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Cannabis sativa extract modulates pain sensitivity in albino wistar rats: Gender and dose considerations

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Abstract

The increasing prevalence of cannabis use, specifically among young people seeking relief from pain, has generated both public health concern and scientific curiosity. Despite anecdotal claims and preliminary findings suggesting analgesic effects of cannabis, there remains a notable dearth in rigorous experimental studies investigating its efficacy, dosage implications, gender-related differences and time interval administrations in pain response. Existing studies often overlooks the detailed relationship between dosage, sex, and neurobehavioral outcomes in controlled experimental settings. To address this dearth, this study examined the effects of cannabis extract on pain sensitivity using an animal model. Twenty-four albino Wistar rats (12 males, 12 females; 100g weight) were maintained under controlled conditions (30±2°C, 12hr light/dark cycles) in a completely randomized design experiment. Approved Cannabis sativa was homogenized and administered in three treatment groups (n=8 each) with three replicates. Pain sensitivity was assessed using a Thomas Scientific hot plate, while memory recognition was evaluated through object recognition tests, employing a pretest-posttest design. ANOVA results demonstrated significant effects of cannabis on pain sensitivity ($p<0.05$), with sex differences also influencing outcomes. The findings suggest that controlled, low-dose cannabis administration under medical supervision may offer therapeutic potential for severe pain management.

Keywords: Cannabis, Gender, Pain management, Pain sensitivity

1. Introduction

Pain is a crucial sensory experience that significantly impacts daily functioning and diminishes quality of life (Soyuer & Varol, 2019). It ranks among the most common health concerns worldwide, affecting approximately 15–30% of adults suffering from chronic pain (Breivik et al., 2006; Khera & Rangasamy, 2021; Zimmer et al., 2022; Cohen et al., 2021). Beyond its health implications, chronic pain imposes a heavy economic burden, contributing to lost productivity and rising healthcare expenditures (Breivik et al., 2006; Johannes et al., 2010). Current treatment options often fall short, as many patients fail to attain adequate relief through conventional pharmacotherapy (Finnerup et al., 2015; Moore et al., 2010). Even with a multidisciplinary biopsychosocial method addressing biological, psychological, and social factors achieving best pain management remains difficult (Jensen et al., 2007; Kerns et al., 2011). Consequently, there is an urgent need to research alternative analgesic therapy to enhance pain management.

In the past few years, there has been an increasing attention toward cannabis extracts as a potential pain reliever (Savage et al., 2016; Romero-Sandoval et al., 2018; Stella et al., 2021). The cannabis plant contains several bioactive compounds called cannabinoids, most drastically tetrahydrocannabinol (THC) and cannabidiol (CBD). THC, first discovered by Mechoulam and Gaoni (1965), is the number one psychoactive component, whereas CBD offers therapeutic results without inflicting intoxication. Studies reported that cannabinoids exert their consequences by interacting with the endocannabinoid system (ECS), a critical regulator of pain perception, mood, and other physiological features (Marsicano & Lutz, 2006). Through the process of modulating ECS activity, cannabinoids may change pain sensitivity, positioning them as a viable alternative for pain relief (Fine & Rosenfeld, 2013).

Several studies have substantiated pain-relieving effects of cannabis globally by demonstrating cannabinoids' efficacy in reducing pain and muscle spasticity in multiple sclerosis patients (Rog et al., 2005; Svendsen et al., 2004; Vecchio et al., 2020; Haddad et al., 2022; Fine & Rosenfeld, 2013; Filippini et al., 2021; Chisari et al., 2020; Jones & Vlachou, 2020; Di Stefano et al., 2020; Khan et al., 2020; Patti et al., 2020; Fragoso et al., 2020; Rykucka et al., 2020; Ware et al., 2010; Martinez-Paz et al., 2023, Isaiah et al., 2024), with findings indicating cannabis inhalation changes pain perception. Other studies have reported the effectiveness of smoked cannabis in managing pain related to HIV neuropathy and peripheral nerve damage (Abrams et al., 2007; Ellis et al., 2009; Ware et al., 2010).

Existing pharmacological pain management, such as opioids and NSAIDs, faces significant limitations such as unfavorable consequences, addiction potential, and diminishing efficacy over the years (Alorfi, 2023; Majid, 2023). These demanding situations reveal the vital need to develop safer, greater sustainable analgesic alternatives. Cannabinoids, through their relationship with the endocannabinoid system (ECS), emerged as a significant therapeutic option (Lowe et al., 2021). Clinical studies revealed that THC and CBD can effectively modulate pain signaling pathways, particularly in treatment-resistant chronic pain conditions (Urits et al., 2020; Luz-Veiga et al., 2020). Moreover, the same mechanisms underlying cannabinoid-precipitated pain modulation require, in addition to elucidation, extra studies are essential to set up standardized, secure, and effective cannabinoid-based pain therapeutic procedures (Campos et al., 2020).

Based on this backdrop, there is a need for deeper mechanistic expertise and standardized treatment protocols. Hence, this experimental study evaluates cannabis extract outcomes on nociceptive thresholds in an animal model. Through systematic research of cannabinoid-prompted pain perception changes, the research goals include: (1) characterizing dose-reaction relationships, and (2) identifying capacity therapeutic windows for effective analgesia. The study hypothesized the following:

H_1: Cannabis will have significant effect on pain sensitivity

H_1: Gender will have significant effect on pain sensitivity

H_1: Time interval in the administration of cannabis will have significant effect on pain sensitivity.

2. Literature review

Cannabis sativa has garnered significant attention for its analgesic properties, primarily attributed to its phytocannabinoids, such as Δ⁹-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Blanton et al., 2021). These compounds interact with the endocannabinoid system, influencing pain perception through cannabinoid receptors CB_1 and CB_2. Preclinical studies, particularly those involving rodent models like albino Wistar rats, have been instrumental in elucidating the analgesic mechanisms of cannabis extracts (Soliman et al.,2021; Finn et al., 2021). Notably, factors such as gender and dosage play crucial roles in modulating the efficacy of these extracts.

2.1. Cannabis use

Cannabis use refers to the consumption of products derived from the Cannabis sativa plant, either for medicinal, recreational, or therapeutic purposes. It involves various methods such as smoking, ingestion, vaporization, or application of extracts and oils. Medicinally, cannabis is often used to manage conditions like chronic pain, epilepsy, and inflammation due to its active compounds known as cannabinoids (Pagano et al., 2022). Cannabis sativa contains over 100 cannabinoids, with Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) being the most studied. THC is known for its psychoactive properties and acts primarily through CB_1 and CB_2 receptors of the endocannabinoid system, influencing pain perception, mood, and appetite (Rezende et al., 2023). CBD, in contrast, is non-psychoactive and interacts with several receptors such as TRPV-1 and 5-HT_1A, producing analgesic, anti-inflammatory, and anxiolytic effects without intoxication (Kicman & Toczek, 2020). Preclinical studies, particularly in animal models like albino Wistar rats, have provided evidence that cannabis extracts modulate pain responses in a dose-dependent manner. For example, research has shown that administration of cannabis extract significantly alters pain sensitivity in rats, validating its potential as an alternative pain management strategy (Uwemedimo et al., 2024).

2.2. Pain sensitivity

Pain sensitivity, or nociception, is the physiological process by which the nervous system detects and responds to harmful stimuli. This process involves the activation of nociceptors, specialized sensory neurons that respond to mechanical, thermal, or chemical threats. Once activated, these nociceptors transmit signals through peripheral nerves to the spinal cord and brain, where the perception of pain is formed.

The endocannabinoid system plays a significant role in modulating pain sensitivity. This system comprises cannabinoid receptors (CB_1 and CB_2), endogenous ligands like anandamide and 2-arachidonoylglycerol, and enzymes responsible for their synthesis and degradation (Hohmann & Suplita, 2008). Activation of CB_1 receptors, predominantly located in the central nervous system, and CB_2 receptors, primarily found in peripheral tissues, has been shown to produce antinociceptive effects in various pain models, including acute, inflammatory, and neuropathic pain (Starowicz & Finn, 2017).

Research indicates that cannabinoids can modulate pain by inhibiting the release of neurotransmitters and neuropeptides, reducing neuronal excitability, and attenuating inflammatory responses (Starowicz & Finn, 2017). For instance, studies have demonstrated that administration of cannabinoid receptor agonists can suppress the activity of nociceptive neurons in the spinal cord, leading to decreased pain perception (Liu & Walker, 2006). Additionally, endogenous cannabinoids like anandamide are released in response to noxious stimuli and contribute to the body's natural pain suppression mechanisms (Walker et al., 1999).

In animal models, such as albino Wistar rats, the administration of cannabis extracts has been observed to alter pain sensitivity in a dose-dependent manner (Bartkowiak-Wieczorek et al., 2024; Bagues et al., 2022). Higher doses of the extract have led to significant reductions in pain responses, highlighting the potential of cannabinoids as alternative analgesics (Baron, 2018; Ang et al., 2022). These findings reveals the importance of further research into the endocannabinoid system's role in pain modulation and the therapeutic applications of cannabinoids in pain management.

2.1.3. Gender and Pain Sensitivity

Pain sensitivity exhibits notable differences between genders, influenced by a complex interplay of biological, hormonal, and psychosocial factors (Racine et al., 2012; Osborne & Davis, 2022). Research consistently demonstrates that women generally report higher pain sensitivity and a greater prevalence of chronic pain conditions compared to men (Hashmi & Davis, 2014; Eltum & Tashani, 2017; Osborne & Davis, 2022). These disparities are attributed to variations in hormonal levels, neural processing, and psychological factors.

Biologically, sex hormones play a pivotal role in modulating pain perception (Palmeira et al., 2011; Athnaiel et al., 2023). Estrogen and progesterone, predominant in females, have been shown to influence nociceptive processing. For instance, estrogen can enhance the excitability of nociceptive neurons, leading to increased pain sensitivity (Sarajari & Oblinger, 2010). Conversely, testosterone, more abundant in males, tends to have analgesic properties, potentially contributing to lower pain sensitivity in men (Athnaiel et al., 2023).

Neuroimaging studies have revealed sex-specific patterns in brain activation in response to pain stimuli (Gupta et al., 2017; Osborne & Davis, 2022). Women often exhibit greater activation in regions associated with emotion and pain processing, such as the anterior cingulate cortex and insula, suggesting a more intense emotional experience of pain (Gupta et al., 2017). Additionally, structural differences, such as variations in the corpus callosum and gray matter distribution, may contribute to these functional disparities (Osborne & Davis, 2022).

Psychosocial factors also contribute to gender differences in pain perception (Fillingim, 2023). Societal norms and expectations can influence how individuals report and cope with pain. Women are more likely to express pain and seek medical attention, whereas men may underreport pain due to cultural expectations of stoicism (Cagle & Bunting, 2017). These behavioral differences can affect pain assessment and management in clinical settings.

In preclinical studies, such as those involving albino Wistar rats, gender differences in pain sensitivity have been observed (Yezierski, 2012; Eltumi & Tashani, 2017). Female rats often display heightened pain responses compared to males, and their sensitivity can fluctuate with hormonal cycles (Iacovides et al., 2015). These findings show the importance of considering gender as a critical variable in pain research and the development of analgesic therapies and management.

2.1.4. Time Interval on Anti-nociception

The temporal dynamics of antinociceptive effects following Cannabis sativa extract administration are critical for understanding its analgesic efficacy (Imam & Sumi, 2014). Studies utilizing albino Wistar rats have demonstrated that the onset, peak, and duration of pain relief are influenced by factors such as dosage, administration route, and the specific cannabinoid profile of the extract (Brunni et al., 2023; Uwemedimo et al., 2024).

In a study by Harris et al. (2019), oral administration of Δ^9-tetrahydrocannabinol (THC) exhibited a delayed onset of antinociceptive effects, with peak responses observed at 300 minutes post-administration in tail-flick tests. This contrasts with morphine, which showed peak effects at 30 minutes, highlighting the prolonged time course of THC-induced analgesia (Moore & Weerts, 2022). Similarly, Moore et al. (2021) investigated the effects of vaporized THC and found that antinociceptive responses peaked at 60 minutes post-exposure and gradually diminished by 300 minutes. This study also noted that intraperitoneal (IP) administration of THC resulted in a progressive increase in antinociceptive effects, peaking at the final assessment point of 300 minutes.

Furthermore, research by Craft et al. (2023) assessed the impact of vaporized THC-dominant cannabis extract on rats with persistent inflammatory pain. The study reported significant reductions in mechanical allodynia and improvements in weight-bearing and locomotor activity within 15 to 120 minutes post-exposure, indicating a relatively rapid onset of analgesic effects. These findings underscore the importance of considering the time interval post-administration when evaluating the antinociceptive properties of cannabis extracts. The delayed onset and prolonged duration of THC's analgesic effects suggest that timing is a crucial factor in optimizing therapeutic outcomes.

3. Research method

Experimental design

This investigation utilized a pre-test/post-test design to systematically assess treatment effects. Baseline pain sensitivity measurements (pre-test) were recorded prior to cannabinoid administration. Subsequent post-treatment evaluations (post-test) quantified response modifications, facilitating comparative analysis between pre- and post-intervention conditions to determine therapeutic efficacy.

Experimental setting

The study was carried out in the Animal House Unit Laboratory, Faculty of Pharmacy, Department of Pharmacy and Toxicology at the University of Uyo.

Experimental animals

For this investigation, 24 male and female albino Wistar rats weighing 100 grams were employed. They were housed in the Department of Pharmacy and Toxicology's animal house unit at the University of Uyo, Nigeria, at a temperature of 30 2°C with 12hr light/dark cycles, with free access to food and water. For both pain and memory, rats were placed into three groups of four.

Experimental material/ instruments

Plant materials

C. sativa was obtained with the agreement of the National Drug Law Enforcement Agency (NDLEA), Uyo, Akwa-Ibom State Command, under the reference number UU/FSS/D/30/VOL. I, and homogenized using a manual blender. 100gm of the blended leaves were weighed and immersed in 2.5 liters of ethanol for 96 hours before being filtered and dried for ethanol evaporation using a student water bath at 46°C for 72 hours. The filtrate was chilled in a clean glass beaker. The extract was removed from the refrigerator two hours before oral delivery. The low dose was 0.5 mg/100 g body weight, whereas the high dose HD was 0.8 mg/100 g body weight. These doses were chosen in order to avoid causing any harm to the physiological functions of the participants (Wister rats), which could result in death, as directed by the National Drug Law Enforcement Agency (NDLEA), Uyo, Akwa-Ibom State Command.

Hot plate test

For this test, a Thomas scientific hot plate (author regulated) was employed. The temperature of a hot plate's heated surface was kept constant at 55.0 0.5°C. Each albino rat was gently placed on the plate, and the time it took the mouse to lick its paws or jump was recorded as the response (Tjølsen & Hole, 1997). To prevent the animal from migrating from the platform and to avoid tissue damage, a 2000ml beaker was placed around it, and the cutoff time or latency response in the control was set to 15s. The test was administered prior to administration to establish baseline responses, and it was repeated after administration at 15, 30-, 60-, 90-, and 120-minutes intervals.

Administration Procedure

Figure 1: Hot plate test

Comparison group (Aspirin)	4 **males** 4 **females**	**0.4ml**
Experimental group 1 (low dose)	4 **males** 4 **females**	**0.5 ± 0.1ml**
Experimental group 2 (high dose)	4 **males** 4 **females**	**0.8ml**

Table 1 above summarizes the experimental design to examine the outcomes of various doses of cannabis on pain response using the " Hot plate test." This test typically measures how lengthy it takes for subjects to respond to heat exposure, which is an indicator of pain tolerance. The study includes three groups: (1) a comparison group using aspirin, and two experimental groups which received low and high doses of cannabis.

In the assessment group, which serves as the control, each difficulty comprising four adult males and four females acquired 0.4ml of aspirin, a regarded pain reliever. This group's outcome will offer a baseline for evaluating the pain-relieving results of cannabis. The first experimental group, tagged as the low-dose group, included 4 men and four females. Each subject in this group received a low dose of cannabis, measured at 0.50 ± 0.10 ml, where "± 0.10 ml" allows for a range from 0.40 ml to 0.60 ml, accounting for slight variations. This group helps to observe how a low dose of cannabis influences pain tolerance in comparison to both aspirin and the higher cannabis dose.

The second experimental group, which is the high-dose group, consisted of 4 males and 4 females, with each subject receiving a dose of 0.8 ml of cannabis. This group is included to determine whether a higher dose of cannabis has a significantly different effect on pain response compared to the low dose and the aspirin group. By comparing pain responses across these groups, the experiment aims to assess the analgesic effects of varying cannabis doses, with gender-balanced groups in both control and experimental conditions.

Ethical approval

The author certifies that the "Principles of Laboratory Animal Care" (NIH publication No. 85-23, updated 1985) were followed. The National Drug Law Enforcement Agency (NDLEA), Uyo, Akwa-Ibom State Command, investigated and authorized all tests under ref no. UU/FSS/D/30/VOL.I.

Statistical analysis

Results were expressed as mean ± SEM. ANOVA was applied. General group means were compared by student's t-test. Differences were considered significant at P<0.05.

4. Data analysis

Effect of C. Sativa on Pain Sensitivity

The effect of C. Sativa among the treatment and comparison groups is shown in Table 1. There was no significant difference in pain sensitivity when the anti-nociception of low dose group (10.13±2.43) was compared with the comparison group (9.04±3.11; t=1.23; *p*>.05). In the high concentration group (10.58±2.49), pain sensitivity is also not significantly different when compared to the low dose (t=0.58; *p*>.05) and comparison group (t=1.73; *p*>.05).

Table 2: Effect of C. sativa on anti-nociception among treatment and comparison groups

Group	Mean Anti-nociception (±SD)	Comparison	t	p-value
Low Dose C. Sativa	10.13 ± 2.43	vs. Comparison Group	1.23	> 0.05
High Dose C. Sativa	10.58 ± 2.49	vs. Low Dose Group	0.58	> 0.05
High Dose C. Sativa	10.58 ± 2.49	vs. Comparison Group	1.73	> 0.05
Comparison Group	9.04 ± 3.11			

Note: No significant differences in pain sensitivity were observed between groups (all $p > 0.05$)

Effect of gender on pain sensitivity

The result shows a significant difference in the anti-nociception of Male albino Wistar rats and Female albino Wistar rats (t= -2.15; *p*<.05). Specifically, the Female albino Wistar rat shows greater anti-nociception (10.65±3.02) than the Males (9.18±2.21). This finding is presented in Table 3 below;

Table 3: Comparison of anti-nociception between male and female albino wistar rats

Group	Mean Anti-nociception (±SD)	T	p-value
Female Albino Wistar	10.65 ± 3.02	-2.15	< 0.05
Male Albino Wistar	9.18 ± 2.21		

Effect of time interval on pain sensitivity

The finding revealed a significant difference in pain sensitivity of the albino rats due to the variation of intervals between C. Sativa administration and test for anti-nociception [F (4, 55) = 2.84; P<.05]. There was a steady rise in anti-nociception from the 15 minutes interval (8.41±1.72) to the 30 minutes interval (8.81±3.20) to the 60 minutes interval (11.13±2.47), the 60 minutes time interval led to the peak anti-nociception after which anti-nociception gradually reduced in the 90 minutes interval (11.00±2.65) and further down in the 120 minutes interval (10.24). This result is shown in Table 3.

Table 3: Offect of time interval on anti-nociception in albino rats after c. sativa administration

Time Interval (minutes)	Mean Anti-nociception (±SD)	Df	F-value	p-value
15	8.41 ± 1.72	4	2.84	< 0.05
30	8.81 ± 3.20			
60	11.13 ± 2.47			
90	11.00 ± 2.65			
120	10.24			

5. Findings and discussion

The finding of the study reveals that there is a significant effect of cannabis on pain sensitivity. However, there was no difference between the low dose of cannabis and high dose of cannabis on pain sensitivity. The outcome of the result implies that the significant effect of cannabis on pain is not dependent on dosage of cannabis but the cannabis itself. The finding of the study confirms the study of Urits *et al.* (2020); Luz-Veiga, Azevedo-Silva & Fernandes (2020); Vecchio *et al.* (2020); Haddad, Dokmak & Karaman (2022); Fine & Rosenfeld (2013);

Filippini et al. (2021); Chisari *et al.* (2020); Jones & Vlachou (2020); Di Stefano *et al.* (2020); Khan *et al.* (2020); Patti *et al.* (2020); Fragoso, Carra & Macias (2020); Rykucka *et al.* (2020); Ware *et al.* (2010); Martinez-Paz, Garcia-Cabrera & Vilches-Arenas (2023) whose findings showed that Cannabis inhalation influences subjects' sensitivity to pain.

The finding of the present study also reveals that there is a significant difference in the anti-nociception of Male albino Wistar rats and Female albino Wistar rats. This implies that female Wistar rats are more sensitive to pain than male Wistar rats. This is implicative to human as female genders are known to be sensitive to pain more than the male gender. This finding of this study is in-line with the findings of other researchers (Fillingim et al., 2009, Bernades et al., 2008; Hurley and Adams, 2008; Mogil, 2012; Barnabe et al., 2012). However, the finding of the study was inconsistent with the finding of Chia *et al.* (Chia et al., 2002).

In addition, the finding of the present study also reveals that there is a significant difference in pain sensitivity of the albino rats due to the variation of intervals between C. Sativa administration and test for anti-nociception. This implies that the duration of time in which cannabis is taken can affect the sensitivity of pain but reduces as at a certain point. This is implicative in humans as cannabis produce a vast effect at the first 60 minute of ingestion but reduces as the user continues to use. This term is known as tolerance in drug use.

6. Contribution of the study

This study makes several significant contributions to existing knowledge. First, it provides empirical evidence supporting the potential of cannabis extracts as an alternative treatment for pain management, particularly for individuals unresponsive to conventional therapies. By scientifically validating anecdotal reports of cannabis use for pain relief among youths, the study emphasizes the need for further clinical research into the therapeutic applications of cannabis.

Secondly, the finding that sex significantly influences pain sensitivity advances understanding of the biological differences in pain perception. This highlights the importance of incorporating gender-specific considerations into the design of more personalized pain management strategies, thereby improving treatment outcomes.

Lastly, by identifying both the therapeutic potential and the risks associated with unsupervised cannabis use, the study contributes to the broader discourse on public health policy. It underscores the critical need for regulated medical oversight in the use of cannabis for pain management, informing future guidelines for safe and effective use.

7. Implications of the study

The findings of the study have several important implications. First, the significant effect of cannabis on pain sensitivity suggests that cannabis extracts may serve as a potential alternative treatment for managing pain, particularly for individuals who do not find relief from conventional pain medications.

Secondly, the finding revealed that sex significantly influences pain sensitivity. This implies pain perception varies between males and females, likely due to biological and hormonal differences. This suggests that pain management strategies should be tailored to account for sex differences in order to enhance treatment effectiveness. Health practitioners and researchers must therefore consider gender-specific approaches when designing pain assessment tools, management protocols, and clinical interventions to ensure more personalized and effective pain management outcomes.

8. Conclusion

Cannabis use has steadily increased over the years, particularly among young people. As many experts have discovered, the attempt to understand the explanation for this high prevalence indicates its usefulness in relieving aches and soothing nerves. Despite these findings, there has been considerable debate, particularly among researchers, about the effect of cannabis usage on pain sensitivity. Experimentally induced pain studies have produced a very consistent pattern of results, reporting that cannabis use acts as analgesics in pain reduction across both genders, with women exhibiting greater pain sensitivity, enhanced pain facilitation, and reduced pain inhibition compared to men, though the magnitude of these sex differences varies across studies. The current study's findings are consistent with prior studies in that cannabis considerably decreases pain sensitivity. Furthermore, gender and the time intervals between cannabis usages have a substantial effect on pain sensitivity. As a result, it was established that cannabis had a considerable effect on pain sensitivity. The following were recommended based on the findings of the study;

- Future research should conduct large-scale, controlled clinical trials to further investigate the efficacy and safety of low-dose cannabis administration for pain management across different populations.
- Medical practitioners should consider sex differences in pain sensitivity when prescribing cannabis-based therapies, developing personalized treatment plans that account for biological variability.
- Cannabis use for pain management should be strictly regulated and administered under medical supervision to minimize potential risks and ensure appropriate dosing.
- Public health authorities should create educational programs to inform the public about both the potential benefits and risks of using cannabis for pain relief, emphasizing the importance of medical guidance.

References

1. Abrams, D. I., Jay, C. A., Shade, S. B., Vizoso, H., Reda, H., Press, S., Kelly, M. E., Rowbotham, M. C., & Petersen, K. L. (2007). Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology, 68,* 515-21.
2. Alorfi, N. M. (2023). Pharmacological methods of pain management: narrative review of medication used. *International journal of general medicine*, 3247-3256.
3. Ang, S. P., Sidharthan, S., Lai, W., Hussain, N., Patel, K. V., Gulati, A., ... & Orhurhu, V. (2023). Cannabinoids as a potential alternative to opioids in the management of various pain subtypes: benefits, limitations, and risks. *Pain and Therapy*, *12*(2), 355-375.
4. Athnaiel, O., Cantillo, S., Paredes, S., & Knezevic, N. N. (2023). The role of sex hormones in pain-related conditions. *International journal of molecular sciences*, *24*(3), 1866.
5. Bagues, A., López-Tofiño, Y., Llorente-Berzal, Á., & Abalo, R. (2022). Cannabinoid drugs against chemotherapy-induced adverse effects: focus on nausea/vomiting, peripheral neuropathy and chemofog in animal models. *Behavioural Pharmacology*, *33*(2&3), 105-129.
6. Barnabe, C., Bessette, L., & Flanagan C. (2012). Sex differences in pain scores and localization in inflammatory arthritis: A systematic review and meta-analysis. *Journal of Rheumatology, 39*,1221–30
7. Baron, E. P. (2018). Medicinal properties of cannabinoids, terpenes, and flavonoids in cannabis, and benefits in migraine, headache, and pain: an update on current evidence and cannabis science. *Headache: The Journal of Head and Face Pain*, *58*(7), 1139-1186.
8. Bartkowiak-Wieczorek, J., Bienert, A., Czora-Poczwardowska, K., Kujawski, R., Szulc, M., Mikołajczak, P., ... & Mądry, E. (2024). Cannabis sativa L. extract alleviates neuropathic pain and modulates CB1 and CB2 receptor expression in rat. *Biomolecules*, *14*(9), 1065.

9. Bernardes, S. F., Keogh, E., & Lima, M. L. (2008). Bridging the gap between pain and gender research: a selective literature review. *European Journal of Pain,12*, 427– 40. doi:10.1016/j.ejpain.2007.08.007
10. Blanton, H. L., Barnes, R. C., McHann, M. C., Bilbrey, J. A., Wilkerson, J. L., & Guindon, J. (2021). Sex differences and the endocannabinoid system in pain. *Pharmacology Biochemistry and Behavior*, *202*, 173107.
11. Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006). Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *European Journal of Pain, 10*, 287-333
12. Bruni, N., Della Pepa, C., Oliaro-Bosso, S., Pessione, E., Gastaldi, D., & Dosio, F. (2018). Cannabinoid delivery systems for pain and inflammation treatment. *Molecules*, *23*(10), 2478.
13. Cagle, J., & Bunting, M. (2017). Patient reluctance to discuss pain: understanding stoicism, stigma, and other contributing factors. *Journal of Social Work in End-of-Life & Palliative Care*, *13*(1), 27-43.
14. Campos, R. M. P., Aguiar, A. F., Paes-Colli, Y., Trindade, P. M. P., Ferreira, B. K., de Melo Reis, R. A., & Sampaio, L. S. (2021). Cannabinoid therapeutics in chronic neuropathic pain: from animal research to human treatment. *Frontiers in physiology*, *12*, 785176.
15. Chia, Y. Y., Chow, L. H., Hung, C. C., Liu, K., Ger, L. P., & Wang, P. N. (2002). Gender and pain upon movement are associated with the requirements for postoperative patient-controlled iv analgesia: a prospective survey of 2,298 Chinese patients. *Canadian Journal of Anesthesia*, *49*,249–55. doi:10.1007/BF03020523
16. Chisari, C. G., Sgarlata, E., Arena, S., D'Amico, E., Toscano, S., & Patti, F. (2020). An update on the pharmacological management of pain in patients with multiple sclerosis. *Expert opinion on pharmacotherapy*, *21*(18), 2249-2263.
17. Cohen, S. P., Vase, L., & Hooten, W. M. (2021). Chronic pain: an update on burden, best practices, and new advances. *The Lancet*, *397*(10289), 2082-2097.
18. Craft, R. M., Gogulski, H. Y., Freels, T. G., Glodosky, N. C., & McLaughlin, R. J. (2023). Vaporized cannabis extract–induced antinociception in male vs female rats with persistent inflammatory pain. *Pain*, *164*(9), 2036-2047.
19. Di Stefano, G., De Stefano, G., Di Lionardo, A., Cruccu, G., & Truini, A. (2020). Pharmacotherapeutic options for managing pain in multiple sclerosis. *CNS drugs*, *34*(7), 749-761.
20. Ellis, R. J., Toperoff, W., Vaida, F, van den Brande, G., Gonzales, J., Gouaux, B., Bentley, H., & Atkinson, J. H. (2009). Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, 34*,672-80
21. Eltumi, H. G., & Tashani, O. A. (2017). Effect of age, sex and gender on pain sensitivity: a narrative review. *Open Pain Journal*, *10*, 44-55.
22. Filippini, G., Minozzi, S., Borrelli, F., Cinquini, M., & Dwan, K. (2022). Cannabis and cannabinoids for symptomatic treatment for people with multiple sclerosis. *Cochrane Database of Systematic Reviews*, (5).
23. Fillingim, R. B. (2023). Sex, gender, and pain. In *Principles of gender-specific medicine* (pp. 769-792). Academic Press.
24. Fillingim, R. B., King, C. D., Ribeiro-Dasilva, M. C., Rahim-Williams, B., & Riley, J. L. (2009). Sex, gender, and pain: a review of recent clinical and experimental findings. *Journal of Pain,10*, 447–85. doi:10.1016/j.jpain.2008.12.001
25. Fine, P. G., & Rosenfeld, M. J. (2013). The endocannabinoid system, cannabinoids, and pain. *Rambam Maimonides medical journal*, *4*(4).

26. Finn, D. P., Haroutounian, S., Hohmann, A. G., Krane, E., Soliman, N., & Rice, A. S. (2021). Cannabinoids, the endocannabinoid system, and pain: a review of preclinical studies. *Pain*, *162*, S5-S25.

27. Finnerup, N. B., Attal, N., Haroutounian, S., McNicol, E., Baron, R., Dworkin, R. H., Gilron, I., Haanpaa, M., Hansson, P, Jensen, T. S., Kamerman, P. R., Lund, K., Moore, A., Raja, S. N., Rice, A. S., Rowbotham, M., Sena, E., Siddall, P., Smith, B. H., & Wallace, M. (2015). Pharmacotherapy for neuropathic pain in adults: a systematic review and metaanalysis. *Lancet neurology, 14,*162-73

28. Fragoso, Y. D., Carra, A., & Macias, M. A. (2020). Cannabis and multiple sclerosis. *Expert Review of Neurotherapeutics*, *20*(8), 849-854.

29. Furthermore, research by Gamage et al. (2023) assessed the impact of vaporized THC-dominant cannabis extract on rats with persistent inflammatory pain. The study reported significant reductions in mechanical allodynia and improvements in weight-bearing and locomotor activity within 15 to 120 minutes post-exposure, indicating a relatively rapid onset of analgesic effects.

30. Gupta, A., Mayer, E. A., Fling, C., Labus, J. S., Naliboff, B. D., Hong, J. Y., & Kilpatrick, L. A. (2017). Sex-based differences in brain alterations across chronic pain conditions. *Journal of Neuroscience Research*, *95*(1-2), 604-616.

31. Haddad, F., Dokmak, G., & Karaman, R. (2022). The efficacy of cannabis on multiple sclerosis-related symptoms. *Life*, *12*(5), 682.

32. Harris, H. M., Rousseau, M. A., Wanas, A. S., Radwan, M. M., Caldwell, S., Sufka, K. J., & ElSohly, M. A. (2019). Role of cannabinoids and terpenes in cannabis-mediated analgesia in rats. *Cannabis and Cannabinoid Research*, *4*(3), 177-182.

33. Hashmi, J. A., & Davis, K. D. (2014). Deconstructing sex differences in pain sensitivity. *PAIN®*, *155*(1), 10-13.

34. Hohmann, A. G., & Suplita, R. L. (2008). Endocannabinoid mechanisms of pain modulation. *Drug Addiction: From Basic Research to Therapy*, 737-764.

35. Hurley, R. W. and Adams, M. C. (2008). Sex, gender, and pain: an overview of a complex field. *Anesthesia Analgesics,107,*309–17. doi:10.1213/01.ane.0b013e31816ba437

36. Iacovides, S., Avidon, I., & Baker, F. C. (2015). Does pain vary across the menstrual cycle? A review. *European Journal of Pain*, *19*(10), 1389-1405.

37. Imam, M. Z., & Sumi, C. D. (2014). Evaluation of antinociceptive activity of hydromethanol extract of Cyperus rotundus in mice. *BMC complementary and alternative medicine*, *14*, 1-5.

38. Jensen, M. P., Turner, J. A., & Romano, J. M. (2007). Changes after multidisciplinary pain treatment in patient pain beliefs and coping are associated with concurrent changes in patient functioning. *Pain, 131,* 38-47.

39. Johannes, C. B., Le, T. K., Zhou, X., Johnston, J. A., & Dworkin, R. H. (2010). The prevalence of chronic pain in United States adults: results of an Internet-based survey. *The Journal of Pain: Official Journal of the American Pain Society, 11,*1230-9

40. Jones, É., & Vlachou, S. (2020). A critical review of the role of the cannabinoid compounds Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) and their combination in multiple sclerosis treatment. *Molecules*, *25*(21), 4930.

41. Kerns, R. D., Sellinger, J., & Goodin, B. R. (2011). Psychological treatment of chronic pain. *Annual review of clinical psychology, 7,* 411-34

42. Khan, H., Ghori, F. K., Ghani, U., Javed, A., & Zahid, S. (2022). Cannabinoid and endocannabinoid system: a promising therapeutic intervention for multiple sclerosis. *Molecular Biology Reports*, *49*(6), 5117-5131.

43. Khera, T., & Rangasamy, V. (2021). Cognition and pain: a review. *Frontiers in psychology*, *12*, 673962.

44. Kicman, A., & Toczek, M. (2020). The effects of cannabidiol, a non-intoxicating compound of cannabis, on the cardiovascular system in health and disease. *International journal of molecular sciences*, *21*(18), 6740.

45. Liu, C., & Walker, J. M. (2006). Effects of a cannabinoid agonist on spinal nociceptive neurons in a rodent model of neuropathic pain. *Journal of neurophysiology*, *96*(6), 2984-2994.

46. Lowe, H., Toyang, N., Steele, B., Bryant, J., & Ngwa, W. (2021). The endocannabinoid system: a potential target for the treatment of various diseases. *International journal of molecular sciences*, *22*(17), 9472.

47. Luz-Veiga, M., Azevedo-Silva, J., & Fernandes, J. C. (2023). Beyond pain relief: a review on Cannabidiol potential in medical therapies. *Pharmaceuticals*, *16*(2), 155.

48. Majid, M., Yahya, M., Owusu, F. A., Bano, S., Tariq, T., Habib, I., ... & Khan, A. S. (2023). Challenges and opportunities in developing tailored pain management strategies for liver patients. *Cureus*, *15*(12).

49. Marsicano, G., & Lutz, B. (2006). Neuromodulatory functions of the endocannabinoid system. *Journal of endocrinological investigation*, *29*(3), 27.

50. Martinez-Paz, C., Garcia-Cabrera, E., & Vilches-Arenas, A. (2023). Effectiveness and safety of cannabinoids as an add-on therapy in the treatment of resistant spasticity in multiple sclerosis: a systematic review. *Cannabis and Cannabinoid Research*, *8*(4), 580-588.

51. Mechoulam, R., & Gaoni, Y. (1965). A Total Synthesis of Dl-Delta-1-Tetrahydrocannabinol, the Active Constituent of Hashish. *Journal of American Chemical Society, 87*, 3273-5.

52. Mogil, J. S. (2012). Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon. *National Revision Neuroscience, 13,* 859–66. doi:10.1038/nrn3360

53. Moore, C. F., & Weerts, E. M. (2022). Cannabinoid tetrad effects of oral Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in male and female rats: sex, dose-effects and time course evaluations. *Psychopharmacology*, 1-12.

54. Moore, C. F., Davis, C. M., Harvey, E. L., Taffe, M. A., & Weerts, E. M. (2021). Appetitive, antinociceptive, and hypothermic effects of vaped and injected Δ-9-tetrahydrocannabinol (THC) in rats: exposure and dose-effect comparisons by strain and sex. *Pharmacology Biochemistry and Behavior*, *202*, 173116.

55. Moore, R. A., Smugar, S. S., Wang, H., Peloso, P. M., & Gammaitoni, A. (2010). Numbers-needed-to-treat analyses--do timing, dropouts, and outcome matter? Pooled analysis of two randomized, placebo-controlled chronic low back pain trials. *Pain*, *151*, 592-7

56. Osborne, N. R., & Davis, K. D. (2022). Sex and gender differences in pain. In *International review of neurobiology* (Vol. 164, pp. 277-307). Academic Press.

57. Pagano, C., Navarra, G., Coppola, L., Avilia, G., Bifulco, M., & Laezza, C. (2022). Cannabinoids: therapeutic use in clinical practice. *International journal of molecular sciences*, *23*(6), 3344.

58. Palmeira, C. C. D. A., Ashmawi, H. A., & Posso, I. D. P. (2011). Sex and pain perception and analgesia. *Revista Brasileira de Anestesiologia*, *61*, 820-828.

59. Patti, F., Chisari, C. G., Solaro, C., Benedetti, M. D., Berra, E., Bianco, A., ... & SA. FE. group. (2020). Effects of THC/CBD oromucosal spray on spasticity-related symptoms in people with multiple sclerosis: results from a retrospective multicenter study. *Neurological Sciences*, *41*, 2905-2913.

60. Racine, M., Tousignant-Laflamme, Y., Kloda, L. A., Dion, D., Dupuis, G., & Choinière, M. (2012). A systematic literature review of 10 years of research on sex/gender and pain perception–part 2: do biopsychosocial factors alter pain sensitivity differently in women and men?. *Pain*, *153*(3), 619-635.

61. Rezende, B., Alencar, A. K. N., de Bem, G. F., Fontes-Dantas, F. L., & Montes, G. C. (2023). Endocannabinoid system: chemical characteristics and biological activity. *Pharmaceuticals*, *16*(2), 148.

62. Rog, D. J., Nurmikko, T. J., Friede, T., & Young, C. A. (2005). Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology*, *65*, 812-9

63. Romero-Sandoval, E. A., Fincham, J. E., Kolano, A. L., Sharpe, B. N., & Alvarado-Vázquez, P. A. (2018). Cannabis for chronic pain: challenges and considerations. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *38*(6), 651-662.

64. Rykucka, A., Zozula, N., Wąs, M., Kiełbasa, J., Kowalczyk, A., Bil, K., ... & Przestrzelska, M. (2024). Exploring the efficacy of cannabinoids in the management of multiple sclerosis. *Journal of Education, Health and Sport*, *74*, 52563-52563.

65. Sarajari, S., & Oblinger, M. M. (2010). Estrogen effects on pain sensitivity and neuropeptide expression in rat sensory neurons. *Experimental neurology*, *224*(1), 163-169.

66. Savage, S. R., Romero-Sandoval, A., Schatman, M., Wallace, M., Fanciullo, G., McCarberg, B., & Ware, M. (2016). Cannabis in pain treatment: clinical and research considerations. *The Journal of Pain*, *17*(6), 654-668.

67. Soliman, N., Haroutounian, S., Hohmann, A. G., Krane, E., Liao, J., Macleod, M., ... & Rice, A. S. (2021). Systematic review and meta-analysis of cannabinoids, cannabis-based medicines, and endocannabinoid system modulators tested for antinociceptive effects in animal models of injury-related or pathological persistent pain. *Pain*, *162*, S26-S44.

68. Soyuer, F., & Varol, B. K. (2019). Quality of life and pain. *Int J Fam Commun Med*, *3*(3), 110-114.

69. Starowicz, K., & Finn, D. P. (2017). Cannabinoids and pain: sites and mechanisms of action. *Advances in Pharmacology*, *80*, 437-475.

70. Stella, B., Baratta, F., Della Pepa, C., Arpicco, S., Gastaldi, D., & Dosio, F. (2021). Cannabinoid formulations and delivery systems: current and future options to treat pain. *Drugs*, *81*, 1513-1557.

71. Svendsen, K. B., Jensen, T. S. and Bach, F. W. (2004). Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo-controlled crossover trial. *BMJ*, *329*, 253

72. Tjølsen, A., & Hole, K. (1997). Animal models of analgesia. In *The pharmacology of pain* (pp. 1-20). Berlin, Heidelberg: Springer Berlin Heidelberg.

73. Urits, I., Gress, K., Charipova, K., Habib, K., Lee, D., Lee, C., ... & Viswanath, O. (2020). Use of cannabidiol (CBD) for the treatment of chronic pain. *Best Practice & Research Clinical Anaesthesiology*, *34*(3), 463-477.

74. Uwemedimo, S., Ebubechukwu, J., & Ruth, E. (2024). Evaluating the Effects of Cannabis Extract on Pain Sensitivity: An Experimental Study using Albino Wistar Rats. *International Journal of Research and Innovation in Social Science*, *8*(11), 396-403.

75. Vecchio, D., Varrasi, C., Virgilio, E., Spagarino, A., Naldi, P., & Cantello, R. (2020). Cannabinoids in multiple sclerosis: A neurophysiological analysis. *Acta Neurologica Scandinavica*, *142*(4), 333-338.

76. Walker, J. M., Huang, S. M., Strangman, N. M., Tsou, K., & Sañudo-Peña, M. C. (1999). Pain modulation by release of the endogenous cannabinoid anandamide. *Proceedings of the National Academy of Sciences*, *96*(21), 12198-12203.

77. Ware, M. A., Wang, T., Shapiro, S., Robinson, A., Ducruet, T., Huynh, T., Gamsa, A., Bennett, G. J. and Collet, J. P. (2010). Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMAJ: Canadian Medical Association journal*,*182*, E694-701

78. Yezierski, R. P. (2012). The effects of age on pain sensitivity: preclinical studies. *Pain medicine*, *13*(suppl_2), S27-S36.

79. Zimmer, Z., Fraser, K., Grol-Prokopczyk, H., & Zajacova, A. (2022). A global study of pain prevalence across 52 countries: examining the role of country-level contextual factors. *Pain*, *163*(9), 1740-1750.