Evaluating the Effects of Cannabis Extract on Pain Sensitivity: An Experimental Study using Albino Wistar Rats

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ABSTRACT

The rate at which cannabis has been utilized by youths is becoming alarming and predominants of them who are being asked reported that it helps them to deal with pains. Therefore, the study was aimed at investigating the effect of cannabis extract on pain sensitivity using rat. A total of 24 consisting of 12 male and 12 female albino Wistar rats of weight 100 gm were used in a completely randomized design (CRD) experiment. They were maintained in the animal house unit of the Department of Pharmacy and Toxicology, University of Uyo, Nigeria, at a temperature of 30 ± 2°C and 12 hr light/dark cycles with free access to food and water. Cannabis sativa was purchased with the approval of the office of the National Drug Law Enforcement Agency (NDLEA), Uyo, Akwa-Ibom State and homogenized using the manual blender. There were three treatments of eights mice each replicated three times with three rats per replicate. Thomas scientific hot plate (author regulated) and Object recognition test were used to test pain sensitivity and memory recognition respectively. The study utilized a pretest-posttest design and the statistics used in analyzing the result in the study was Analysis of Variance (ANOVA). Result revealed that Cannabis significantly affects pain sensitivity. Result also revealed that sex significantly affect pain sensitivity. It was therefore concluded that cannabis have significant effect on pain sensitivity. The study recommend that little or low dose of cannabis use with doctors' supervision may be helpful to people who go through severe pain.

Keywords: Cannabis, Pain sensitivity.

INTRODUCTION

Pain is a fundamental sensation that affects human functionality, often leading to impairment and a decreased quality of life. It is one of the most prevalent health issues globally, with estimates suggesting that between 15-30% of the general adult population experiences chronic pain (Breivik et al., 2006; Khera & Rangasamy, 2021; Zimmer, Fraser, Grol-Prokopczyk & Zajacova, 2022; Cohen, Vase, & Hooten, 2021). The widespread nature of pain poses not only significant health challenges but also results in substantial economic expenditures, with considerable societal impacts due to loss of productivity and increased healthcare costs (Breivik et al., 2006; Johannes et al., 2010). Despite the various available treatments, chronic pain remains inadequately managed, as many patients do not achieve sufficient pain relief with current pharmacotherapy options (Finnerup et al., 2015; Moore et al., 2010). Furthermore, even with a biopsychosocial approach incorporating biological, psychological, and social treatment strategies, effective pain management continues to be a challenge (Jensen, Turner, & Romano, 2007; Kerns, Sellinger, & Goodin, 2011). This has necessitated the exploration of alternative analgesics to improve pain management outcomes.

In recent years, there has been growing interest in the use of cannabis extracts for pain relief. Cannabis contains various active compounds known as cannabinoids, including the well-known tetrahydrocannabinol (THC) and cannabidiol (CBD). THC, first identified by Mechoulam & Gaoni (1965), is primarily responsible for the

psychoactive effects of cannabis, while CBD is recognized for its therapeutic benefits without inducing psychoactive reactions. Research indicates that cannabinoids interact with the body's endocannabinoid system (ECS), which plays a key role in pain modulation, mood regulation, and other physiological processes (Marsicano & Lutz, 2006). Through the ECS, cannabinoids can influence pain sensitivity, making them a promising option for pain management (Fine & Rosenfeld, 2013).

The analgesic properties of cannabis have been supported by various studies. For example, cannabinoids have been shown to alleviate pain and muscle spasms in patients with multiple sclerosis (Rog et al., 2005; Svendsen, Jensen & Bach, 2004; 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). Furthermore, other research has demonstrated that smoked cannabis can reduce pain associated with conditions such as HIV neuropathy and peripheral nerve damage (Abrams et al., 2007; Ellis et al., 2009; Ware et al., 2010). Despite these promising findings, the effects of cannabis extracts on pain sensitivity have not been extensively explored in many regions, particularly in countries like Nigeria, where there is a lack of legal distinction between medicinal and recreational use. This legal framework has contributed to the scarcity of literature on the therapeutic effects of cannabis, limiting the awareness and potential application of cannabinoid-based treatments.

Current conventional pain management approaches have limitations, including the risk of side effects, dependency, and the development of tolerance to medications such as opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Consequently, there is an urgent need to explore alternative treatments that can offer safer, effective, and long-term pain relief solutions. Cannabinoids, by interacting with the ECS, present a potential avenue for addressing these challenges. Clinical trials have suggested that THC and CBD can modulate pain pathways and provide relief, particularly in chronic pain conditions that are often resistant to traditional therapies (Urits *et al.*, 2020; Luz-Veiga, Azevedo-Silva & Fernandes, 2020). However, the precise mechanisms through which cannabinoids affect pain sensitivity remain under investigation, and more research is necessary to develop standardized, safe, and effective cannabinoid-based analgesics (Campos *et al*., 2020).

Given the need for more comprehensive understanding and standardized therapeutic approaches, this study aims to investigate the effects of cannabis extracts on pain sensitivity using an animal model. By focusing on how cannabinoids influence pain perception, this research seeks to provide valuable insights that could lead to the development of safer and more effective pain management strategies. 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

METHODS

Experimental Design

A pre-test and post-test design was adapted to establish and compare responses before administration and after administration. This design involves assessing participants' responses at two different time points: before and after the administration of the treatment. In this study, the pre-test serves as a baseline measure, capturing initial levels of the variable under investigation (e.g., pain sensitivity) prior to the application of cannabis extracts. Following this, the treatment (cannabis extracts) is administered, and a post-test is conducted to observe any changes in responses, allowing for a comparison between the pre-treatment and post-treatment conditions.

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

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**

The table summarizes an experiment designed to examine the effects of different doses of cannabis on pain response using the "hot plate test." This test typically measures how long it takes for subjects to respond to heat exposure, which is an indicator of pain tolerance. The experiment includes three groups: a comparison group using aspirin, and two experimental groups receiving low and high doses of cannabis.

In the comparison group, which serves as the control, each subject—comprising 4 males and 4 females—received 0.4 ml of aspirin, a known pain reliever. This group's results will provide a baseline for evaluating the pain-relieving effects of cannabis. The first experimental group, designated as the low-dose group, also

includes 4 males and 4 females. Each subject in this group received a low dose of cannabis, measured at 0.5 ± 0.1 ml, where "± 0.1 ml" allows for a range from 0.4 ml to 0.6 ml, accounting for slight variations. This group helps to observe how a low dose of cannabis impacts pain tolerance in comparison to both aspirin and the higher cannabis dose.

The second experimental group, referred to as the high-dose group, also consists 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 mean were compared by students t-test. Differences were considered significant at $P<0.05$.

RESULT

Effect of C. Sativa on Pain Sensitivity

The effect of C. Sativa among the treatment and comparison group is shown in Figure 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; $p>.05$).

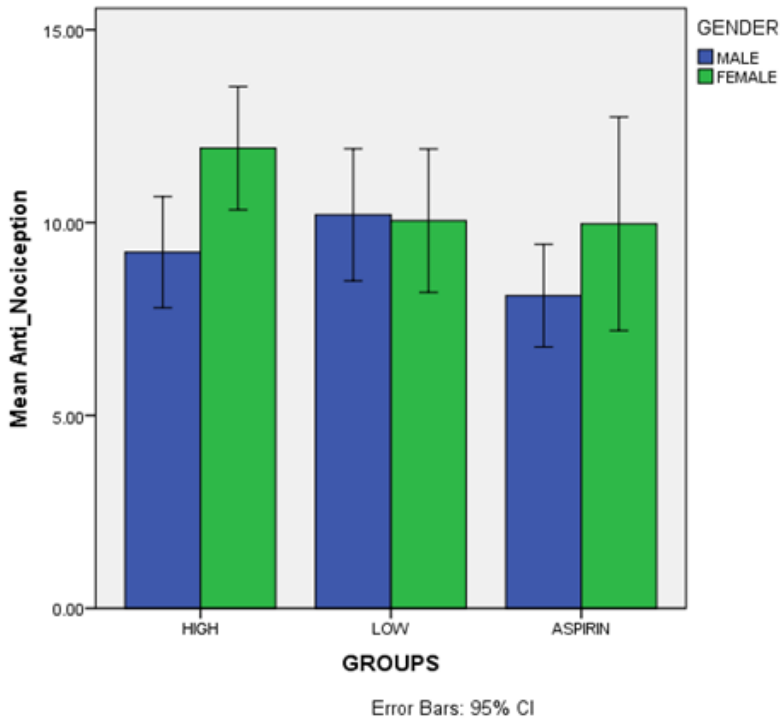

Figure 1: Effect of time C. Sativa and gender on Mean Anti-nociception

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 show greater anti-nociception (10.65±3.02) than the Males (9.18±2.21). This finding is presented in figures 1 and 2

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 Figure 2.

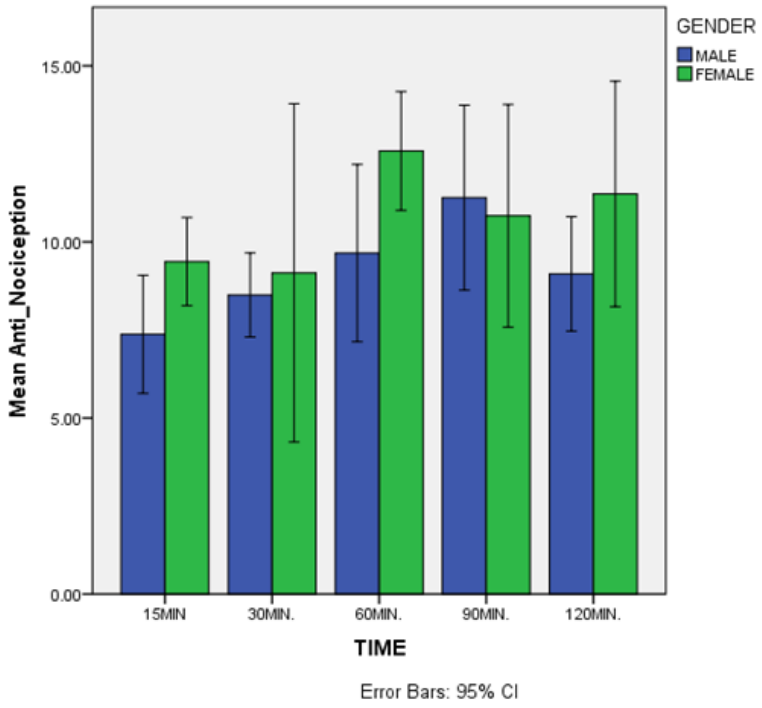

Figure 2: Effect of time interval and gender on Mean Anti-nociception

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 Fillingim *et al*. (2009);

Bernades *et al.* (2008); Hurley and Adams, (2008); Mogil, (2012) and Barnabe *et al.* (2012). However, the finding of the study was inconsistent with the finding of 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.

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.

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. This aligns with anecdotal reports of cannabis use among youths, who claim it helps them cope with pain, and highlights the need for more controlled clinical studies to explore this effect in humans.

Secondly, the study's discovery that sex significantly influences pain sensitivity emphasizes the necessity of considering gender differences when developing pain management protocols. This could lead to more personalized treatment strategies that account for biological differences in pain perception.

Finally, the study raises important considerations for public health and regulation. While cannabis may have potential therapeutic benefits, uncontrolled use without medical supervision can pose risks. Therefore, the results underscore the need for proper regulation and medical oversight when considering cannabis as a treatment option for pain relief.

RECOMMENDATIONS

1. Given the significant effects of cannabis on pain sensitivity observed in the study, it is recommended that small, controlled doses of cannabis be considered under strict medical supervision for patients experiencing chronic or severe pain. This can provide an alternative to traditional analgesics, particularly for patients who do not respond well to standard treatments.
2. Since the study found that sex significantly affects pain sensitivity, future research should investigate these differences in more detail. Understanding how gender influences the effectiveness of cannabis in pain management could lead to more personalized and effective treatment plans, ensuring that both men and women receive optimal care.
3. To mitigate the misuse of cannabis, especially among youths, it is essential to strengthen public health education regarding the potential risks and benefits of cannabis use. Additionally, regulatory frameworks should be put in place to ensure that cannabis is only used for therapeutic purposes under medical supervision, reducing the likelihood of abuse and associated health risks.

Conflict of Interest: The authors declare no conflict of interest.

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