ISSN: 2476-8642 (Print)
ISSN: 2536-6149 (Online)
www.annalsofhealthresearch.com
African Index Medicus, Crossref, African Journals Online, Scopus, C.O.P.E & Directory of Open Access Journals

Annals of HEALTH RESEARCH

(The Journal of the Medical and Dental Consultants' Association of Nigeria, OOUTH, Sagamu, Nigeria)

Volume 11 | No. 3 | Jul. - Sep., 2025

IN THIS ISSUE

PUBLISHED BY THE MEDICAL AND DENTAL CONSULTANTS ASSOCIATION OF NIGERIA, OOUTH, SAGAMU, NIGERIA.
www.mdcan.oouth.org.ng

Annals of Health Research

(The Journal of the Medical and Dental Consultants' Association of Nigeria, OOUTH, Sagamu, Nigeria)

Volume 11, Issue 3: 253-267
September 2025
doi:10.30442/ahr.1103-04-291

ORIGINAL RESEARCH

Effect of *In-Utero* Cannabinoid Exposure on Foetal Growth and Placental Efficiency

Taiwo-Ola Dorcas O[1], Sulaiman Isa A[2], Akanji Omotosho D[1], Ariyo Joseph A[1], Ehireme Samuel E[1], Bamgbose Opeyemi A[1], Fakunle Ponle B[1], Shallie Philemon D[3]

[1]Department of Anatomy, Faculty of Basic Medical Sciences, Olabisi Onabanjo University, Ago Iwoye, Ogun State, Nigeria
[2]Department of Anatomy, Crescent University, Abeokuta, Ogun State, Nigeria
[3]University of Missouri-Kansas City, Missouri, United States of America

Correspondence: Shallie Philemon Dauda, University of Missouri-Kansas City, Missouri, United States of America. E-mail: shallie.philemon@gmail.com, ORCID - https://orcid.org/0000-0001-9910-3584.

Citation: Taiwo-Ola DO, Sulaiman IA, Akanji OD, Ariyo JA, Ehireme SE, Bamgbose OA, Fakunle PB, Shallie PD. Effect of *In-Utero* Cannabinoid Exposure on Foetal Growth and Placental Efficiency. Ann Health Res 2025;11:253-267. https://doi.org/10.30442/ahr.1103-04-291.

Abstract

Background: *Cannabis sativa. L.* contains over 550 components, including cannabinoids like tetrahydrocannabinol (THC) and cannabidiol (CBD), which affect the endocannabinoid system and influence human neurodevelopment and physiological functions. Although it has therapeutic potential, cannabis use during pregnancy can disrupt foetal development, especially in the brain and placenta.
Objective: To examine the prenatal exposure to THC and CBD on foetal growth and placental health using a Wistar rat model.
Methods: A total of 24 female rats were divided into four groups; each received orally 150mg/kg/day of THC, CBD, or a combination (CBD and THC) at 150 mg/kg/day. The control received only water and feed. The early-phase administration of cannabinoids occurred from day 6 to 19.
Results: There were substantial reductions in foetal weight. The mean weight was 3.78g in the control group. The THC-exposed group showed a 36% reduction (2.41g), the CBD-exposed group had a 41% reduction (2.22g), and the combined THC/CBD group had a decrease of 3.51g. Significant alterations in placental morphological architecture were observed. The THC and CBD exposure groups exhibited pronounced structural distortions and increased trophoblast degeneration, respectively, whereas the combined exposure showed milder placental changes. The foetal-to-placental weight ratio was significantly reduced in all cannabis-exposed groups.
Conclusion: This study shows prenatal THC and CBD harm foetal growth and placental health. THC caused the most severe effects of reduced foetal weight and placental changes. Therefore, public health initiatives should be intensified to alert pregnant women regarding the risks of using cannabis.
Keywords: Cannabinoids, Foetal growth, Placental health, Prenatal exposure, Tetrahydrocannabinol (THC).

Introduction

Cannabis sativa L., known for its psychoactive and medicinal properties, has been used for centuries in various therapeutic and industrial contexts. [1] The plant comprises over 550 natural components, including cannabinoids such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which engage with the endocannabinoid system to modulate neurodevelopment and physiological functions. [2,3] Despite its therapeutic potential, cannabis use during pregnancy remains a concern, as prenatal exposure can disrupt foetal development, particularly in the brain and placenta. [4] Marijuana remains the most commonly used addictive substance during pregnancy, with self-reported usage rates ranging from 2% to 5% within the general population and reaching as high as 15% to 28% among women residing in low socioeconomic metropolitan areas. [5] In some regions, particularly where it has been legalised, prevalence can reach 22.6%. [5-7] Interestingly, between 34% and 60% of marijuana users keep using it during pregnancy, usually thinking it is fairly safe. [5-7] THC is responsible for the psychoactive effects of cannabis, while CBD offers anxiolytic, antipsychotic, and anticonvulsant properties. [8,9] Research indicates an increasing trend in cannabis consumption during pregnancy, with contributing factors including mental health, socioeconomic status, and peer influence. [10-12]

Studies have associated prenatal cannabis exposure with higher risks of preterm birth, low birth weight, and foetal growth restriction (FGR), a condition associated with impaired placental development, a condition that remains incompletely understood [13-16] Furthermore, prenatal marijuana exposure (PME) has been correlated with neurodevelopmental issues such as attention deficits, behavioral problems, and an increased risk of attention-deficit/hyperactivity disorder (ADHD). [17,18] The endocannabinoid system (ECS) plays a crucial role in placental development and function, with Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) exerting notable effects through their interactions with this system. THC primarily binds to CB1 receptors in the placenta, disrupting trophoblast functions essential for placental development and nutrient transfer. This activation may lead to increased vascular resistance, hindered formation of new blood vessels, and complications such as placental insufficiency and intrauterine growth restriction. [19,20] It also triggers the release of inflammatory cytokines, which contribute to chronic inflammation that can harm foetal development. [21] In contrast, CBD does not primarily bind to CB1 or CB2 receptors; instead, it enhances endocannabinoid levels by inhibiting fatty acid amide hydrolase (FAAH), thereby increasing anandamide availability. This measure enhances trophoblast activity and fosters optimal placental development. [22] Moreover, the anti-inflammatory properties of CBD may mitigate THC-induced inflammation, thereby creating a more conducive environment for foetal growth. [23] THC causes the psychoactive effects of cannabis; however, CBD has anxiolytic, antipsychotic, and anticonvulsant effects. [8,9]

Reduced head circumference due to cannabis exposure, especially in the first trimester, may lead to neurodevelopmental deficits. [24-26] The placenta, a temporary organ during pregnancy, plays a crucial role in maternal-foetal exchange, with the labyrinth zone (LZ) being key for the transfer of nutrients and oxygen. [27-29] Limited research exists on cannabis' effects on placental health, with existing studies indicating that THC may impair placental function, potentially impacting foetal development. [16] Given the increasing prevalence of cannabis consumption among pregnant individuals, it is imperative to

examine its effects on foetal development at different stages. In this work, we analysed the effects of THC, CBD, and their combination on foetal weight and placental health, emphasising the need for further investigation into how prenatal cannabis exposure impacts placental function and foetal neurodevelopment.

Methods

This study was primarily conducted at Olabisi Onabanjo University (OOU), with supplementary analyses conducted in collaboration with the Shock and Reanimation Laboratory at the University of Kansas, Kansas City, Missouri, United States. Ethical approval for this study was obtained from the University Ethical Review Committee (UERC), Olabisi Onabanjo University, Ago Iwoye (OOU/SCIENG/EC/240924).

Twenty-four female and 12 male Wistar rats, weighing 90-120 g, were used in the experiment, sourced from Peter's Farm (Nig.) Enterprises Ibadan. The animals were housed in wire mesh plastic cages measuring 40 cm × 60 cm × 20 cm (30) within the animal house at the Department of Anatomy, OOU, under standard laboratory conditions. A total of 12 cages were used to house the animals, ensuring sufficient space and adherence to the highest standards of animal welfare. The cages were kept under controlled conditions, including a 12-hour light/dark cycle, a temperature of 22 ± 2°C, and regular monitoring to ensure the animals' health and comfort. The male rats were selected based on their weight, palpation for a prominent scrotal sac containing the testes, and observable activity. These males were used to mate with the female rats at a 2:1 (female: male) ratio. Mating was confirmed by the presence of a sperm plug (vaginal plug) or sperm cells observed under a microscope and was marked as gestational day one (GD1). The rats were acclimatised for 2 weeks. The rats had unlimited access to water and feed. They were given Growers Match, sourced from Joyful Feed Limited in Sagamu, Ogun State, Nigeria. The animal feed ingredients include corn, rice polishing, canola meal, guar meal, soybean meal, fish meal, limestone, and di-calcium phosphate.

Cannabis sativa was obtained from the National Drug Law Enforcement Agency (NDLEA); the extract was prepared from the dried leaves of the plant. The identification was conducted by the NDLEA, with reference number NDLEA/SD/2024/2170. Voucher specimen was deposited in Elikaf Herbarium, Department of Plant Science, Olabisi Onabanjo University, Ago Iwoye, and was assigned Voucher no: EH/2024/19002. It was soaked in 95% ethanol for 72 hours. [31] It was then filtered using a filter paper and then taken to the department of pharmacognosy, OOU, for concentration with a Rotary Evaporator Yamato (RE-601-CW) with a chiller at 40 °C with reduced pressure. [32] Solvent-solvent extraction and fractionation were done. Thin-layer chromatography (TLC) procedures were performed to confirm the identity of the products. The percentage yield was calculated using this formula:

$\frac{Final\ Weight}{Initial\ Weight}\ X\ 100$. The initial weight was 278.7g, and the final weight was 23.52g, resulting in an 8.44% yield through the preparation process. Retention values were obtained for the THC (0.336 ± 0.017) and CBD (0.305 ± 0.012). [33] The study featured two groups: a control group and an experimental group, which received treatments of THC, CBD, or a combination of both.

Experimental groups

Control Groups: A total of 6 female Wistar rats were used as controls, provided with feed and water ad libitum. They were further divided into two subgroups (n = 3): GD6 to GD19 and GD6 to animal litter.

Early THC Group (ETHC): In this group, six (6) female Wistar rats were provided with feed,

clean water, and a 150 mg/kg dose of THC for specific durations of gestational days based on the subgroup.

Early CBD Group (ECBD): Six female Wistar rats, which were subdivided into two groups, n = 3. They were provided with feed, clean water, and a 150 mg/kg dose of CBD for specific durations of gestational days based on the subgroup.

Early THC/CBD (ETHC/CBD) Group: Six female Wistar rats were provided with feed, clean water, and a 150 mg/kg dose of THC/CBD from gestational day 6 to day 19 and till animal litter.

The doses were selected based on previous evaluations in rats. [34] On day GD 19, three animals from each group were sacrificed, and placentae were extracted for macro-morphometric measurements and morphological analysis. The remaining three animals in each group were allowed to litter, and their pups were permitted to grow. (Figure 1). After harvesting the placenta from the fetus, its dimensions were measured using a Vernier calliper. The placenta's weight was determined with a sensitive weighing scale. Thickness was measured by inserting a calibrated knitting needle at the centre of the placenta and recorded in centimetres, with an accuracy of 0.1 cm. The area was calculated by multiplying the length by the breadth.

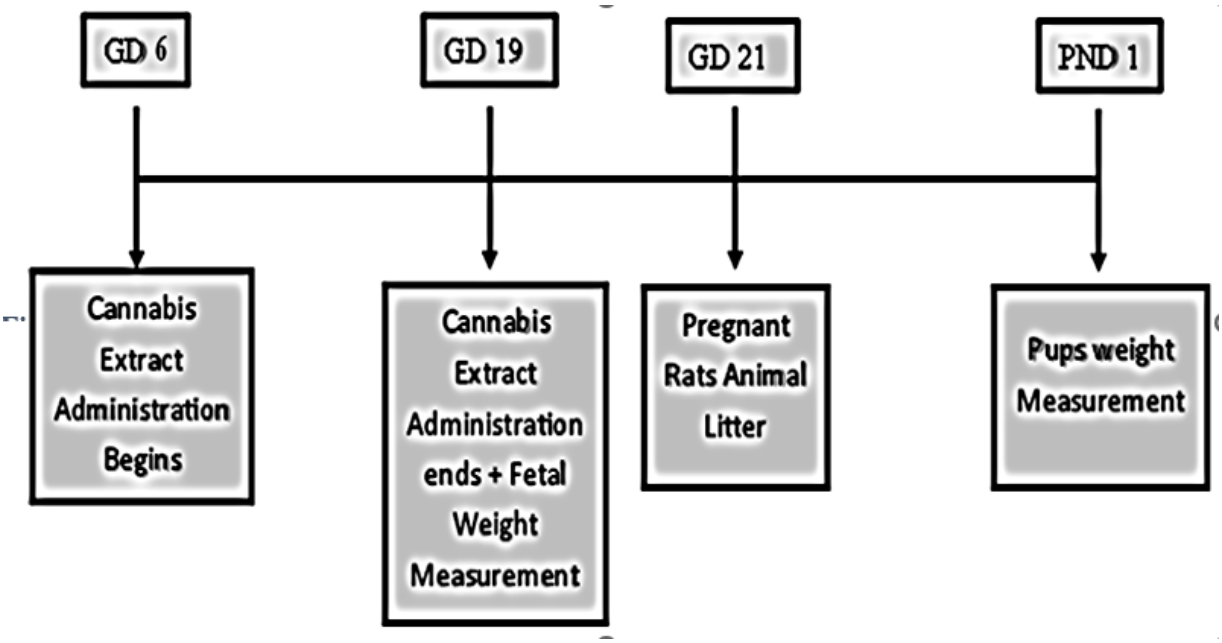

Figure 1: Procedural timeline for the study

The placenta tissues were examined in the Histology Laboratory of the Department of Anatomy at Olabisi Onabanjo University, Shagamu, Ogun State, Nigeria. The normal placenta displayed a well-maintained three-layered structure, with intact syncytiotrophoblasts in the labyrinthine zone and clearly organised junctional and decidual zones. This suggests normal trophoblast function and effective maternal-foetal exchange, with no evidence of necrosis, other abnormalities, or degeneration. For image acquisition and analysis, a light microscope with a 10–20X magnification objective was used. A digital camera (AmScope MD500A) attached to a PC-HP was employed, and Java Application Software was utilised.

Data analysis

This was performed using GraphPad Prism. For comparisons between two groups, a Student's t-test was used; for multiple groups, a one-way ANOVA was used. Results are presented as Mean ± SEM, and statistical significance was defined as $p < 0.05$.

Results

Physical observation: Instances of vaginal bleeding and cannibalism of pups were observed in the CBD-treated group. Additionally, maternal mortality occurred in some dams within the experiment.

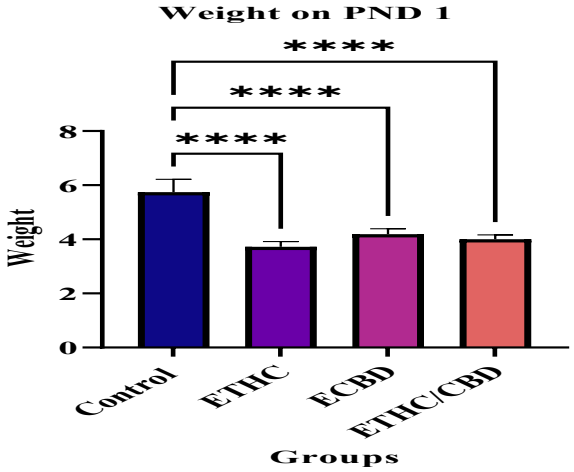

Figure 2: Comparison of Gestational Day 19 Weight and Postnatal Day 1 (PND 1) Weight Across Experimental Groups.

The bar charts displayed mean weights for gestational day 19 (left) and PND 1 (right) in control, THC-exposed (ETHC), CBD-exposed (ECBD), and combined THC/CBD-exposed (ETHC/CBD) groups. Statistical significance is denoted by asterisks (*p < 0.05, ****p < 0.0001)

Offsprings Weight

On gestational day 19, all experimental groups showed lower foetal weights than the control (see Figure 2). The control group's average foetal weight was 3.78 ± 0.043g. The ETHC group experienced a roughly 36% decrease, with an average weight of 2.41 ± 0.085g, while the ECBD group had an even larger reduction of approximately 41%, weighing 2.22 ± 0.022g. The ETHC/CBD group experienced a moderate weight loss of approximately 7% (3.51 ± 0.064 kg). These results show that both separate and combined prenatal exposure to THC and CBD significantly hinder foetal growth. Interestingly, exposure to THC and CBD alone caused the most noticeable decrease in foetal weight. Conversely, the combination of THC and CBD led to a smaller reduction in weight compared to individual exposures.

The trend of weight reduction persisted postnatally, as indicated by weight measurements on Postnatal Day 1 (PND 1) across the experimental groups (Figure 2). The control group showed the highest average weight (5.74 ± 0.081g), indicating normal neonatal growth, while all the exposed groups had significantly lower weights ($p < 0.0001$). THC exposure caused the most significant reduction (3.72 ± 0.040g), representing a 35% decrease, followed by CBD exposure (4.19 ± 0.043g), which resulted in approximately a 27% reduction. The combined

THC/CBD group showed an intermediate weight reduction (4.00 ± 0.031g), reflecting a 30% decrease, suggesting that CBD may partially offset the adverse effects on neonatal weights caused by THC.

Foeto-Placenta Weight Ratio

The control group had a healthy fetoplacental ratio (8.69 ± 0.032), while the ETHC group showed a significantly lower ratio (4.84 ± 0.100), indicating severe placental insufficiency that likely affected foetal growth and development. The ECBD (6.61 ± 0.051) and ETHC/CBD (6.59 ± 0.077) groups showed intermediate fetoplacental ratios, suggesting mild placental insufficiency that was less severe than in the ETHC group. When comparing foetal weights before birth with neonatal weights after birth, the control group consistently had the highest weights at both gestational day 19 and postnatal day 1. The ETHC group experienced a significant decline in weight at both time points in comparison to the control, highlighting the negative impact of THC exposure on foetal and neonatal development. Among the experimental groups, the ECBD group exhibited the lowest weight at both gestational day 19 and postnatal day 1, indicating that CBD exposure alone may contribute to foetal growth restrictions. Notably, the ETHC/CBD group showed an intermediate weight, higher than both the ETHC and ECBD groups, yet still below the control group. This suggests that combined THC and CBD exposure might partially offset some negative impacts of individual cannabinoid exposure on foetal growth.

.

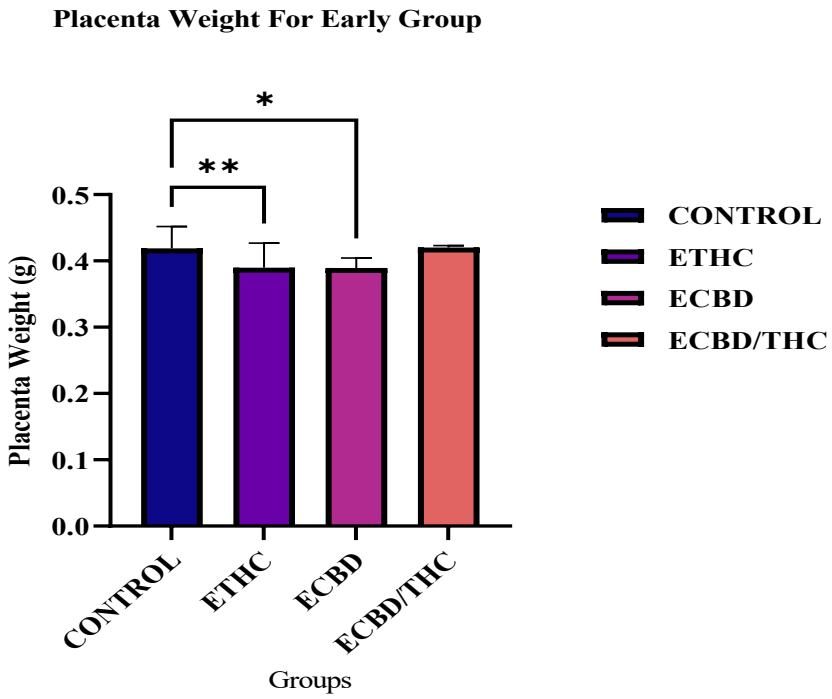

Figure 3: Placenta weight comparison for the early gestation group across experimental conditions (Control, ETHC, ECBD, and ECBD/THC). Significant differences are denoted by * ($p < 0.05$) and ** ($p < 0.01$)

Placental Morphometry

Prenatal exposure to cannabis extracts caused notable changes in placental thickness. The ETHC group showed a marked decrease in breadth, while the ECBD group experienced a significant increase. However, the ETHC/CBD

group exhibited intermediate results, indicating a partial reduction of the effects seen in the individual exposure groups. The recorded breadth values were control (1.70 ± 0.008 cm), ETHC (1.25 ± 0.039 cm), ECBD (1.225 ± 0.016 cm), and ETHC/CBD (1.26 ± 0.024 cm) (Figure 5). Similarly, placental length measurements varied across the groups. The ETHC group showed a significant decrease in length (1.50 ± 0.033 cm) compared to the control group (1.40 ± 0.004 cm). The ECBD group measured 1.39 ± 0.006 cm, while the ETHC/CBD group showed an intermediate length of 1.45 ± 0.022 cm, suggesting that combined exposure may reduce some of the structural changes caused by THC or CBD alone. (Figure 6). These findings indicate that prenatal cannabis exposure causes morphological changes in the placenta, which could affect placental function and foetal development.

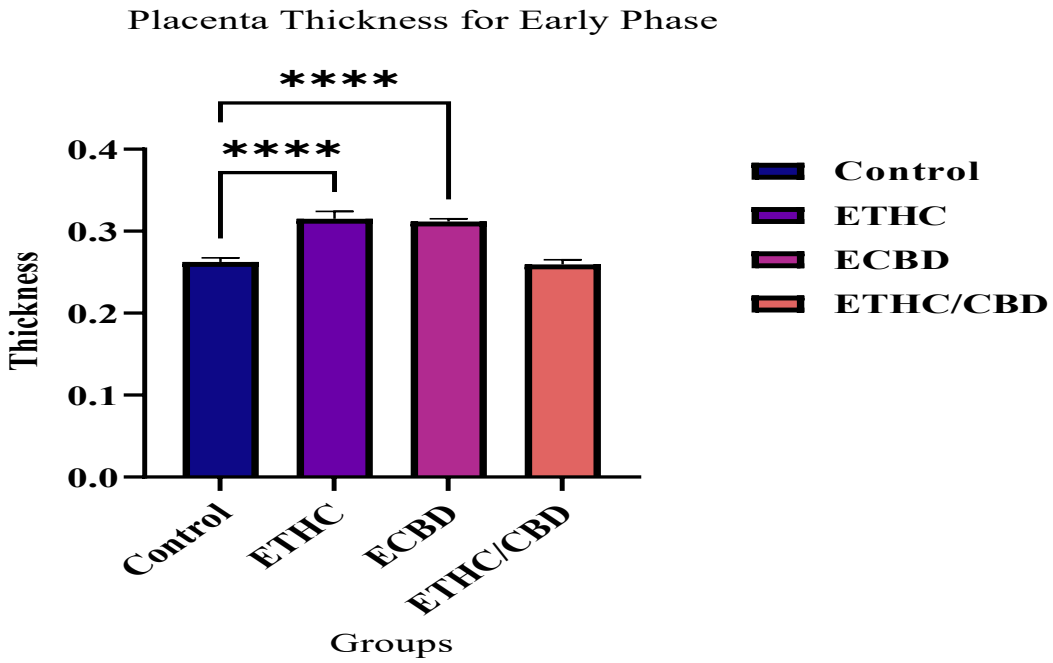

Figure 4: Comparison of placental thickness in the early gestation phase across experimental groups (Control, ETHC, ECBD, and ETHC/ CBD). Significant differences are indicated by ** ($p < 0.0001$)**

Histological Analysis of Placental Structure

(A) Control Group

The placental structure in the control group showed a well-maintained three-layered makeup, with clearly defined and intact zones. The syncytiotrophoblast layer (STL) within the labyrinthine area was distinctly visible, characterised by an abundance of trophoblasts. This structural soundness suggests normal placental function, supporting effective maternal-foetal nutrient transfer. The junctional and decidual zones were also properly organised, with no evidence of necrosis or cell deterioration.

(B) THC-Exposed Group

The placental structure in the THC-exposed group showed notable morphological abnormalities. The decidual zone was highly distorted, displaying disorganisation and structural breakdown. There was also a significant increase in trophoblast glycogen cells, resulting in a larger junctional zone, which may be a compensatory response to placental stress.

The labyrinthine layer exhibited mild necrosis and a marked decrease in trophoblasts, suggesting compromised exchange functions and possible impairment of foetal nutrient supply.

(C) CBD-Exposed Group

Exposure to CBD caused severe histopathological changes throughout all placental layers. The decidual zone showed significant disruptions, indicating tissue damage and potential functional impairment. The junctional zone showed cytolysis of both spongiotrophoblasts and glycogen cells, suggesting excessive cell death and compromised structural integrity.

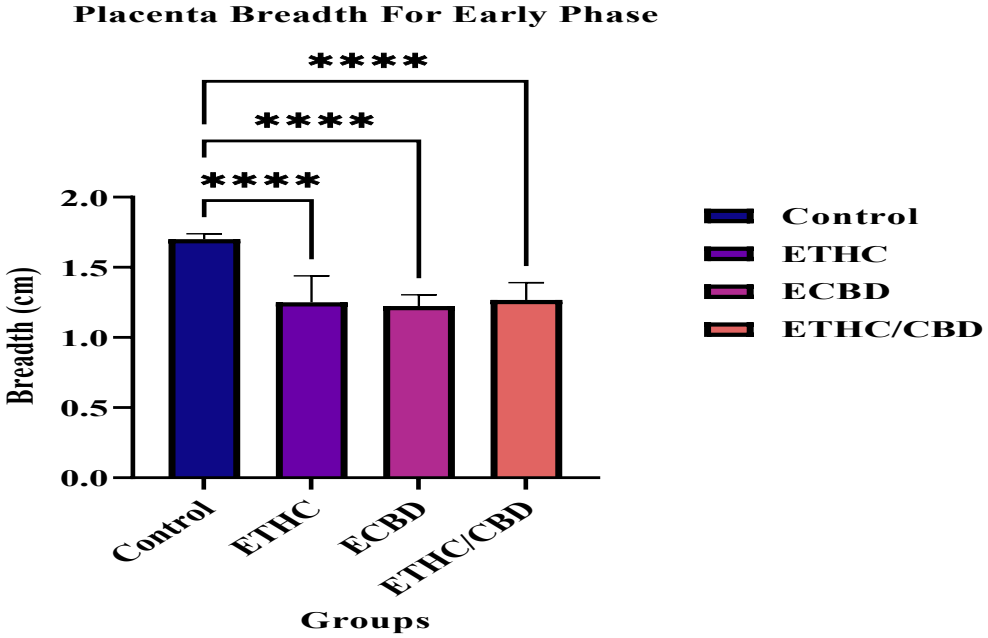

Figure 5: Comparison of placental breadth in the early gestation phase across experimental groups (Control, ETHC, ECBD, and ETHC/ CBD). Significant differences are indicated by ** ($p < 0.0001$).**

Additionally, trophoblast degeneration and extensive labyrinthine necrosis were observed, indicating severe disruption of placental architecture that could harm foetal development.

(D) Combined THC/CBD-Exposed Group

Placental sections from the THC-CBD co-exposed group showed milder pathological changes compared to the individual THC and CBD groups. Although abnormalities were found in all three zones, the damage was significantly less severe. Mild structural distortions appeared in the decidual zone, but the overall integrity of the placenta remained relatively intact. Compared to THC or CBD alone, the combined exposure resulted in less labyrinthine necrosis and fewer degenerative changes in trophoblasts, indicating a possible mitigating effect of THC and CBD interaction on placental pathology.

Analysis of Periodic Acid-Schiff (PAS) Staining

Glycogen content in the placenta plays a crucial role in ensuring proper foetal development and overall pregnancy health. The placenta stores glycogen as a critical energy reserve, which fuels the metabolic activities of the placenta itself and supports the developing fetus. This glycogen

reserve is vital for maintaining placental function, facilitating nutrient transfer, and supporting foetal growth, especially during periods of increased metabolic demand. Disruption of glycogen deposition or metabolism can impair placental function, leading to developmental delays or pregnancy complications. PAS staining revealed differential glycogen deposition in the placental tissue across the control and experimental groups. In the control group (A), PAS staining intensity was strong and consistent. The CBD group (B) exhibited a noticeable reduction in PAS staining intensity, reflecting a potential decrease in glycogen deposition. The THC-exposed group (C) showed a marked disruption in glycogen cells, characterised by irregular PAS staining and the presence of trophoblast syncytialisation (TS), indicating altered placental morphology. In the combined CBD-THC group (D), PAS positivity decreased, showing fewer glycogen cells and disrupted tissue structure, yet some preservation remained compared to the THC group alone. Quantitative analysis (bar graph) demonstrated a significant reduction (**p< 0.01) in PAS staining intensity across all experimental groups compared to the control, with the most pronounced effect observed in the THC group.

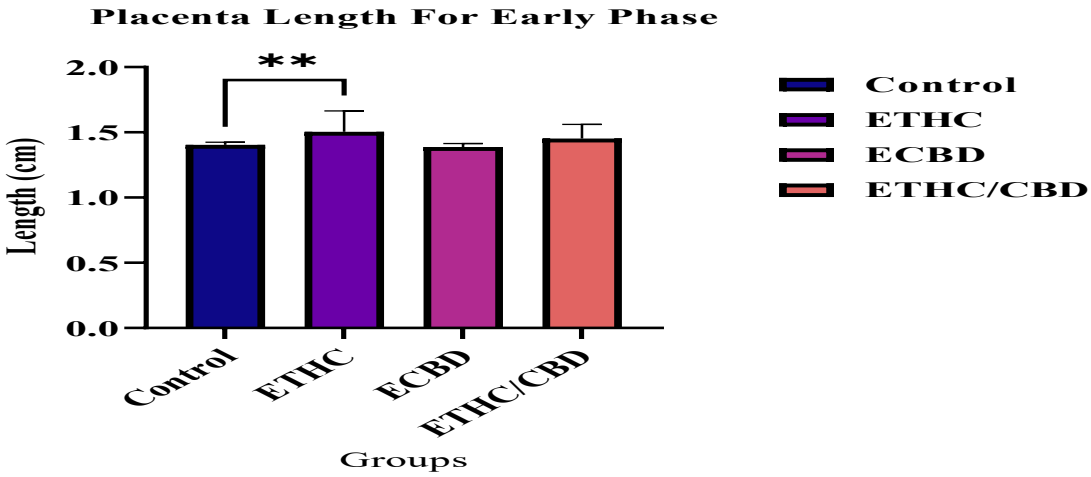

Figure 6: Comparison of placental length in the early gestation phase across experimental groups (Control, ETHC, ECBD, and ETHC/CBD). Significant differences are denoted by * (p < 0.05) and ** (p < 0.01).

Discussion

Cannabis use during pregnancy has been associated with reduced foetal weight, a finding that aligns with our study results. [35,36] However, some studies have reported contrasting outcomes, such as an increase in foetal weight following exposure to 3 mg/kg of delta-9-THC. [13,35] Interestingly, CBD exposure at the same dose consistently resulted in foetal weight reduction, corroborating our findings. [36] The combined administration of THC and CBD produced an intermediate effect on foetal weight, suggesting a potential interaction between the two cannabinoids, with CBD possibly mitigating THC-induced growth restriction.

Placental weight by itself does not necessarily reflect placental function efficiency. [37] A more dependable indicator is the foetal-to-placental weight ratio (FPR), which illustrates the

placenta's ability to sustain foetal growth. [13] This study observed a significant decrease in FPR across all cannabis-exposed groups, indicating impaired nutrient transfer and supporting the hypothesis that prenatal cannabis exposure disrupts placental function. Previous studies observed similar trends, particularly regarding stillbirths, although some analyses [37] did not demonstrate a significant association. Notably, THC exposure caused the greatest decrease in FPR, with CBD leading to a lesser effect, and the combined exposure showing an intermediate impact. These findings suggest that while CBD might mitigate some of THC's adverse effects, it does not completely restore placental function.

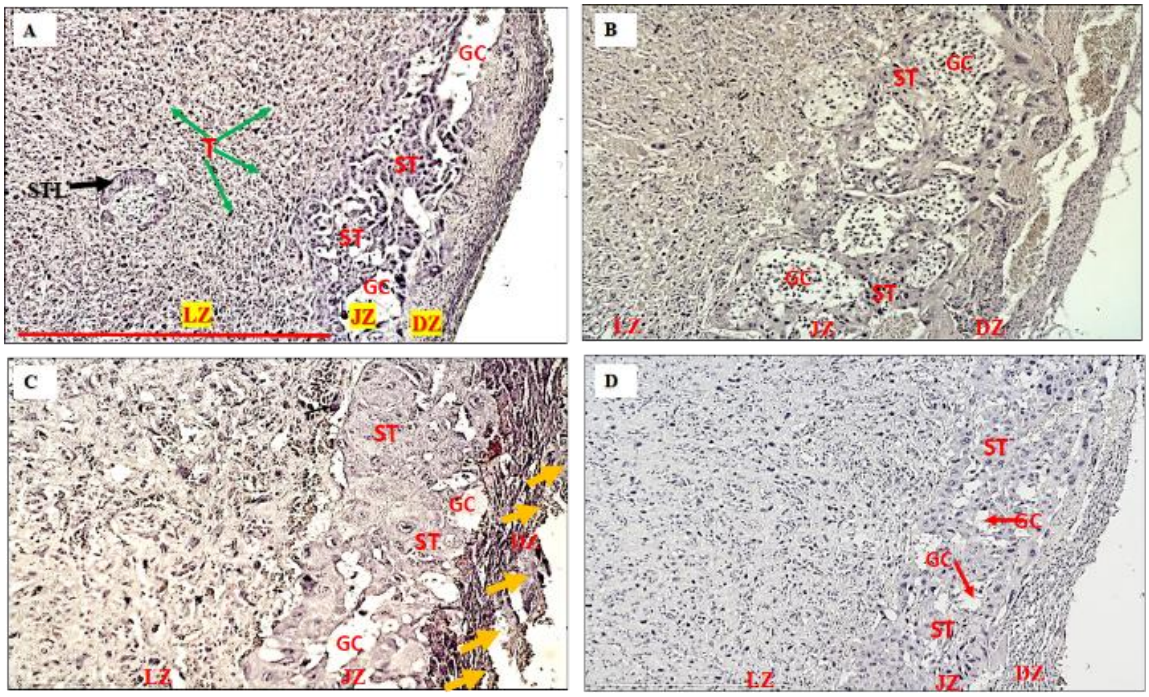

Figure 7: Representative Evos FL Auto 2 Placental Images depict H&E, x100
(Placental Layers Under Different Experimental Conditions LZ represents the labyrinth zone, JZ represents the junctional zone and DZ represents the decidual zone, Glycogen Cell GC, Spongiotrophoblast (ST), Trophoblast (T), syncytiotrophoblast layer (STL), Yellow arrows=Deranged Decidua

The reductions in foetal weight observed at gestational day 19 and postnatal day 1 indicate that cannabis exposure causes foetal growth restriction (FGR). This issue likely results from disruptions in placental function and nutrient transfer, rather than temporary growth delays. Continued growth restriction after birth raises worries about potential long-term metabolic and physiological effects. [38] Some studies have observed postnatal catch-up growth in cannabis-exposed offspring by day 21. However, this compensatory response might be influenced by factors like postnatal nutrition and hormonal regulation. [39] Our findings suggest that although the THC/CBD group showed less severe growth restriction compared to the THC-only and CBD-only groups, these offspring remained significantly growth-restricted at birth. The degree and timing of potential catch-up growth in this population need further study. Placental thickness is strongly correlated with gestational age, as well as biparietal diameter (BPD), head circumference (HC), and abdominal circumference (AC) during the second and third trimesters, although small gestational age has been linked to a thinner placenta. [40]

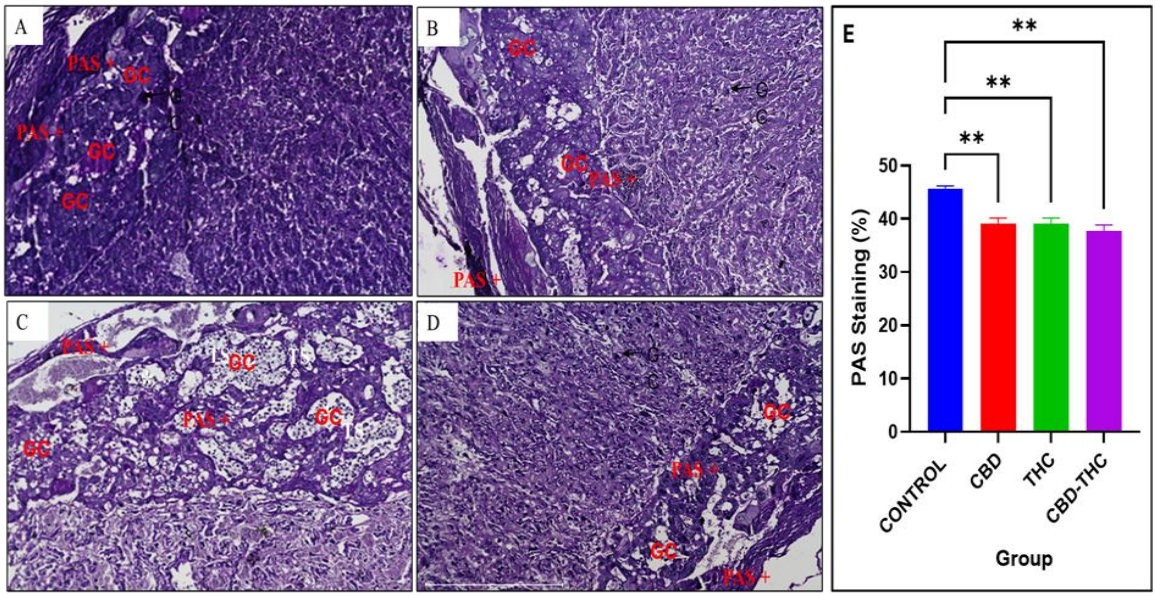

Figure 8: Histological sections stained with PAS at 200× magnification, showing glycogen.
(A) The control group displays normal glycogen deposits. (B), (C) and (D) The groups show depletion in the glycogen deposit in the Glycogen Cells. The accompanying bar graph illustrates the percentage of PAS staining, with a notable decrease in the THC and CBD+THC groups compared to the control group, as indicated by statistical significance markers. GC indicates giant cells filled with glycogen. PAS staining quantification (E) was conducted using a one-way analysis of variance (ANOVA) with post hoc Dunnett adjustment. The data are presented as mean ± SEM. **p < 0.01.

Placental morphometric analysis showed significant changes in cannabis-exposed groups, with increased placental thickness in the THC and CBD groups, while combined exposure showed no significant difference. Placental breadth decreased notably in the THC group but increased in the CBD group, and the combined exposure resulted in intermediate values. These morphological changes indicate that prenatal cannabis exposure modifies placental structure, which could impact its functional capacity. [41] The reductions in FPR and foetal weight observed in these groups in this study further support this notion. [13]

Histological examination of the placenta revealed structural disruptions in the cannabis-exposed groups. The control group showed a healthy, three-layered placental structure with a clearly defined syncytiotrophoblast layer and abundant trophoblasts. In contrast, THC exposure caused significant disruption of the decidual zone, fewer trophoblast cells, an enlarged junctional zone, and mild labyrinth necrosis. CBD exposure caused even more severe disruptions, including cytolysis of spongiotrophoblast and glycogen cells, trophoblast degeneration, and prominent labyrinth degeneration necrosis. [42] The combined THC/CBD exposure resulted in milder pathology across all three zones, further indicating a modulatory interaction between the two cannabinoids. [43]

Glycogen concentration, a vital energy reserve for foetal development, was decreased in all cannabis-exposed groups, consistent with previous studies showing dose-dependent glycogen depletion after cannabinoid exposure. However, glycogen depletion has been reported to decrease toward term. [44] The reduction was most significant in the THC group, followed by CBD, with the combined exposure causing intermediate effects. The formation of glycogen islands within maternal blood spaces in THC-exposed placentas further highlights the extent of

placental disruption. [45] These findings indicate that prenatal cannabis exposure impairs placental glycogen storage, which could result in insufficient energy supply for the developing fetus.

Conclusion

This study demonstrates that prenatal exposure to THC, CBD, or their combination hampers foetal growth and placental efficiency. These findings underscore the harmful effects of cannabis on placental structure and function, emphasising the need for further research on the mechanisms involved and potential therapeutic interventions to safeguard maternal and foetal health.

Acknowledgement: The authors wish to thank the National Drug Law Enforcement Agency (NDLEA) Abeokuta Command, Nigeria, Mr Adeoti of the Department of Pharmacognosy, Faculty of Pharmacy, OOU, Sagamu Campus, Mr Kemiki Olamilekan, Mrs Joy and all the staff of the Molecular Laboratory, Babcock Teaching Hospital, Ilishan-Remo. Miss Ebohimen Doris and all the staff of the Department of Anatomy, Faculty of Basic Medical Sciences, OOU and Prof. Bolanle Fetuga, the Provost of the OACHS, OOU, Sagamu Campus, are also deeply appreciated.

Authors' Contributions: T-ODO and SPD conceived and designed the study. SIA and AJA did the literature review. T-ODO, AOD, FPB and SPD analysed and interpreted the data. T-ODO, AJA and SPD drafted the manuscript. SIA and AOD revised the draft for sound intellectual content. All the authors approved the final version of the manuscript.

Conflicts of interest: None.

Funding: Self-funded.

Publication History: Submitted 01 February 2025; **Accepted** 20 August 2025.

References

1. Bonini SA, Premoli M, Tambaro S, Kumar A, Maccarinelli G, Memo M. Cannabis sativa: A comprehensive ethnopharmacological review of a medicinal plant with a long history. J Ethnopharmacol 2018;227:300–315. https://doi.org/10.1016/j.jep.2018.09.004.
2. Rock EM, Parker LA. Constituents of Cannabis Sativa. In: Murillo-Rodriguez E, Pandi-Perumal SR, Monti JM, editors. Cannabinoids and Neuropsychiatric Disorders [Internet]. Cham: Springer International Publishing; 2021. p. 1–13. (Advances in Experimental Medicine and Biology; vol. 1264). DOI:10.1007/978-3-030-57369-0_1
3. Wishart DS, Hiebert-Giesbrecht M, Inchehborouni G, Cao X, Guo AC, LeVatte MA. Chemical Composition of Commercial Cannabis. J Agric Food Chem 2024;72:14099. https:..doi.org/10.1021/acs.jafc.3c06616.
4. Navarrete F, García-Gutiérrez MS, Gasparyan A, Austrich-Olivares A, Femenía T, Manzanares J. Cannabis Use in Pregnant and Breastfeeding Women: Behavioral and Neurobiological Consequences. Front Psychiatry 2020;11:586447. https://doi.org/10.3389/fpsyt.2020.586447.
5. Thompson A, Koren G, McGowan J. Cannabis use during pregnancy: A review of the literature. J Matern Fetal Neonatal Med 2019;32:2027-2034. https://doi.org/10.1080/14767058.2018.1441853.
6. Mark K, McCaffrey D, Larkins A. Prenatal cannabis exposure: Potential implications for child development and behavior. Child Dev Perspect 2017;11:42-48. https://doi.org/10.1111/cdep.12202.
7. Singh T, Bhandari S, Kaur S. The impact of prenatal cannabis exposure on fetal and neonatal outcomes: A systematic review. Neurotoxicology 2020;78:106849. https://doi.org/10.1016/j.ntt.2020.106849.
8. Kroon E, Kuhns L, Hoch E, Cousijn J. Heavy cannabis use, dependence and the brain: a clinical perspective. Addiction 2020;115:559–572. https://doi.org/10.1111/add.14776.
9. De Camargo RW, De Novais Júnior LR, Da Silva LM, Meneguzzo V, Daros GC, Da Silva MG. Implications of the endocannabinoid system and the therapeutic action of cannabinoids in autism spectrum disorder: A

literature review. Pharmacol Biochem Behav 2022;221:173492.
10. Montgomery L, Dixon S, Mantey DS. Racial and Ethnic Differences in Cannabis Use and Cannabis Use Disorder: Implications for Researchers. Curr Addict Rep 2022;9:14. https://doi.org/10.1007/s40429-021-00404-5
11. Mulligan MK, Hamre KM. Influence of prenatal cannabinoid exposure on early development and beyond. Adv Drug Alcohol Res 2023;3:10981. https://doi.org/10.3389/adar.2023.10981.
12. Cameron LD, Fleszar-Pavlović SE, Yepez M, Manzo RD, Brown PM. Beliefs about marijuana use during pregnancy and breastfeeding held by residents of a Latino-majority, rural region of California. J Behav Med 2022;45:544–557. https://doi.org/10.1007/s10865-022-00299-1.
13. Andrade C. Maternal Cannabis Use During Pregnancy and Maternal and Neonatal Adverse Outcomes. J Clin Psychiatry 2024;85:57493. https://doi.org/10.4088/JCP.24f15611.
14. Avalos LA, Oberman N, Alexeeff SE, Croen LA, Davignon MN, Adams SR, *et al.* Early Maternal Prenatal Cannabis Use and Child Developmental Delays. JAMA Netw Open 2024;7:e2440295. https://doi.org/10.1001/jamanetworkopen.2024.40295
15. Bligard KH, Odibo AO. Fetal Growth Restriction. In: Spong CY, Lockwood CJ, editors. Queenan's Management of High-Risk Pregnancy [Internet]. 1st ed. Wiley; 2024; p. 392–8. https://doi.org/10.1002/9781119636540.ch44
16. Natale BV, Gustin KN, Lee K, Holloway AC, Laviolette SR, Natale DRC, *et al.* Δ9-tetrahydrocannabinol exposure during rat pregnancy leads to symmetrical fetal growth restriction and labyrinth-specific vascular defects in the placenta. Sci Rep 2020;10:544. https://doi.org/10.1038/s41598-019-57318-6.
17. Sharapova SR, Phillips E, Sirocco K, Kaminski JW, Leeb RT, Rolle I. Effects of prenatal marijuana exposure on neuropsychological outcomes in children aged 1-11 years: A systematic review. Paediatr Perinat Epidemiol 2018; 32:512–532. https://doi.org/10.1111/ppe.12505.
18. Vishnubhotla RV, Ahmad ST, Zhao Y, Radhakrishnan R. Impact of prenatal marijuana exposure on adolescent brain structural and functional connectivity and behavioural outcomes. Brain Commun 2024;6:fcae001. https://doi.org/10.1093/braincomms/fcae001
19. Boggs DL, Nguyen JD, Morgenson D, Taffe MA, Ranganathan M. Clinical and Preclinical Evidence for Functional Interactions of Cannabidiol and Δ9-Tetrahydrocannabinol. Neuropsychopharmacology 2018;43:142-154. https://doi.org/10.1038/npp.2017.197.
20. Galve-Roperh I, Sánchez C, Cortés ML, Fernández-Ruiz J. The endocannabinoid system in development and perinatal events. Trends Pharmacol Sci 2002;23:83-87. https://doi.org/10.1016/S0165-6147(01)01635-2.
21. Hernández ME, Rojas C, Salazar L. Cannabinoid receptors and their modulation in the placenta. Front Pharmacol 2018;9:964. https://doi.org/10.3389/fphar.2018.00964.
22. Maccarrone M, Guzman M, Macarulla T. Endocannabinoid signalling in the regulation of immune responses. J Neuroimmune Pharmacol 2015;10:212-223. https://doi.org/10.1007/s11481-015-9586-6.
23. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol 2008;153:199-215. https://doi.org/10.1038/sj.bjp.0707442.
24. Mayrink ML de S, Villela LD, Méio MDBB, Soares FVM, de Abranches AD, Nehab SRG, *et al.* The trajectory of head circumference and neurodevelopment in very preterm newborns during the first two years of life: a cohort study. J Pediatr (Rio J) 2024;100:483–490. https://doi.org/10.1016/j.jped.2024.04.005.
25. Brown S. Indiana's Punitive Responses to Prenatal Marijuana Use: A Recommendation

for the Indiana Legislature. Indiana Health Law Review. 2025; 22(1):125-54. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; http://www.ncbi.nlm.nih.gov/books/NBK570616/PMID: 34033378

26. Dodge P, Nadolski K, Kopkau H, Zablocki V, Forrestal K, Bailey BA. The impact of timing of in utero marijuana exposure on fetal growth. Frontiers Pediatr 2023.11:1103749. https://doi.org/10.3389/fped.2023.1103749
27. Peng S, Li C, Xie X, Zhang X, Wang D, Lu X. Divergence of Iodine and Thyroid Hormones in the Fetal and Maternal Parts of Human-Term Placenta. Biol Trace Elem Res 2020;195:27–38. https://doi.org/10.1007/s12011-019-01834-z.
28. Furukawa S, Tsuji N, Sugiyama A. Morphology and physiology of rat placenta for toxicological evaluation. J Toxicol Pathol 2019;32:1-17. https://doi.org/10.1293/tox.2018-0042
29. Sarkar AA, Sabatino JA, Sugrue KF, Zohn IE. Abnormal labyrinthine zone in the Hectd1-null placenta. Placenta 2016;38:16–23. https://doi.org/10.1016/j.placenta.2015.12.002.
30. Miller GM, Smith D, Shukitt-Hale B. Effects of Housing on Rodent Behavior: Wire vs. Solid Plastic Caging. Anim. Husb Dairy Vet Sci 2020;4:1-5.
31. Rashid S, Majeed LR, Nisar B, Nisar H, Bhat AA, Ganai BA. Phytomedicines: Diversity, extraction, and conservation strategies. In: Phytomedicine. Elsevier; 2021. p.1–33. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780128241097000091
32. Fiardilla, F., Warsiki, E., & Sugiarto. The experiment of activity and stability of antioxidant extracted from Senduduk (Melastoma malabathricum L) leaves at various conditions of concentration, pH values, and temperatures. IOP Conference Series: Earth Environ Sci 2020;472:012003. https://doi.org/10.1088/1755-1315/472/1/012003
33. Liu Y, Victoria J, Wood M, Staretz ME, Brettell TA. High Performance Thin-Layer Chromatography (HPTLC) data of Cannabinoids in ten mobile phase systems. Data Brief 2020;31:105955. https://doi.org/10.1016/j.dib.2020.105955
34. Chan P. Toxicity and Carcinogenicity of Δ9-Tetrahydrocannabinol in Fischer Rats and B6C3F1 Mice. Fundam Appl Toxicol 1996;30:109–117. https://doi.org/10.1006/faat.1996.0048
35. Allen S, Natale BV, Ejeckam AO, Lee K, Hardy DB, Natale DRC. Cannabidiol Exposure During Rat Pregnancy Leads to Labyrinth-Specific Vascular Defects in the Placenta and Reduced Fetal Growth. Cannabis Cannabinoid Res. 2024;9:766–780. https://doi.org/10.1089/can.2023.0166.
36. Sathasivam R, Selliah P, Sivalingarajah R, Mayorathan U, Munasinghe BM. Placental weight and its relationship with the birth weight of term infants and the body mass index of the mothers. J Int Med Res 2023;51:03000605231172895. https://doi.org/10.1177/03000605231172895.
37. Metz TD, Allshouse AA, Pinar H, Varner M, Smid MC, Hogue C. Maternal Marijuana Exposure, Feto-Placental Weight Ratio, and Placental Histology. Am J Perinatol 2022;39:546–553. https://doi.org/10.1055/s-0040-1717092.
38. Armengaud JB, Yzydorczyk C, Siddeek B, Peyter AC, Simeoni U. Intrauterine growth restriction: Clinical consequences on health and disease at adulthood. Reprod Toxicol 2021;99:168–176. https://doi.org/10.1016/j.reprotox.2020.10.005.
39. Lee K, Laviolette SR, Hardy DB. Exposure to Δ9-tetrahydrocannabinol during rat pregnancy leads to impaired cardiac dysfunction in postnatal life. Pediatr Res 2021;90:532–539. https://doi.org/10.1038/s41390-021-01511-9.
40. Vinchurkar KN, Aiyappan SK, Prem Kumar C, Shanmugam V, Singh A. Correlation of placental thickness with gestational age in second and third trimester using ultrasonography. Egypt J Radiol Nucl Med

2023;54:164. https://doi.org/10.1186/s43055-023-01112-y.

41. Vrooman LA, Xin F, Bartolomei MS. Morphological and molecular changes in the placenta: What we can learn from environmental exposures. Fertil Steril 2016;106:930–940. https://doi.org/10.1016/j.fertnstert.2016.08.016.
42. Furukawa S, Hayashi S, Usuda K, Abe M, Hagio S, Ogawa I. Toxicological Pathology in the Rat Placenta. J Toxicol Pathol. 2011;24(2):95–111. doi: 10.1293/tox.24.95
43. Mortuza A, Fahim N, Ahmed M, Mustafa A. Effects of CBD (Cannabidiol) on the physiology of Nile tilapia (Oreochromisn niloticus) as a chronic stress mitigating agent In-vivo. PLOS ONE 2023 15;18:e0290835. https://doi.org/10.1371/journal.pone.0290835
44. Shafrir E, Barash V. Placental glycogen metabolism in diabetic pregnancy. Isr J Med Sci 1991;27:449–461.
45. Akison LK, Nitert MD, Clifton VL, Moritz KM, Simmons DG. Review: Alterations in placental glycogen deposition in complicated pregnancies: Current preclinical and clinical evidence. Placenta 2017;54:52–58. https://doi.org/10.1016/j.placenta.2017.01.114.