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Research Article

# TO STUDY THE EFFICACY OF TROPICAL APPLICATION OF CANNABIS IN CHRONIC KNEE JOINT PAIN PATIENTS

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**ABSTRACT**

**Objectives:** The objective of this study was to study the decrease in pain at specified time intervals after tropical application of cannabis oil in chronic joint pain patients and to study the change in the visual analog score (VAS) and numeric rating scale (NRS) scoring of patient's pain before and after the application.

**Methods:** Patients were pre-informed about the process. VAS and NRS scores were noted before tropical application of the Cannabis oil. Cannabis oil was applied tropically on patients with chronic joint pain on the specified site, that is, B/L knee joints. Then, the decrease in the severity of pain at specific time interval was recorded on the pre-set pro forma. The VAS score and NRS score were recorded 30 min after the application. The final data were represented in the form of tables and graphs.

**Results:** The mean improvement values at 0–5 min, 5–10 min, 15–20 min, and 20–30 min were 35.90%, 41.80%, 47.90%, and 56.50%, respectively. The mean VAS score before application 7.00 reduced significantly to 2.32 after 30 min of application ($p<0.05$). Similarly, the mean NRS score also reduced significantly to 2.52 from mean value 7.08 at before application ($p<0.05$), that is, pain is significantly reduced.

**Conclusion:** From the data analysis, we reach to the conclusion that tropical application of Cannabis oil is effective in B/L knee joint osteoarthritis chronic pain.

**Keywords:** Chronic knee joint pain, Cannabis oil, Osteoarthritis.

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## INTRODUCTION

Osteoarthritis (OA) knee is the deterioration of the joints disease by having chronic and permanent articular cartilage damage. The destruction of the articular cartilage occurs slowly and continuously [1]. When people perform daily activities of life in inappropriate postures or had an accident in the knee joint, the damage can cause the cartilage to rub against one another. The rubbing results in pain, swelling, stiffness, inflammation, decreased ability to move, and cause a deformity of the knee joint. OA knee is a chronic illness that occurred in the middle age to the elderly [2,3]. The prevalence of knee pain in OA knee around the Asian region ranged from 38.1% to 50.0% in the-elderly [4,5]. Knee pain is a common symptom in OA knee and caused disability. As per the data as early as 2737 B.C., the mystical Emperor Shen Neng of China was prescribing marijuana tea for the treatment of gout, rheumatism, joint pain, malaria, and, oddly enough, poor memory [6]. The drug's popularity as a medicine spread throughout Asia used marijuana for religious purposes and stress relief. Ancient physicians prescribed marijuana for everything from pain relief to earache to childbirth.

### Basic science

Pain is a fundamental experience with a complex and multi-layered neurobiological basis. Tissue damage leads to the release of inflammatory mediators by activated nociceptors or non-neural cells that reside within or infiltrate into the injured area, including mast cells, basophils, platelets, macrophages, neutrophils, endothelial cells, keratinocytes, and fibroblasts. This "inflammatory soup" of signaling molecules includes serotonin, histamine, glutamate, ATP, adenosine, substance P, calcitonin gene-related peptide (CGRP), bradykinin, eicosanoids prostaglandins, thromboxane, leukotrienes, endocannabinoids, nerve growth factor, tumor necrosis factor a, interleukin-1β, extracellular proteases, and protons. These factors act directly on the nociceptor by binding to one or more cell surface receptors, including G protein-coupled receptors (GPCR), TRP channels, as depicted on the peripheral nociceptor terminal. Pain is the most common manifestation of both acute and chronic inflammation that often challenges patients with rheumatic disease. There is a complex interplay of interactions between cytokines, mediators of inflammation, and ion channels that influence the final immune response and our perception of pain.

The cannabis plant has many species, but the three main species are *Cannabis sativa, Cannabis indica,* and *Cannabis ruderalis*. More than 500 compounds have been isolated from cannabis species, approximately 100 of which are compounds known as cannabinoids, a molecule with a 21-carbon terpenophenolic skeleton. Cannabinoids in the cannabis plant are called phyto-cannabinoids. They produce more than 100 naturally occurring chemicals. The most abundant chemicals are Δ-9-tetrahydrocannabinol (THC), cannabidiol (CBD), terpenes, and flavonoids. THC is a psychotropic chemical that makes people feel "high," whereas CBD is a non-psychotropic chemical. Cannabinoids are low-molecular-weight lipophilic compounds (approximately 300 Da). They were originally obtained from *C. sativa* which contains more than 60 different CBs [7].

### Aim

This was to study the efficacy of tropical application of cannabis oil in chronic knee joint pain patients.

**Objectives**

The objectives of this study were as follows:

1. To study the decrease in pain at specified time intervals after tropical application of cannabis in chronic joint pain patients.
2. To study the change in the visual analog score (VAS) and numeric rating scale (NRS) scoring of patient's pain before and after the tropical application of Cannabis oil.

**Physiology of cannabis**

*Cannabinoid receptors*

G protein-coupled receptors are distributed throughout the CNS and PNS which are activated by cannabinoids. The CB1 and CB2 receptors play important roles in nociception and pain [8,9]. CB1 receptors act to reduce or enhance propagation of pain signals to the brain. CB1 receptors are highly expressed on presynaptic neurons in the brain, spinal cord, and dorsal root ganglia. CB2 receptors play an important role in pain signaling, especially in the development of chronic pain states, by inhibiting the release of proinflammatory and pro-nociceptive mediators, thereby attenuating the inflammatory and hyperalgesia responses. CB2 receptors are primarily expressed in immune cells, including myeloid, macrophage, microglia, lymphoid, and mast cell.

CBs activate GPCRs with seven transmembrane domain architectures which couple to heterotrimeric G-proteins. GPCR-ligand binding activates the G-protein's a-subunit (by exchanging GTP for GDP), which then dissociates and influences downstream signaling events. CBRs are negatively coupled to adenylate cyclase and positively coupled to mitogen-activated protein kinase. They also regulate the activity of calcium and potassium channels [10]. Some CBs can bind to other receptors at lower affinities including the transient receptor potential vanilloid receptor 1 (TRPV1) at which capsaicin is active [11].

**Endocannabinoids**

The endocannabinoid system (ECS) is an endogenous biological system that regulates functions including cognition, sleep, energy metabolism, pain, and inflammation. It modulates different neurotransmitter systems in the brain, including dopamine, glutamate, and GABA using two major lipid-based mediators, anandamide (ANA) and arachidonoyl-glycerol (2-AG) that act through type one and type two cannabinoid receptors (CB1 and CB2). ECS plays an important role in the modulation of nociceptive and pain states. ANA and 2-AG have been shown to have analgesic or anti-nociceptive effects at peripheral, spinal, and central levels, mainly by virtue of their ability to stimulate the activity of the cannabinoid receptors, and other receptors (i.e., TRPV1).

They are not stored in vesicles, but are rapidly synthesized *de novo* from post-synaptic membrane-lipid precursors [12]. Their formation results from at least two signaling pathways. Pre-synaptic neurotransmitter release stimulates a post-synaptic GPCR, which activates phospholipase C. Membrane phosphatidyl inositol 4,5-bisphosphate is cleaved to form inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 mobilizes intracellular calcium stores, which, along with DAG, activates DAG lipase to form 2-arachidonoylglycerol (2-AG). Alternatively, stimulated post-synaptic calcium channels can elevate intracellular calcium stores, which activate N-acyl transferase. This produces N-arachidonoyl-phosphatidyl-ethanolamine (NAPE) from phosphatidyl-ethanolamine and phosphatidyl-choline. NAPE is cleaved by phospholipase D to produce anandamide (AEA). The eCBs, then, diffuse across the synaptic cleft and bind to pre-synaptic CB1R, which are negatively coupled to membrane calcium channels. The subsequent decrease in pre-synaptic calcium concentrations reduces the probability of further neurotransmitter release. 2-AG is cleaved to arachidonic acid and glycerol by monoacylglycerol lipase, while ANA is metabolized to arachidonic acid and ethanolamine by fatty acid amide hydrolase [13].

Phytocannabinoids obtained from the cannabis plant comprise a range of CBR agonists, partial agonists, and antagonists. CBR may possess constitutive activity and CB ligands which abolish this are known as inverse agonists [14]. Recent work comparing global CB1R knockout mice with wild-type animals confirms that CB1R is expressed in a major population of nociceptive neurons in adult DRG [15]. CB1R also has an allosteric binding site, which may permit modulation of endogenous signaling activity. CBRs are found in all of the nociceptive neuroanatomical pathways. They participate in descending supraspinal pain modulation through the pre-aqueductal gray and rostral ventromedial medulla. The principal actions of CB1R decrease pre-synaptic intracellular calcium concentrations and activate inward-rectifying potassium channels which depress neuronal excitability and reduce transmitter release. Coadministration of intraspinal CBs alongside their topical application markedly enhanced this degree of anti-nociception and also synergized with topical morphine preparations. Methanandamide (a metabolically stable analog of ANA) suppressed pain behavior and prevented the longer term synaptic changes seen after intraplantar formalin injection. Topical administration of the CB agonist HU210 to human skin suppressed capsaicin-evoked thermal hyperalgesia and touch-evoked allodynia [16]. CBs also reduced capsaicin-evoked CGRP release (CECR) both in the periphery and in dorsal horn [17].

**The pharmacological effect of cannabis terpenoids**

It enhances the analgesic effect by stimulating the release of endogenous opioids through $\alpha$2-adrenergic receptor. It synergizes the anti-nociceptive and anti-inflammatory effects by inhibiting cycloxygenase-2 (COX-2) dependent prostaglandin E2. It increases serotonin and dopamine 5-HT1A receptors. Multimodal mechanisms of action produces analgesia including modulation of neuronal nociceptive processing, inhibition of proinflammatory molecule release, inhibition of mast cell activation, and modulation of endogenous opioid receptors in primary afferent pathways. The ECS, in the skin, is implied in cutaneous function such as cell differentiation modulation, growth and survival, inflammatory and immune responses, nociception, and hair growth. *C. Sativa* has analgesic and anti-inflammatory effects on topical application. It downregulates the production of proinflammatory cytokine in keratinocytes. It inhibits production of reactive oxygen species. It improves beta-endorphin levels through μ receptor (opioid receptor) [18]. It decreases nociceptive and inflammatory prostaglandins through suppressing COX-2. It increases the level of endocannabinoids, ANA, and 2-AG. The ECS, in the skin, is implied in cutaneous function such as cell differentiation modulation, growth and survival, inflammatory and immune responses, nociception, and hair growth. *C. Sativa* downregulates that the production of proinflammatory cytokine in keratinocytes inhibits production of reactive oxygen species, improves beta-endorphin levels through μ receptor (opioid receptor), and decreases nociceptive and inflammatory prostaglandins through suppressing COX-2 [12].

**METHODS**

**Type of study**

This was a prospective observational study.

**Study center**

This was Bhopal spine and pain relief center.

**Study duration and study population**

This was 6 months, that is, from January 2023 to June 2023.

50 ASA Grades I, II, and III patients experiencing chronic joint pain were recruited for the study.

**Source of data**

Patients treated at Bhopal spine and pain relief center.

**Inclusion criteria**

The following criteria were included in the study:

1. All patients with chronic B/L knee joint pain with Kallgren and Lawrence scale score Grade II and Grade III
2. All patients between 40 and 80 years of age of both genders.
3. All patients having knee pain ASA Grades I, II, and III with different chronic diseases.

**Exclusion criteria**

The following criteria were excluded from the study:

1. All patients not following the inclusion criteria.
2. All patients not willing to participate in the study.
3. Individuals with neurological and severe psychiatric illness, that is, with intellectual disability.
4. Patients who had undergone previous knee surgery.
5. Patients having local area infection or allergy.

**Methodology**

Patients were pre-informed about the process and consent was taken for the same. Detailed pre-anesthetic evaluation was done including pain and its characteristics, any associated comorbidities. VAS and NRS were noted before tropical application of the Cannabis oil.

Vitals were measured and cannabis oil was applied tropically on patients with chronic joint pain on the specified site, that is, B/L knee joints.

Then, the decrease in the severity of pain at specific time interval was recorded on the pre-set pro forma and patient was also questioned about any side effects experienced. The VAS score and NRS were recorded 30 min after the application.

**Statistical analysis plan**

- Data were collected and entered into the Excel Sheet; the analysis was done using the SPSS versus 16.0 software.
- The pre-post comparison of VAS and NRS score was determined by paired t-test.
- $p \leq 0.05$ was considered as statistically significant. The final data were represented in the form of tables and graphs.

**OBSERVATION AND RESULTS**

In Table 1, the age distribution shows higher values 42% and 36% for age group 60–70 years and 50–60 years, respectively. The proportion of female patients was 80%, whereas male patients were only 20%. The proportion of burning and itching was only 2% and 4%, respectively, whereas, in 94% patients, no side effects were found.

**Table 1: Age and gender distribution**

| Parameter | Group | Frequency | Percentage |
|---|---|---|---|
| Age Group | 40–50 Years | 2 | 4.0 |
| | 50–60 Years | 18 | 36.0 |
| | 60–70 Years | 21 | 42.0 |
| | 70–80 Years | 9 | 18.0 |
| Sex | Female | 40 | 80.0 |
| | Male | 10 | 20.0 |
| Side Effects | Burning | 1 | 2.0 |
| | Itching | 2 | 4.0 |
| | None | 47 | 94.0 |

**Table 2: Reduction in the severity of pain in specific time intervals**

| Values | Follow-up duration | | | |
|---|---|---|---|---|
| | 0–5 MIN | 5–10 MIN | 15–20 MIN | 20–30 MIN |
| Mean | 35.90% | 41.80% | 47.90% | 56.50% |
| SD | 13.24% | 11.77% | 10.40% | 11.92% |
| Minimum | 0.00% | 10.00% | 15.00% | 20.00% |
| Maximum | 70.00% | 70.00% | 80.00% | 80.00% |

In Table 2, the mean improvement for different follow-up durations shows an increasing trend. The mean improvement values at 0–5 Min, 5–10 min, 15–20 min, and 20-30 min were 35.90%, 41.80%, 47.90%, and 56.50%, respectively.

In Table 3, the pre-post comparison of VAS and NRS score was determined by paired t-test, which shows statistically significant reduction in pain scores ($p<0.05$). The mean VAS score before application 7.00 reduced significantly to 2.32 at after application time interval. Similarly, the mean NRS score also reduced significantly to 2.52 at after application time interval from mean value 7.08 at before time interval ($p<0.05$).

**DISCUSSION**

It is observed that osteoarthritis is more women compared to men [19]. Through our study, we found the proportion of female patients who were 80%, whereas male patients were only 20%. It is stated in some texts that it is more in women due to hormonal differences.

In our study, the age distribution shows higher values 42% and 36% for age group 60–70 years and 50–60 years, respectively. Postmenopausal women, in particular, have increased risk of development of osteoarthritis [20].

The aging changes are observed in the cells and extracellular matrix of joint tissues likely increase susceptibility of older adults to osteoarthritis.

In this study, we observed reduction in pain recorded in specific time intervals after the application of cannabis oil. The mean improvement for different follow-up durations shows an increasing trend.

The mean improvement values at 0–5 Min, 5–10 min, 15–20 min, and 20–30 min were 35.90%, 41.80%, 47.90%, and 56.50%, respectively. Hence, there was significant reduction in pain which was highest 30 min after the application of cannabis oil so the peak effect is achieved after 20–30 min duration of application.

In this study, we also recorded NRS before and after the application and observed that the mean NRS score also reduced significantly to 2.52 at after application time interval from mean value 7.08 at before time interval of 30 minutes ($p<0.05$). Hence, there was significant reduction in pain after the application of cannabis oil.

In this study, we also recorded visual analog scale before and after the application and observed that the mean VAS score before application 7.00 reduced significantly to 2.32 at after application time interval of 30 min ($p<0.05$). Thus, there was significant reduction in pain after the application of cannabis oil.

We observed minimal side effects in this study; notably, the proportion of burning and itching was only 2% and 4%, respectively, whereas, in 94% patients, no side effects were found. These side effects were mild and self-limiting. No major side effects observed with the application of cannabis oil.

**Table 3: Change in VAS score and NRS score before and after application**

| Method | Time period | N | Mean score | SD | Paired t test | p-value | Result |
|---|---|---|---|---|---|---|---|
| VAS | Before Application | 50 | 7.00 | 1.088 | 29.689 | 0.000 | Sig |
| | After Application | 50 | 2.32 | 0.741 | | | |
| NRS | Before Application | 50 | 7.08 | 0.877 | 35.546 | 0.000 | Sig |
| | After Application | 50 | 2.52 | 0.789 | | | |

## CONCLUSION

In this study, we included 50 ASA Grades I, II, and III elderly patients both male and female suffering from chronic bilateral osteoarthritis knee with pain and applied tropical cannabis oil on the affected area and observed reduction in pain post the application of oil and compared it with the pain scores before the application of cannabis oil.

Hence, after analyzing the observations and results of our study, we conclude that-

1. Occurrence of osteoarthritis is found more in females than in males.
2. Prevalence of osteoarthritis is more after 50 years of age, that is, more in postmenopausal women.
3. Tropical application of cannabis oil over the affected area significantly reduces pain scores in a patient with peak levels at 30 min after the application.
4. Tropical application of cannabis oil significantly reduces NRS scores compared to the scores before the application.
5. Tropical application of cannabis oil significantly reduces visual analog scale scores compared to the scores before the application.
6. There were minimal side effects observed with the tropical application of cannabis oil particularly burning and itching in few patients which were mild and self-limiting.

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Nil.

## CONFLICTS OF INTEREST

None declared.

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