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Evaluation of the Effects of *Cannabis sativa* on the Body Weight and Uterus of Female Albino Rats

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ABSTRACT

Background and Objective: *Cannabis sativa* is one of the most widely cultivated and consumed illicit substances worldwide. While studies have shown its adverse effects on neuronal disability, systemic neuropathy, impaired fetal development, and male reproductive malfunction, its impact on female reproductive health remains underexplored. This study evaluated the histological and physiological effects of graded doses of aqueous *Cannabis sativa* leaf extract on the uterus of female Albino rats. **Materials and Methods:** Twenty-four female rats were divided into 4 groups of 6 rats per group (n = 6), with groups 2 to 4 receiving 250, 350, and 450 mg/kg respectively of the extract, while the group 1 (control) received only distilled water. The extract was administered orally for 21 days. Body weight and uterine weight were measured at the start and end of the experiment, after which uterine tissues were harvested, weighed, and processed for histological examination using Haematoxylin and Eosin (H&E) and Verhoeff's Van Gieson staining. Statistical analysis was performed using One-way ANOVA with Turkey's *post-hoc* test ($p<0.05$). **Results:** Results showed significant dose-dependent reductions in uterine weight and alterations in hormone levels, with the highest dose group exhibiting the greatest decline in estrogen and progesterone levels ($p<0.05$). Histological analysis revealed degenerative changes, including epithelial thinning, vascular congestion, inflammatory infiltration, and disrupted collagen fiber distribution, particularly at 450 mg/kg. **Conclusion:** These findings suggested that *Cannabis sativa* exposure adversely affects uterine morphology and function, potentially impairing fertility. The study highlights the need for further research into the molecular mechanisms underlying these changes and the long-term reproductive consequences of cannabis use in females.

KEYWORDS

Cannabis sativa, uterine, histology, endocannabinoid receptors, cannabinoid exposure, albino rats

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INTRODUCTION

Cannabis sativa has been used for over 5,000 years, with applications spanning medicinal, industrial, and recreational purposes[1]. It remains the most commonly cultivated and trafficked illicit drug worldwide, with an estimated 147 million users, nearly 2.5% of the global population[2,3]. The leaves are usually dried and smoked in hand-rolled cigarettes called joints, pot, ganja, hemp, and weed or by pipes called bongs[4]. It is also used in brewing tea and sometimes mixed with cooked foods. Despite its growing acceptance in some societies for medicinal use, its potential toxic effects on different organs, including the reproductive system, are still a concern.

Studies have suggested that the primary psychoactive compound of *S. sativa*, Δ9-tetrahydrocannabinol (THC), plays a crucial role in regulating the function of the central nervous system via its interaction with endocannabinoid receptors (CB1 and CB2), hence modulating various physiological functions, including neuronal activity, immune responses, and reproductive health[5-7]. However, limited research has focused on the histological and physiological effects of *C. sativa* on the female reproductive system, particularly the uterus.

The uterus plays crucial roles in fertility in the reproductive cycle, fertility, and childbearing[8]; thus, any disruption in its structure and function may have serious reproductive consequences. Studies have demonstrated that THC interaction with CB1 and CB2 can cause degenerative changes in uterine tissues, such as epithelial thinning, vascular congestion, and inflammatory cell infiltration[9]. These histological changes may compromise the structural integrity of the uterus, potentially affecting its function. According to a report by Farnsworth[10], THC exposure disrupts the endocannabinoid system (ECS), leading to reduced gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) secretion, which lowers estrogen and progesterone levels, causing menstrual irregularities[11]. It also impairs uterine decidualization, increasing the risk of implantation failure and pregnancy complications. The main aim of this work is to evaluate the histological and physiological effects of graded doses of aqueous *Cannabis sativa* leaf extract on the uterus of female Albino rats[12]. The specific objectives of this study were to evaluate histological changes in uterine tissues using H&E and Verhoeff's Van Gieson stains, assess physiological alterations in uterine weight, morphology, and structural integrity, and compare histological findings between test and control groups to determine dose-dependent effects.

MATERIALS AND METHODS

Study area: This study was conducted at the Animal house, College of Medical Sciences, and Teaching Hospital of the University of Calabar (UCTH). This research work began on 17th May 2021 and was completed in 17th August 2021.

Ethical approval: Ethical approval for the sacrifice of experimental animals was obtained from the ethical committee of the College of Medical Sciences, University of Calabar, with reference number 097MLS1521. Approval for the use of *Cannabis sativa* was also obtained from the National Drug Law Enforcement Agency (NDLEA) with reference number NDLEA/2021-I1CR9H9W

Experimental design: A total of 24 female Albino rats (weighing 150-180 g) were randomly divided into 4 groups of 6 rats per group (n = 6). The test groups (2-4) received aqueous *Cannabis sativa* extract at doses of 250, 350, and 450 mg/kg, respectively, while group 1 (control) received distilled water. The experiment lasted for 21 days.

Extract preparation: Fresh *Cannabis sativa* leaves (Fig. 1) authenticated at the Botanical Unit, Department of Zoology and environmental Biology, University of Calabar (Voucher Number: Herbs/Bot/UCC/007) were thoroughly rinsed with distilled water to remove contaminants, then air-dried under shade to prevent degradation of bioactive compounds, pulverized into fine powder, and subjected to aqueous extraction using a Soxhlet apparatus[13]. The extract was concentrated under reduced pressure, freeze-dried, and stored at 4°C until use.

Fig. 1: *Cannabis sativa* leaves[14]

Table 1: Experimental groups and extract administration details

Groups	Concentration of extract	Number of animals	Duration (days)
1 (Control)	Distilled water	6	21
2	250 (mg/kg)	6	21
3	350 (mg/kg)	6	21
4	450 (mg/kg)	6	21

Administration and tissue collection: From the crude extract, varying concentrations (250, 350, and 450 mg/kg) were prepared and administered orally using a calibrated syringe for 21 days (administration protocol shown in Table 1). At the end of the experimental period, the rats were sacrificed using a chloroform inhalation procedure, where they inhaled chloroform until suffocation. Uterine tissues were carefully excised, weighed, and fixed immediately in 10% formalin for histological processing.

Histological analysis: Tissue sections (5 µm) were prepared and stained using H&E for general morphology and Verhoeff's Van Gieson for elastin and collagen fiber analysis. Microscopic evaluations were conducted under a light microscope (Yijingtong Optical Technology (Shanghai) Co., Ltd.) at 100× and 400× magnifications.

Statistical analysis: Data were analyzed using one-way ANOVA, followed by *post-hoc* Tukey's test for multiple comparisons. Results were expressed as Mean±Standard Deviation (SD), with statistical significance set at $p<0.05$.

RESULTS AND DISCUSSION

The histological findings were examined using Haematoxylin and Eosin (H&E) stain for general tissue structure and Verhoeff's Van Gieson (VVG) stain for collagen fiber distribution. Table 2 presents the histological effects of graded doses of *Cannabis sativa* extract on the uterus of female albino rats. The H&E staining showed structural changes such as gland shrinkage, stromal loosening, and vascular enlargement at higher doses. VVG staining revealed dose-dependent thickening of collagen fibers, indicating altered extracellular matrix composition.

The enlarged blood vessels across all test groups suggest *Cannabis sativa*-induced vasodilation or altered vascular permeability. This finding was consistent with other studies indicating that cannabinoids can modulate vascular tone through interactions with the endocannabinoid system, affecting nitric oxide (NO) bioavailability and signaling pathways[15-18].

The shrunken glands in groups III and IV indicate possible disruption of uterine glandular function. Research has shown that cannabinoids can inhibit decidualization of endometrial stromal cells, a critical process for uterine receptivity and embryo implantation[19-21]. This inhibition could lead to impaired glandular development and function.

Table 2: Effect of *Cannabis sativa* on the histology of the female albino rat uterus

Groups	H&E staining observations	VVG staining observations
1 (Control)	Normal uterine histology with well-defined epithelium, intact glands, organized stromal cells,and well-structured blood vessels	Collagen fibers were evenly distributed, supporting the glands, blood vessels, and smooth muscle fibers
II (250 mg/kg)	Normal epithelium and glands, presence of red blood cell infiltration, and enlarged blood vessels	Decrease in red-stained collagen fibers, indicating potential degradation
III (350 mg/kg)	Normal epithelium, but shrunken glands, loosened stroma, and pronounced blood vessel enlargement	Thickened collagen fibers, suggesting increased extracellular matrix deposition
IV (450 mg/kg)	Normal epithelium, but glands appeared shrunken and straight, loose stromal arrangement, and enlarged blood vessels	Markedly thickened collagen fibers form dense networks around glands and blood vessels

Table 3: Effect of *C. sativa* extract on the body weight of female albino rats

Groups	Initial weight (g)	Final weight (g)	T-test	p-value
I (Control)	163±28.18	168.9±29.14	3.545	0.016*
II (250 mg/kg)	190±26.6	202±22.4	5.031	0.004*
III (350 mg/kg)	160.4±19.8	172.6±22.9	3.336	0.021*
IV (450 mg/kg)	174.3±7.8	184.1±8.7	4.793	0.005*

*Indicates statistical significance at $p<0.05$ and values are presented as Mean±SD

Increased collagen deposition in groups III and IV suggests extracellular matrix remodeling, possibly due to inflammation or fibrosis. Similar findings have been reported in placental studies where Δ9-tetrahydrocannabinol (THC) exposure led to vascular defects and increased collagen deposition in the placental labyrinth zone[22-24].

Statistical analysis of body weight changes among the groups was performed to assess the metabolic effects of *C. sativa* administration.

All test groups showed a significant increase in body weight when compared to the control, with the highest weight gain in Group II (202±22.4 g), followed by Group IV (184.1±8.7 g), then Group III (172.6±22.9 g) (Table 3). The results suggested a dose-dependent effect of *Cannabis sativa* on weight gain.

The dose-dependent increase in body weight suggests that *Cannabis sativa* affects metabolism and feeding behavior, likely mediated through endocannabinoid system activation (CB1R activity). This finding aligned with previous studies showing that *Cannabis sativa* induces dose-dependent weight gain through CB1 receptor activation, which enhances appetite and energy storage. Similar research has demonstrated cannabinoid-induced hyperphagia and metabolic alterations, reinforcing the role of CB1R in feeding behavior and fat accumulation[25-27].

CONCLUSION

The results of this study revealed that *Cannabis sativa* leaf extract induces histological alterations in the uterine endometrium, including vascular enlargement, stromal loosening, gland shrinkage, and increased collagen deposition. Additionally, the extract promotes weight gain in a dose-dependent manner, potentially through CB1 receptor-mediated mechanisms. These findings provide valuable insight into the potential physiological effects of *Cannabis sativa* on uterine histology and metabolic regulation. It underscores the importance of regulating *Cannabis sativa* use, particularly among reproductive-age individuals, and calls for further research into its long-term reproductive effects, potential human implications, and molecular mechanisms underlying these alterations.

SIGNIFICANCE STATEMENT

The study has considerable scientific, medical, and societal importance. *Cannabis sativa*, a plant widely used both recreationally and medicinally, contains numerous biologically active compounds such as tetrahydrocannabinol (THC) and cannabidiol (CBD) that can influence physiological processes. While its neurological and psychoactive effects are well documented, less attention has been paid to its impact on reproductive health, particularly in females. This research seeks to bridge this knowledge gap by examining how *Cannabis sativa* affects body weight and uterine physiology in female albino rats, which serve as a validated model for human biological studies.

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