alternative compared to other current pain therapies.

Conclusion

Cannabinoids sourced from the leaf extract of *Cannabis sativa*, are available in topical formulations as oils or gels. Cannabinoids reduce nerve transmission of pain at multiple levels like desensitization of nociceptive receptors, modulation of postsynaptic excitability and presynaptic neurotransmitter release, inhibition of ascending nociceptive pain transmission, and activation of descending inhibitory pain pathways. Preparation in suitable vehicles like seed oil can further enhance cannabinoid extract penetration and also provide anti-inflammatory and antioxidant action. Topical cannabinoid preparations may be also combined with conventional counterirritant and rubefacient soothing agents. Such topical preparations can be useful for effectively managing chronic musculoskeletal and neuropathic pain, especially when recurrent and impacting quality of life. Topical cannabinoids have not shown any significant adverse effects and can thereby help reduce the usage of oral NSAIDs, opioids or gabapentinoids, and their associated adverse effects and tolerability issues. Therefore, topical Cannabinoids are a useful addition to pain management therapies. More randomized clinical studies with larger sample size, as well as post-marketing and real-world evidence are required and recommended to further confirm clinical effectiveness, and add more insights to management of chronic musculoskeletal pain with cannabinoids.

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