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Aframomum Melegueta protects against Lithium Chloride-Pilocarpine-Induced Epilepsy via HPG axis, Regulates Oxidative Stress and enhances Ovarian Histoarchitectural Integrity in Female Wistar Rats

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Abstract

Epilepsy is a global neurological disorder frequently associated with reproductive and endocrine dysfunctions in both males and females. Antiepileptic drug such as *Aframomum melegueta* has been reported to possess antioxidant and medicinal properties, but its effects on epilepsy-induced ovarian dysfunction remain unexplored. This study evaluates the effects of *Aframomum melegueta* on reproductive hormones, oxidative stress markers and ovarian histoarchitectural changes in lithium chloride-pilocarpine-induced epileptic female rats. Twenty-four adult female Wistar rats were randomly assigned into four groups (n = 6): control, epileptic (untreated), *A. melegueta*-treated epileptic and standard antiepileptic drug-treated epileptic groups. Epilepsy was induced using intraperitoneal injection of lithium chloride and pilocarpine. Treatments were administered orally for 21 days. Body and ovarian weights were recorded, serum samples were analyzed for reproductive hormones and oxidative stress indices, and ovarian tissues were examined histologically following sacrifice under diethyl ether anesthesia. Treatment with *A. melegueta* resulted in a significant increase ($p < 0.05$) in relative ovarian weight, superoxide dismutase activity, follicle-stimulating hormone, and luteinizing hormone levels compared with the epileptic control and standard drug groups. Malondialdehyde levels significantly reduced in the *A. melegueta*-treated group relative to the epileptic control but remained higher than those in the standard drug group. Histological analysis of ovaries from epileptic rats showed follicular degeneration, oocyte loss and necrotic changes, whereas these alterations were markedly attenuated in *A. melegueta*-treated rats. These findings suggest *Aframomum melegueta* exhibited protective and restorative effects against epilepsy-induced ovarian damage by improving hormonal balance, enhancing antioxidant defense, and preserving ovarian histoarchitecture.

Keywords: Epilepsy; *Aframomum melegueta*; Lithium chloride-pilocarpine; Reproductive hormones; Diazepam; ovary

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1 Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures resulting from abnormal electrical activity in the brain [1]. It affects more than 50 million people worldwide and remains one of the most prevalent non-communicable neurological conditions, with an estimated 4-10 per 1,000 individuals living with active epilepsy at any given time 2. Beyond its neurological manifestations, epilepsy imposes a substantial burden on physical health, psychosocial wellbeing, and economic productivity, with stigma and discrimination often compounding the challenges faced by affected individuals and their families [2, 3]. Although epilepsy is traditionally viewed as a disorder of the central nervous system, research has shown that its impact extends to multiple physiological systems, including the endocrine and reproductive systems [4, 5]. In females, epilepsy has been associated with disturbances in the hypothalamic–pituitary–gonadal (HPG) axis, leading to menstrual irregularities, altered reproductive hormone profiles, and impaired fertility [6–8]. Neurochemical alterations related to seizures, chronic inflammation, and oxidative stress have been implicated in the disruption of ovarian function and follicular development, suggesting that epilepsy may directly or indirectly influence ovarian structure and endocrine regulation [9–11]. Furthermore, several antiepileptic drugs have been reported to exert adverse effects on reproductive hormones and ovarian morphology, thereby complicating reproductive health outcomes in women with epilepsy [10, 12]. These observations highlight the need for therapeutic strategies that not only control seizures but also preserve reproductive function and tissue integrity. Experimental animal models have been instrumental in elucidating the mechanisms underlying epilepsy and its systemic consequences. The lithium chloride–pilocarpine model is widely used to induce epilepsy and reproduce key behavioral and neuropathological features of temporal lobe epilepsy. Pilocarpine, a muscarinic acetylcholine receptor agonist, induces seizures through cholinergic hyper activation, while lithium pre-treatment enhances its epileptogenic potential and allows the use of lower pilocarpine doses [13, 14]. This model has been shown to mimic many aspects of human epilepsy, making it a valuable platform for investigating both central and peripheral effects, including neuroendocrine and reproductive alterations [15].

In recent years, increasing attention has been directed toward medicinal plants as sources of bioactive compounds with neuroprotective, antioxidant, and anti-inflammatory properties. Aframomum melegueta, a perennial herb belonging to the Zingiberaceae family and widely distributed in West Africa, has long been used in traditional medicine for diverse therapeutic purposes, including the treatment of gastrointestinal disorders, inflammation, and reproductive conditions. Phytochemical constituents of A. melegueta seeds have demonstrated significant antioxidant, anti-inflammatory, and anti-nociceptive activities, suggesting potential protective effects against tissue damage mediated by oxidative stress and inflammation [16, 17]. Given that oxidative stress and inflammatory processes play critical roles in both epileptogenesis and ovarian dysfunction, A. melegueta emerges as a promising candidate for mitigating epilepsy-related reproductive complications. However, while the neurological aspects of epilepsy have been extensively studied, the interaction between seizure activity, ovarian histoarchitecture, and reproductive hormone regulation remains incompletely understood. More importantly, there is limited experimental evidence on whether plant-derived bioactive compounds can modulate epilepsy-induced ovarian damage and hormonal deregulation. Understanding these relationships is essential for advancing knowledge of the systemic consequences of epilepsy and for identifying therapeutic approaches that integrate neuroprotection with reproductive health preservation.

Therefore, this study investigates the effect of Aframomum melegueta on reproductive hormone levels and histoarchitectural changes in the ovaries of female rats subjected to lithium chloride-pilocarpine-induced epilepsy. By integrating hormonal, histological, oxidative stress, inflammatory, and immunohistochemical analyses, this work seeks to provide mechanistic insights into epilepsy-related ovarian alterations and to evaluate the potential of Aframomum melegueta as a protective or restorative agent against reproductive dysfunction associated with epilepsy.

2 Material and methods

2.1 Experimental Animals

Twenty-four (24) young adult female Wistar rats were used in this study. The animals were procured from the Animal Holding Facility of Babcock University, Ilishan-Remo, Ogun State, Nigeria. On arrival, the rats were housed in well-ventilated plastic cages under standard laboratory conditions (12 h light/12 h dark cycle, controlled temperature and humidity). Wood shavings were used as bedding and replaced every three days to maintain hygiene and prevent

ammonia accumulation. The animals were fed standard pelletized rat chow and provided water ad libitum. They were allowed to acclimatize for seven days prior to the commencement of the experiment. All animal handling and experimental procedures were conducted in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals 18 and relevant institutional guidelines.

2.2 Ethical Approval

Ethical approval for this study was obtained from the Babcock University Health Research Ethics Committee (BUHREC 1099/24) through the School of Basic Medical Sciences Ethical Review Committee. All procedures were carried out in compliance with the Institutional Animal Care and Use Committee (IACUC) guidelines to ensure humane treatment of animals and minimization of pain and distress.

2.3 Chemicals and Reagents

Pilocarpine hydrochloride and lithium chloride were obtained from Sigma-Aldrich (USA). Carbamazepine and diazepam were sourced from the Pharmaceutical Department of Babcock University Teaching Hospital, Ilishan-Remo, Nigeria. All other chemicals and reagents used were of analytical grade.

2.4 Plant Material and Extraction of Aframomum melegueta

Seeds of *Aframomum melegueta* were obtained from the Flora Reserve for Agriculture Masters and Education (FRAME), Ibadan, Oyo State, Nigeria, and authenticated by a qualified botanist. The seeds were air-dried and ground into a fine powder (113090). Approximately 1 kg of the powdered plant material was macerated in 70% ethanol for 48 hours with intermittent stirring. The mixture was filtered, and the filtrate was concentrated using a water bath at controlled temperature to obtain the crude ethanolic extract. The extract was weighed and stored in airtight containers until use [19].

2.5 Experimental Design

A total of twenty-four (24) female adult Wistar rats obtained from Babcock University Animal House, ilisan-Remo, Ogun State were recruited for the study. They were housed in ventilated plastic cages under standard laboratory condition of Temperature and 12h light and dark succession. The twenty-four (24) female adult Wistar rats were randomly assigned into 4 groups of six (6) rats each. After one (1) week acclimatization, epilepsy was induced for 21 days using intraperitoneal injection of lithium chloride-pilocarpine. Rats in Groups B-D were administered lithium chloride (127 mg/kg, intraperitoneally). After 24 hours, pilocarpine (30 mg/kg, intraperitoneally) was administered. Seizure activity was monitored and scored using the Racine scale. Upon the onset of sustained seizures, 10mg/kg of Diazepam was administered intramuscularly to terminate status epilepsy and reduce mortality. Group A (control group) received 1ml of intraperitoneal administration of normal saline. Group C and D received 400mg/kg of *Aframomum melegueta* extract and 100mg/kg of carbamazepine (standard drug) respectively [20].

Table 1 The experimental grouping and treatment of the animals

Groups	No of animals	Doses	Rationale
GROUP A	6	Received 1 mL of normal saline intraperitoneally and served as the healthy control.	Control group
GROUP B	6	Received lithium chloride (127 mg/kg body weight) followed by pilocarpine (30 mg/kg body weight) intraperitoneally to induce epilepsy.	Epileptic untreated
GROUP C	6	Received lithium chloride and pilocarpine as in Group B, followed by oral administration of *Aframomum melegueta* extract (400 mg/kg body weight) for 21 days.	Epileptic + *Aframomum melegueta* group

GROUP D	6	Received lithium chloride and pilocarpine as in Group B, followed by oral administration of carbamazepine (100 mg/kg body weight) for 21 days	Epileptic + standard drug group

2.6 Drug and Extract Administration

Lithium chloride and pilocarpine were administered intraperitoneally using sterile syringes. Diazepam was administered intramuscularly. Carbamazepine and *Aframomum melegueta* extract were administered orally using an orogastric cannula. Treatments were continued daily for 21 days.

2.7 Animal Sacrifice and Sample Collection

Twenty-four hours after the final treatment, the animals were humanely sacrificed under anesthesia induced by diethyl ether inhalation. Blood samples were collected via cardiac puncture and transferred into heparinized tubes for biochemical and hormonal analyses. The ovaries were carefully excised, blotted dry, weighed and fixed with 10% neutral buffered formalin

2.8 Histological Processing and Staining

Fixed ovarian tissues were processed using standard histological techniques. Tissues were dehydrated in ascending grades of ethanol, cleared in xylene, and embedded in paraffin wax. Sections of 5–8 µm thickness were cut using a rotary microtome and mounted on glass slides. Routine hematoxylin and eosin (H&E) staining was performed to evaluate ovarian histoarchitecture [21]. Special histochemical stains such as Periodic Acid-Schiff (PAS) and Masson's trichrome, were employed to assess carbohydrate content and connective tissue distribution, respectively [23].

2.9 Biochemical Assays

Blood samples were centrifuged at 3000 rpm for 20 minutes, and the plasma was separated for biochemical analysis. Oxidative stress markers were assessed using standard spectrophotometric methods. Superoxide dismutase (SOD) activity was determined using the WST-based method, while lipid peroxidation was evaluated by measuring malondialdehyde (MDA) levels using the thiobarbituric acid reactive substances (TBARS) assay [22]. Tumor necrosis factor-alpha (TNF-α) levels were quantified using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions, based on antigen–antibody interactions and colorimetric detection [23].

2.10 Hormonal Assay

Serum levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were determined using commercial ELISA kits based on the sandwich immunoassay principle. Procedures were carried out in accordance with the manufacturers' protocols, and absorbance was measured using a microplate reader at 450 nm.

2.11 Immunohistochemical Analysis

Immunohistochemical staining was performed to evaluate the expression of B-cell lymphoma 2 (BCL2), an anti-apoptotic marker. Paraffin-embedded ovarian sections were deparaffinized, rehydrated, and subjected to antigen retrieval using citrate buffer (pH 6.0). Endogenous peroxidase activity was blocked, and sections were incubated with primary anti-BCL2 antibody, followed by HRP-conjugated secondary antibody. Visualization was achieved using diaminobenzidine (DAB), and sections were counterstained with hematoxylin.

2.12 Statistical Analysis

Data were analyzed using GraphPad Prism software (version 8). Results were expressed as mean ± standard error of mean (SEM). Differences among groups were analyzed using one-way analysis of variance (ANOVA), followed by Student-Newman-Keuls post hoc test. Statistical significance was set at $p < 0.05$

3 Results

Figure 1: BODY WEIGHT Showed no significant difference in the weight of the negative control, *A. melegueta,* and standard antiepileptic drug when compared to the positive control group ($p < 0.05$).

Figure 2: RELATIVE OVARIAN WEIGHT Showed a significant difference in the relative ovarian weight of the negative control group (0.237 ± 0.017) when compared to the positive control group (0.340 ± 0.014) and an observable difference (increase) in the group treated with A. melegueta (0.445 ± 0.035). There was no significant difference in the group treated with the standard antiepileptic drug (0.343 ± 0.020) compared to the positive control group ($p < 0.05$).

Figure 3: SUPEROXIDE DISMUTASE Showed a significant difference in the negative control (0.028 ± 0.001) and *A-melegueta* (0.036 ± 0.0005) groups when compared to the positive group (0.031 ± 0.0004). However, there was no significant difference in the standard antiepileptic drug group compared to the positive control group.

Figure 4: MALONDIALDEHYDE (MDA) Showed a significant differences in the negative control (0.034 ± 0.0004), *A.melegueta* (0.033 ± 0.0004), and standard antiepileptic drug (0.029 ± 0.0008) groups when compared to the positive control group (0.025 ± 0.0006) ($p < 0.05$)

Figure 5: TNF Alpha Showed a significant differences in the negative control (0.026 ± 0.0008), *A. melegueta* (0.003 ± 0.0003), and standard antiepileptic drug (0.013 ± 0.0008) groups when compared to the positive control group (0.019 ± 0.0008) ($p < 0.05$)

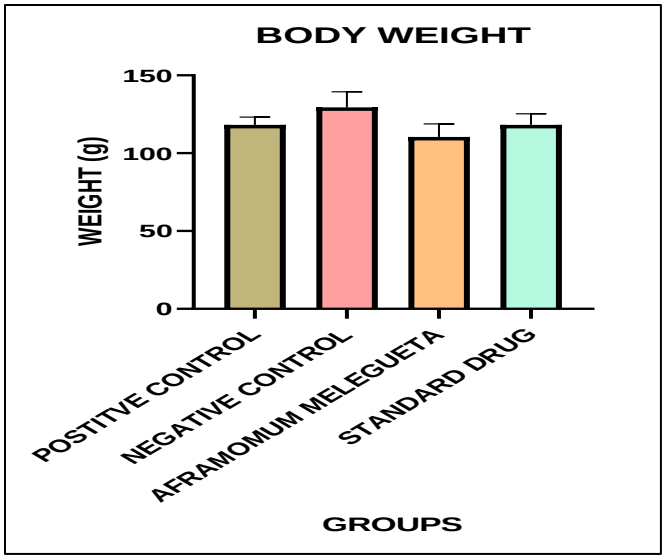


Figure 1 Effects of Aframomum Melegueta on Body Weight in Lithium Chloride-Pilocarpine-Induced Epilepsy male Wistar rats

Figure 6: FSH Showed a significant differences in the negative control (0.011 ± 0.0004), *A.melegueta* (0.015 ± 0.0006), and standard antiepileptic drug (0.095 ± 0.0001) groups when compared to the positive control group (0.019 ± 0.0001) ($p < 0.05$)

Figure 7: LUTEINIZING HORMONE (LH) Showed a significant differences in the negative control (0.015 ± 0.0004), *A.melegueta* (0.019 ± 0.0008), and standard antiepileptic drug (0.013 ± 0.0004) groups when compared to the positive control group (0.016 ± 0.0004) ($p < 0.05$)

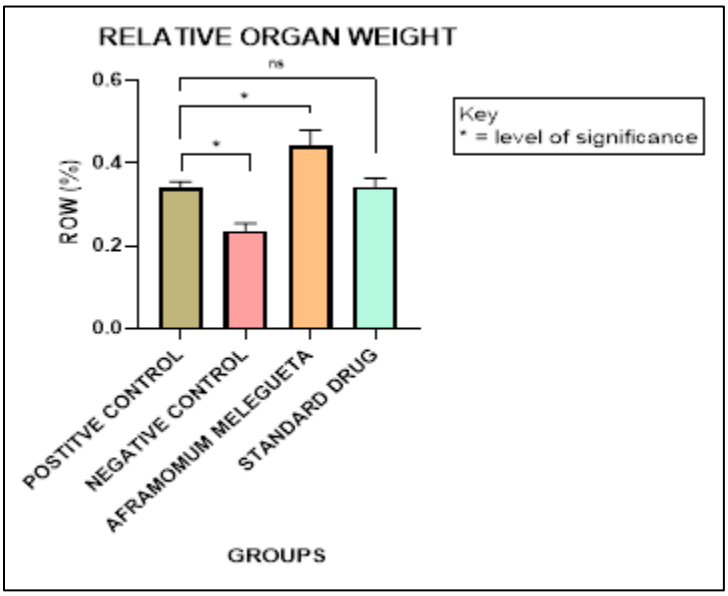


Figure 2 Effects of Aframomum Melegueta on Relative Organ Weight in Lithium Chloride-Pilocarpine-Induced Epilepsy male Wistar rats

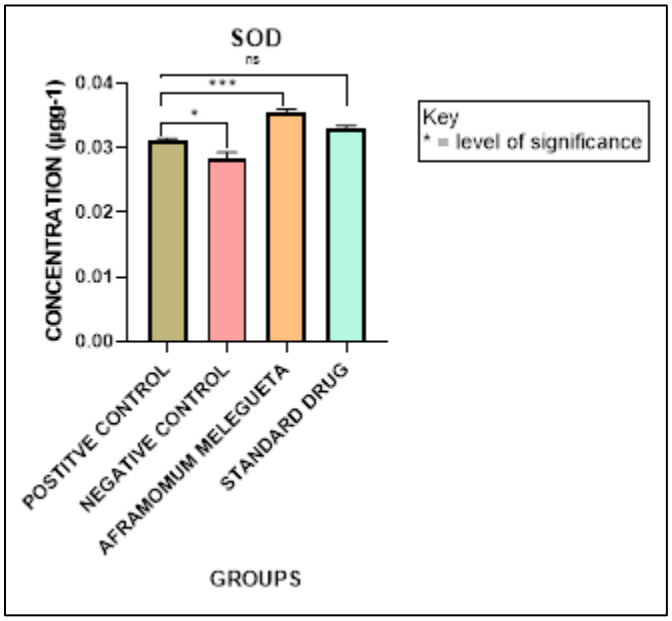


Figure 3 Effects of Aframomum Melegueta on Superoxide Dismutase in Lithium Chloride-Pilocarpine-Induced Epilepsy male Wistar rats

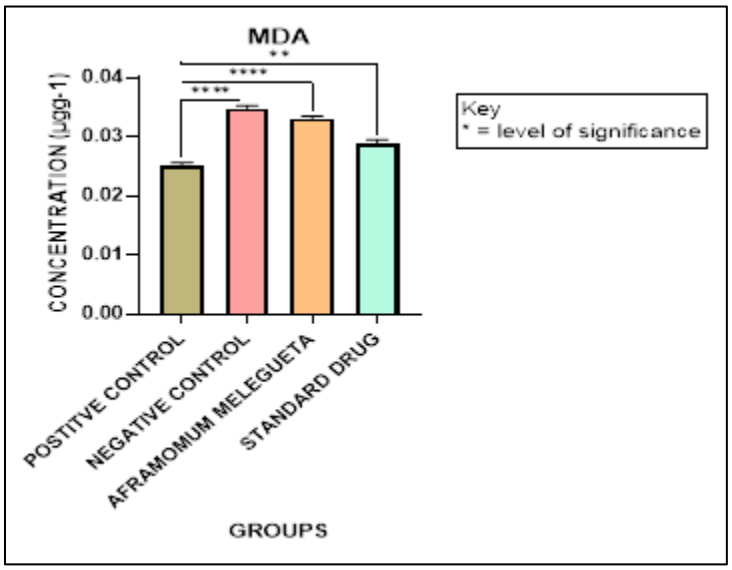


Figure 4 Effects of Aframomum Melegueta on Malondialdehyde in Lithium Chloride-Pilocarpine-Induced Epilepsy male Wistar rats

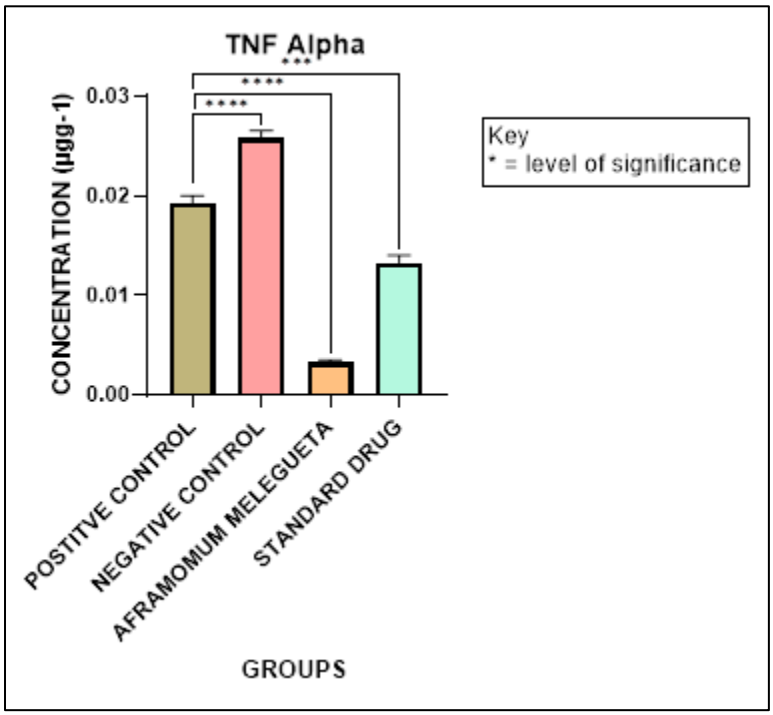


Figure 5 Effects of Aframomum Melegueta on TNF Alpha in Lithium Chloride-Pilocarpine-Induced Epilepsy male Wistar rats

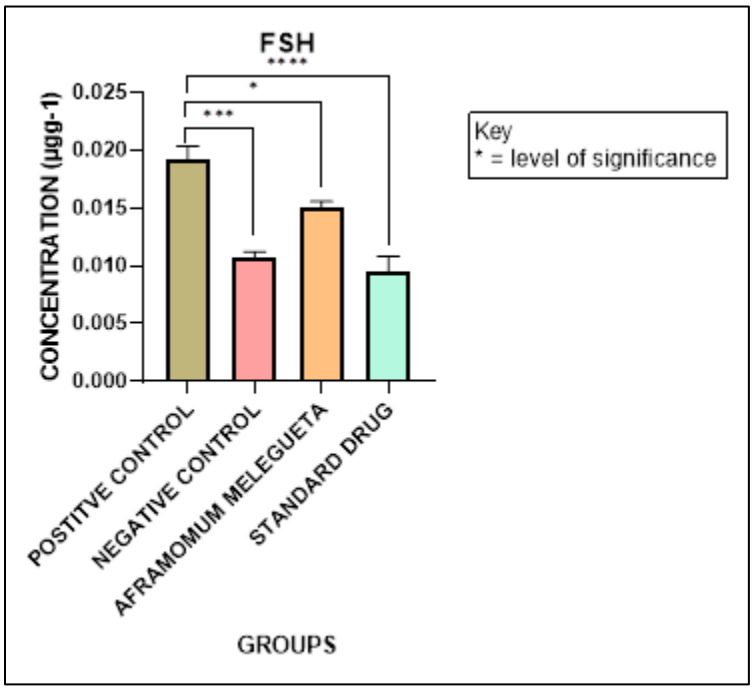


Figure 6 Effects of Aframomum Melegueta on luteinizing Hormone in Lithium Chloride-Pilocarpine-Induced Epilepsy male Wistar rats

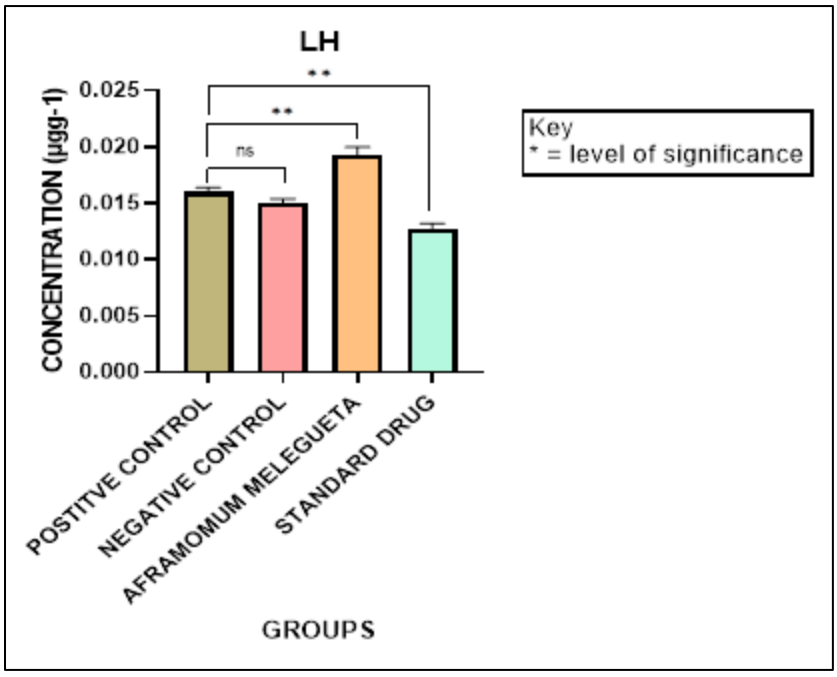
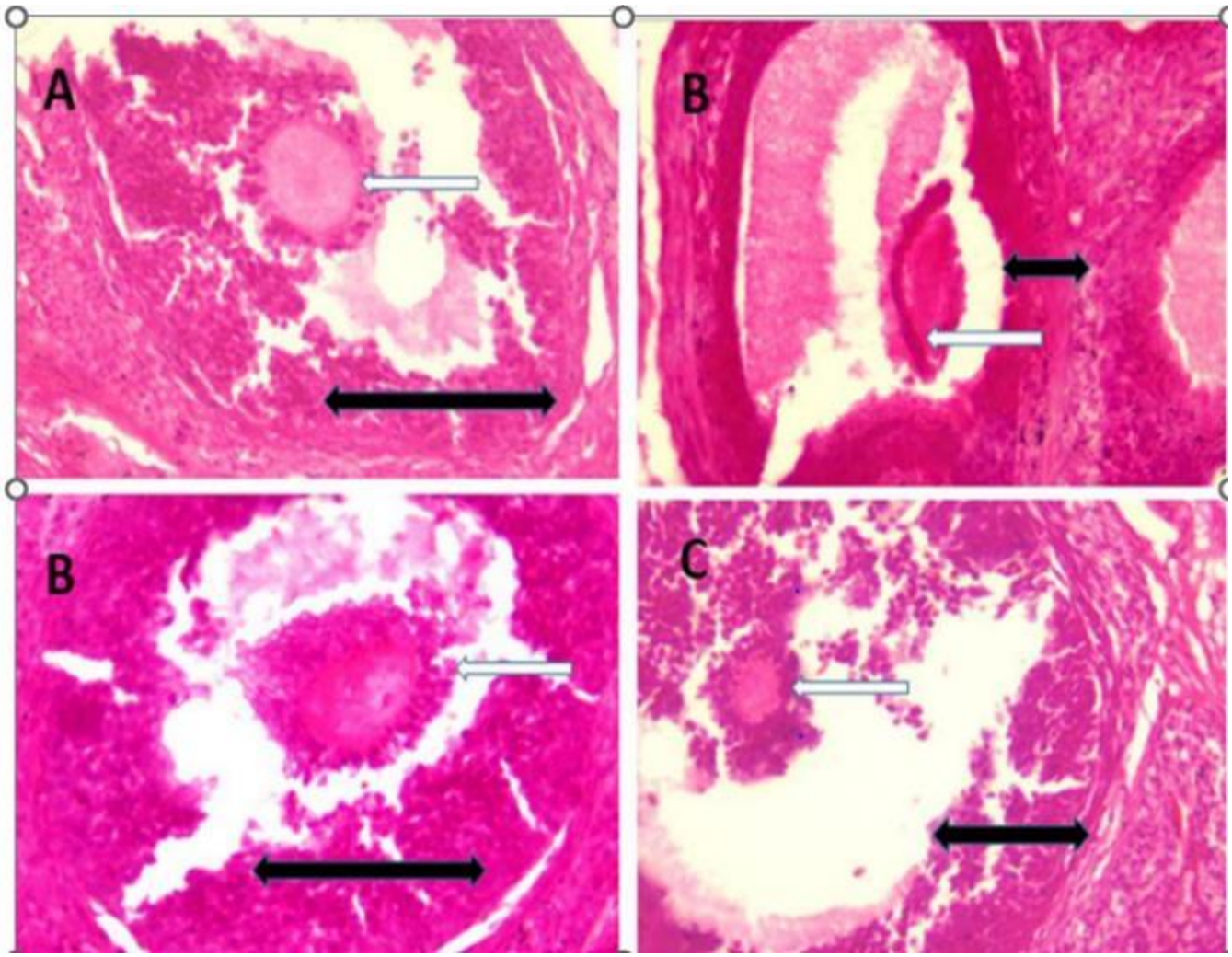


Figure 7 Effects of Aframomum Melegueta on Follicle Stimulating Hormone in Lithium Chloride-Pilocarpine-Induced Epilepsy male Wistar rats

3.1 Histological analysis

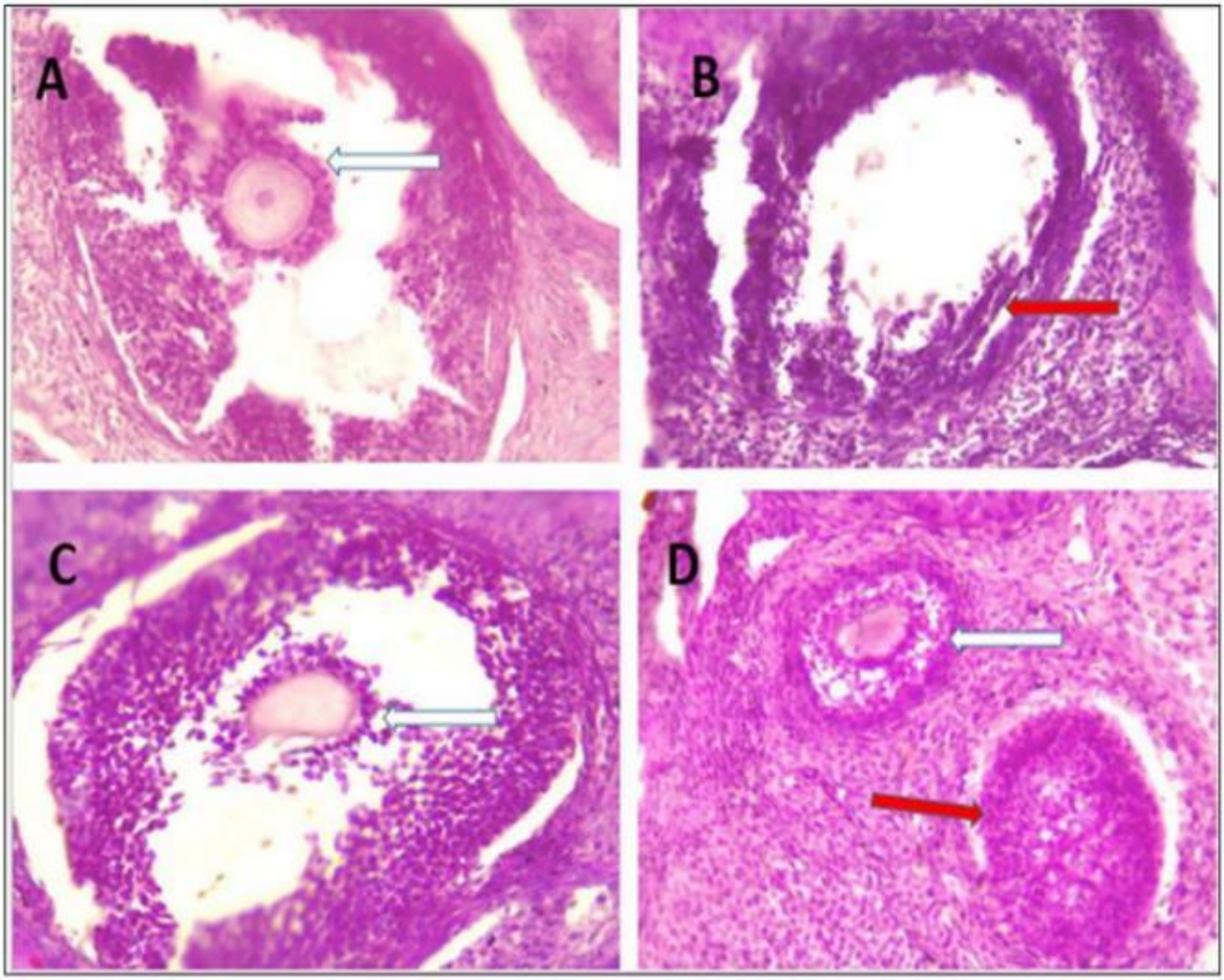
3.1.1 Photomicrograph of the ovary



A- Control, B- Epilepsy Untreated, C- Epilepsy + *Aframomum melegueta* , D- Epilepsy + Carbamazepine. Note; Black arrow= degenerating follicles at various stages, loss of oocytes and granulosa cells and presence of necrotic cells. [X400 Mag.]

Figure 8 Photomicrograph section of the ovary in experimental animals stained with Hematoxylin and Eosin (H&E) for general histoarchitecture.

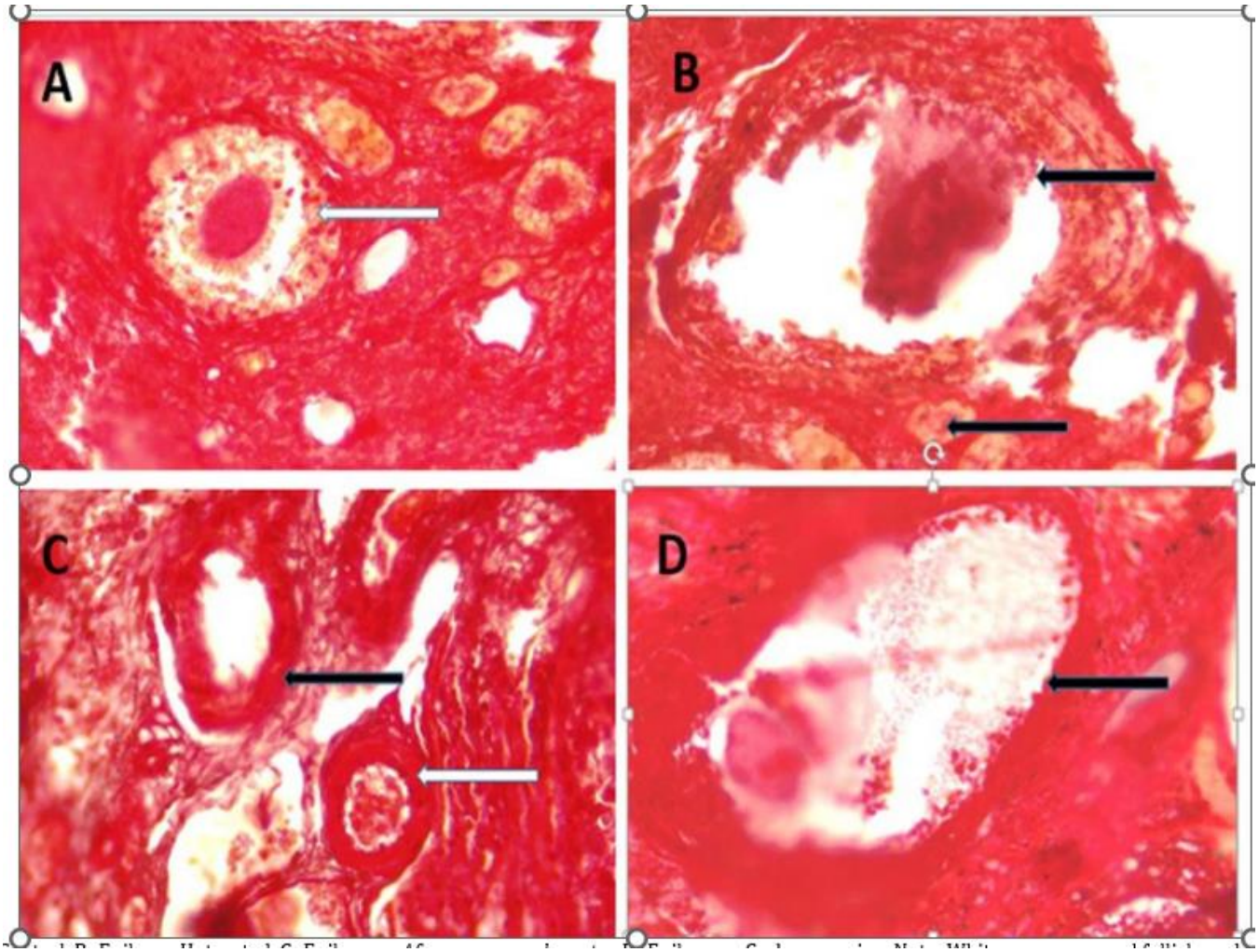
3.1.2 Periodic acid schiff (pas)



A- Control, B- Epilepsy Untreated, C- Epilepsy + *Aframomum melegueta* , D- Epilepsy + Carbamazepine. Note; White arrow= growing follicle and Red arrow= degenerating follicles at various stages, loss of oocytes and granulosa cells and presence of necrotic cells. [X400 Mag.]

Figure 9 Photomicrograph section of the ovary in experimental animals stained with Periodic Acid Schiff (PAS) for general histoarchitecture.

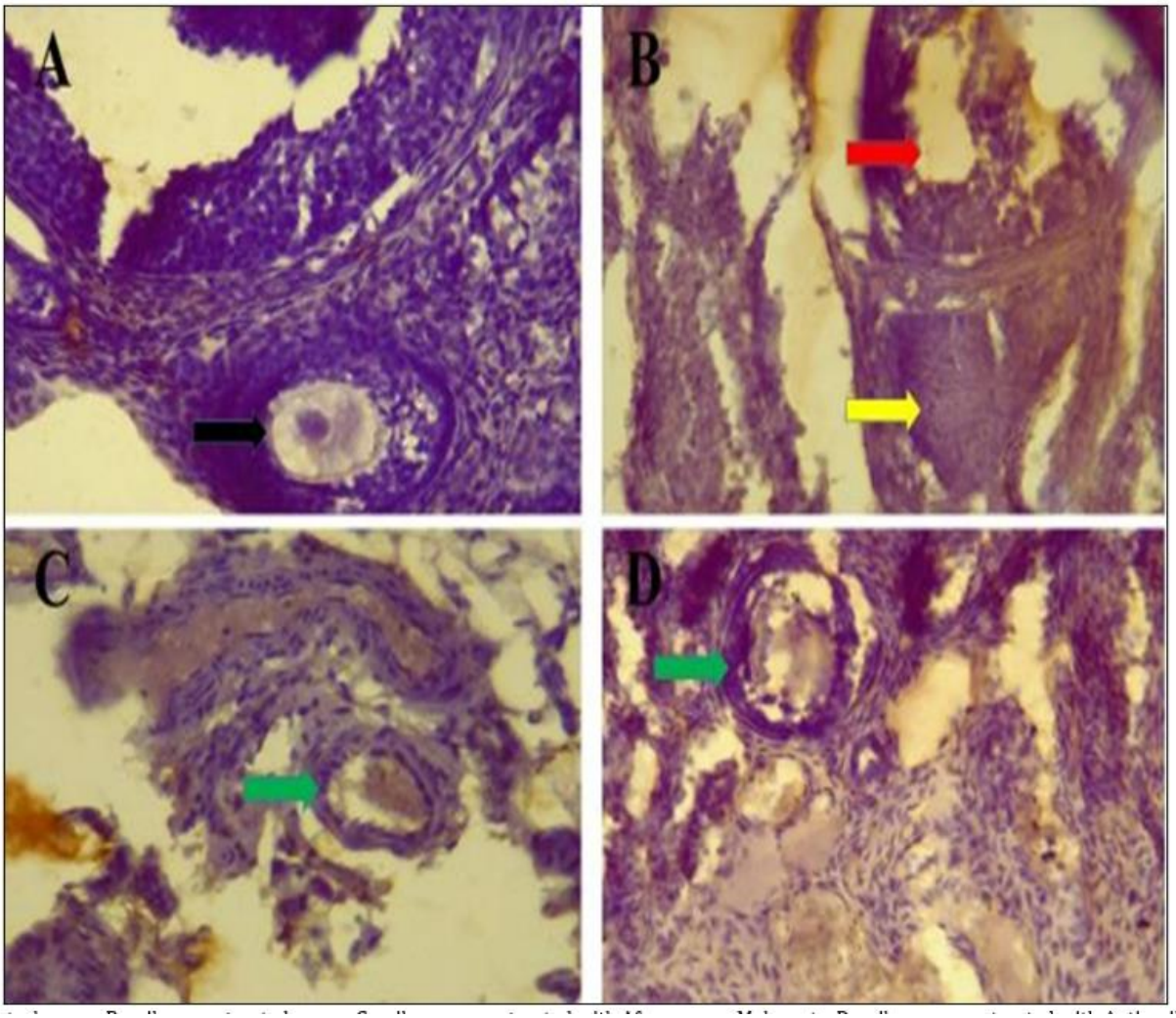
3.1.3 Masson trichrome



A-Control, B- Epilepsy Untreated, C- Epilepsy + *Aframomum melegueta* , D- Epilepsy + Carbamazepine. Note; White arrow=normal follicle and black arrow=collagen deposit thickening and scar formation. [X400Mag]

Figure 10 Photomicrograph of histological findings of the ovary of experimental animals stained with Masson Trichrome for collagen deposit.

3.1.4 Immunohistochemical analysis



A- Control group; B-epilepsy untreated group; C-epilepsy group treated with Aframomum Melegueta, D-epilepsy group treated with Anti-epileptic drug (Carbamazepine). Note; Black arrow= normal graffian follicle, green arrow= affected but recovering follicles, Yellow arrow= corpus albican and Red arrow=Athreptic/abnormal follicle. [X400 Mag]

Figure 11 Photomicrograph of immunohistochemistry findings of Ovary stained with BCL2.

4 Discussion

Interest in medicinal plants as sources of therapeutic agents keeps increasing due to their diverse bioactive constituents and relatively low toxicity profiles. Plant-derived compounds have been shown to exert antioxidant, anti-inflammatory, neuroprotective, and endocrine-modulating effects, making them good alternatives for managing complex disorders involving oxidative stress and hormonal dysregulation [24, 25]. Aframomum melegueta, commonly known as grains of paradise, has been widely reported to possess pharmacological activities including antioxidant, anti-inflammatory, and neuroprotective properties, largely attributed to its phenolic compounds and flavonoids [16, 26, 27]. These biological activities suggest that Aframomum melegueta may influence neuroendocrine and reproductive processes, especially under pathological conditions. Epilepsy is increasingly recognized as a systemic disorder with consequences extending beyond the central nervous system. Experimental and clinical studies indicate that seizure activity and associated neurochemical alterations can disrupt the hypothalamic-pituitary-gonadal (HPG) axis, leading to hormonal imbalance and reproductive dysfunction [6–8, 11]. The lithium chloride-pilocarpine model is widely used to induce temporal lobe epilepsy and has been shown to produce neuroendocrine disturbances and reproductive tissue damage through mechanisms involving oxidative stress, inflammation, and neuronal hyperexcitability [13, 14]. This present study investigated whether Aframomum melegueta could modulate epilepsy-induced hormonal, biochemical, and structural alterations in the ovaries of female rats.

Body weight and relative organ weight are important indicators of systemic metabolic status and organ-specific pathology. Although lithium chloride-pilocarpine induction resulted in variations in body weight across groups, these changes were not statistically significant. The slight reduction in body weight observed in the rats treated with Aframomum melegueta may reflect metabolic regulation rather than toxicity. Similar findings have been reported in studies showing that phytochemical-rich plant extracts can influence energy metabolism without causing significant weight loss [28, 29].

Relative ovarian weight provides insight into ovarian integrity and functional capacity. In the present study, lithium chloride-pilocarpine induction tended to reduce ovarian weight, consistent with reports that seizure-related oxidative stress and hormonal disruption can impair ovarian structure and function [30, 31]. Treatment with Aframomum melegueta seemed to have normalized the ovarian weight, suggesting a protective effect against ovarian damage induced by epilepsy. This observation aligns with previous studies demonstrating that plant-derived antioxidants can preserve reproductive organ morphology and function under conditions of toxic or oxidative stress [32, 33].

Alterations in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels observed in this study further support the presence of HPG axis dysregulation following epilepsy induction. Disruption of gonadotropin secretion is a recognized consequence of epilepsy and has been associated with menstrual irregularities, anovulation, and reduced fertility in both experimental models and clinical populations [34, 35]. The untreated epileptic group exhibited significant hormonal imbalance, whereas Aframomum melegueta treatment tended to restore LH and FSH levels toward physiological ranges. The restoration of gonadotropin levels suggests that Aframomum melegueta may exert regulatory effects on neuroendocrine signaling and ovarian responsiveness. Similar hormonal modulatory effects have been reported in previous studies regarding Aframomum melegueta for its antioxidant and endocrine-regulatory properties [36, 37]. These findings indicate that Aframomum melegueta may mitigate epilepsy-induced reproductive dysfunction through mechanisms involving stabilization of the HPG axis and reduction of oxidative stress.

Oxidative stress and inflammation are major mechanisms underlying both epileptogenesis and reproductive tissue damage. In this study, lithium chloride–pilocarpine induction significantly increased malondialdehyde (MDA) and tumor necrosis factor-alpha (TNF-α) levels, indicating enhanced lipid peroxidation and inflammatory activity within ovarian tissue. These findings are consistent with previous reports demonstrating that seizure activity can trigger systemic oxidative stress and inflammatory responses affecting peripheral organs [38–40]. Treatment with Aframomum melegueta significantly reduced MDA and TNF-α level, highlighting its antioxidant and anti-inflammatory potential. The reduction of oxidative and inflammatory markers is consistent with earlier studies showing that Aframomum melegueta and related phytochemicals can attenuate oxidative damage and cytokine production in tissue injury [16, 41]. These findings affirm the role of oxidative stress and inflammation in ovarian damage related to epilepsy and suggests that Aframomum melegueta may counteract these processes through its bioactive constituents.

The activity of superoxide dismutase (SOD), a key antioxidant enzyme, was significantly reduced in the untreated epileptic group, reflecting compromised endogenous antioxidant defense. Depletion of antioxidant enzymes is a hallmark of oxidative stress and has been implicated in reproductive dysfunction and tissue degeneration [42]. In this study, Aframomum melegueta treatment significantly enhanced SOD activity, indicating restoration of antioxidant capacity within ovarian tissue. Similar upregulation of antioxidant enzymes following treatment with Aframomum melegueta has been reported in experimental studies of oxidative stress and reproductive toxicity [33, 43]. The enhancement of SOD activity likely contributed to the observed improvements in hormonal balance and ovarian histoarchitecture.

Histological findings provided structural evidence supporting the biochemical and hormonal results. Hematoxylin and eosin staining revealed marked ovarian damage in the untreated epileptic group, including follicular degeneration, granulosa cell loss, oocyte depletion, and necrotic changes. These alterations are consistent with previous studies demonstrating that epilepsy and seizure-induced oxidative stress can impair folliculogenesis and disrupt ovarian architecture [11, 30]. In contrast, ovaries from rats treated with Aframomum melegueta showed improved follicular morphology, reduced cellular degeneration, and better preservation of tissue organization. The reduction in follicular atresia and necrosis suggests that Aframomum melegueta enhances ovarian resilience under epileptic conditions. Periodic acid–Schiff staining further revealed disruption of basement membrane integrity and extracellular matrix components in the untreated epileptic group. Such changes reflect impaired glycoprotein synthesis and structural instability within ovarian tissue. Treatment with Aframomum melegueta restored basement membrane integrity and extracellular matrix organization, indicating improved tissue stability and repair. These findings support the hypothesis that Aframomum melegueta promotes structural recovery through modulation of oxidative and inflammatory pathways [42, 43]. Masson's trichrome staining demonstrated increased collagen deposition and fibrosis in the ovaries of

untreated epileptic rats, indicative of chronic tissue injury and scarring. Fibrosis is a recognized consequence of persistent oxidative stress and inflammation and has been associated with impaired reproductive function [42]. Aframomum melegueta treatment significantly reduced collagen deposition, suggesting attenuation of fibrotic remodeling and enhancement of tissue regeneration.

Immunohistochemical analysis of Bcl-2 expression provided insights into apoptosis-related mechanisms. Reduced Bcl-2 expression in the untreated epileptic group indicates increased susceptibility to apoptosis, consistent with oxidative stress–induced cell death. In contrast, Aframomum melegueta treatment enhanced Bcl-2 expression, suggesting improved cell survival and resistance to apoptotic signaling. This anti-apoptotic effect is likely mediated by the plant's antioxidant and anti-inflammatory properties, which stabilize cellular homeostasis and mitochondrial function. Interestingly, carbamazepine treatment exhibited mixed effects, partially preserving Bcl-2 expression while still showing evidence of oxidative stress and structural alterations. This observation reflects previous reports that antiepileptic drugs, while effective in seizure control, may exert adverse effects on reproductive tissues and hormonal regulation [44, 45]. The findings highlight the potential value of plant-based therapies in mitigating reproductive toxicity associated with epilepsy and its pharmacological management. The findings of this study demonstrate that Aframomum melegueta exerts protective effects against lithium chloride-pilocarpine-induced ovarian damage. The convergence of hormonal normalization, oxidative stress reduction, inflammation suppression, structural preservation, and anti-apoptotic signaling seen in this study suggests that Aframomum melegueta acts through integrated biochemical and cellular mechanisms. These findings are consistent with broader evidence associating oxidative stress and neuroendocrine dysregulation to reproductive dysfunction related to epilepsy and support the therapeutic potential of phytochemicals in addressing systemic consequences of epilepsy.

This study demonstrates that *Aframomum melegueta* significantly ameliorates lithium chloride–pilocarpine-induced ovarian damage by restoring hormonal balance, enhancing antioxidant defenses, reducing inflammatory responses, preserving ovarian histoarchitecture, and promoting anti-apoptotic signaling. The findings highlight the vulnerability of the reproductive system to epilepsy-related oxidative and neuroendocrine disturbances and show the potential of *Aframomum melegueta* as a natural therapeutic agent for protecting ovarian function under epileptic conditions. By integrating biochemical, hormonal, and structural evidence, this study advances understanding of the systemic effects of epilepsy and provides a foundation for future research into plant-based interventions for reproductive dysfunction in epileptic condition.

Compliance with ethical standards

Acknowledgments

Appreciation goes to all the authors for their participation, contributions and involvements throughout the course of this experiment.

Disclosure of conflict of interest

The authors declare no conflict of interest

Statement of ethical approval

Ethical approval for this study was obtained from the Babcock University Health Research Ethics Committee (BUHREC 1099/24) through the School of Basic Medical Sciences Ethical Review Committee.

References

[1] Wright P, Zvartau-Hind M (2012) 27 - Organic psychiatry and epilepsy. In: Wright P, Stern J, Phelan M (eds) Core Psychiatry (Third Edition). W.B. Saunders, Oxford, pp 391–420

[2] Chen Z, Brodie MJ, Ding D, Kwan P (2023) Editorial: Epidemiology of epilepsy and seizures. Frontiers in Epidemiology. https://doi.org/10.3389/fepid.2023.1273163

[3] Allers K, Essue BM, Hackett ML, Muhunthan J, Anderson CS, Pickles K, Scheibe F, Jan S (2015) The economic impact of epilepsy: a systematic review. BMC Neurol 15:245

[4] Cutia CA, Christian-Hinman CA (2023) Mechanisms linking neurological disorders with reproductive endocrine dysfunction: Insights from epilepsy research. Front Neuroendocrinol. https://doi.org/10.1016/j.yfrne.2023.101084

[5] Tamijani SMS, Karimi B, Amini E, Golpich M, Dargahi L, Ali RA, Ibrahim NM, Mohamed Z, Ghasemi R, Ahmadiani A (2015) Thyroid hormones: Possible roles in epilepsy pathology. Seizure 31:155–164

[6] Abady MM, Jeong JS, Kwon HJ, Assiri AM, Cho J, Saadeldin IM (2024) The reprotoxic adverse side effects of neurogenic and neuroprotective drugs: current use of human organoid modeling as a potential alternative to preclinical models. Front Pharmacol. https://doi.org/10.3389/fphar.2024.1412188

[7] Singh P, Singh M, Cugati G, Singh A (2011) Effect of epilepsy on female fertility and reproductive abnormalities. J Hum Reprod Sci 4:100–101

[8] Kobylarek D, Zakryś K, Gierszewska J, Pagidela BR, Lan YY, Kovinthapillai R, Rajczewski A, Kozubski W, Michalak S (2025) The neuroendocrine puzzle of epilepsy and infertility: what are we missing? Front Neurol. https://doi.org/10.3389/fneur.2025.1658284

[9] Li S, Zhang L, Wei N, Tai Z, Yu C, Xu Z (2021) Research Progress on the Effect of Epilepsy and Antiseizure Medications on PCOS Through HPO Axis. Front Endocrinol (Lausanne). https://doi.org/10.3389/fendo.2021.787854

[10] Li Q, Zhang Z, Fang J (2024) Hormonal Changes in Women with Epilepsy. Neuropsychiatr Dis Treat 20:373–388

[11] Scharfman H, Kim M, Hintz T, Maclusky N (2008) Seizures and Reproductive Function: Insights from Female Rats with Epilepsy. Ann Neurol 64:687–697

[12] Khan M, Bankar NJ, Bandre GR, Dhobale A V, Bawaskar PA (2023) Epilepsy and Issues Related to Reproductive Health. Cureus. https://doi.org/10.7759/cureus.48201

[13] Reddy DS, Zaayman M, Kuruba R, Wu X, Reddy DS (2021) Comparative profile of refractory status epilepticus models following exposure of cholinergic agents pilocarpine, DFP, and soman.

[14] Müller CJ, Bankstahl M, Gröticke I, Löscher W (2009) Pilocarpine vs. lithium–pilocarpine for induction of status epilepticus in mice: Development of spontaneous seizures, behavioral alterations and neuronal damage. Eur J Pharmacol 619:15–24

[15] Wang H, Zhao Y, Zhang D, Li J, Yang K, Yang J, Li B (2024) Neuroprotective effects of quinpirole on lithium chloride pilocarpine-induced epilepsy in rats and its underlying mechanisms. Eur J Med Res 29:121

[16] Adefegha A, Oboh G (2011) Water Extractable Phytochemicals from Some Nigerian Spices Inhibit Fe2+- Induced Lipid Peroxidation in Rat's Brain – In Vitro. J Food Process Technol. https://doi.org/10.4172/2157-7110.1000104

[17] Dzoyem J, Mcgaw L, Kuete V, Bakowsky U (2017) Anti-inflammatory and Anti-nociceptive Activities of African Medicinal Spices and Vegetables. In: Medicinal Spices and Vegetables from Africa: Therapeutic Potential Against Metabolic, Inflammatory, Infectious and Systemic Diseases. pp 239–270

[18] National Institutes of Health (1985) Guide for the Care and Use of Laboratory Animals. NIH Publication Number 85-23, US Department of Health, Education and Welfare, Bethesda, MD.

[19] Samson EO (2025) Effects of Spondias mombin aqueous leaf extract against heavy metals-triggered changes in hematological, antioxidant and semen quality indices in Male Wistar rats. GSC Biological and Pharmaceutical Sciences 30:311–321

[20] Amanlou A, Eslami F, Shayan M, Mortazavi P, Dehpour A (2021) Anticonvulsive evaluation and histopathological survey of thalidomide synthetic analogs on lithium-pilocarpine-induced status epilepticus in rats. Res Pharm Sci 16:586

[21] Drury RA, Wallington EA (1980) Carleton's Histological Techniques, 5th Edition. Oxford University Press, New York

[22] Varshney R, Kale RK (1990) Effect of calmodulin antagonists on radiation induced lipid peroxidation in microsomes. Int J Biol 158:733–741

[23] Eyles DW, Burne THJ, McGrath JJ (2013) Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. Front Neuroendocrinol 34:47–64

[24] Newman DJ, Cragg GM (2020) Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. J Nat Prod 83:770–803

[25] Ekor M (2014) The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. Front Neurol. https://doi.org/10.3389/fphar.2013.00177

[26] Oyinloye B, Basiru A, Ojo O, Musa H, Onikanni S, Ojo A (2016) Ameliorative potential of Aframomum melegueta extract in cadmium-induced hepatic damage and oxidative stress in male Wistar rats. J Appl Pharm Sci 7:94–99

[27] Okoli C, Akah P, Nwafor S, Ihemelandu U, Amadife C (2007) Anti-Inflammatory Activity of Seed Extracts of Aframomum melegueta. J Herbs Spices Med Plants 13:11–21

[28] Tucci S (2010) Phytochemicals in the Control of Human Appetite and Body Weight. Pharmaceuticals 3:748–763

[29] Sugita J, Yoneshiro T, Sugishima Y, Ikemoto T, Uchiwa H, Suzuki I, Saito M (2014) Daily Ingestion of Grains of Paradise (Aframomum melegueta) Extract Increases Whole-Body Energy Expenditure and Decreases Visceral Fat in Humans. J Nutr Sci Vitaminol (Tokyo) 60:22–27

[30] Herzog A (2015) Disorders of reproduction in patients with epilepsy. Zeitschrift für Epileptologie. https://doi.org/10.1007/s10309-015-0012-7

[31] Rashad N, Ashour W, Allam R, Saraya Y, Emad G (2020) Oxidative stress and risk of polycystic ovarian syndrome in women with epilepsy: implications of malondialdehyde and superoxide dismutase serum levels on female fertility. Egypt J Intern Med 31:609–619

[32] Liu X, Zeng T, Zhang E, Bin C, Liu Q, Wu K, Luo Y, Wei S (2025) Plant-based bioactives and oxidative stress in reproduction: anti-inflammatory and metabolic protection mechanisms. Front Nutr. https://doi.org/10.3389/fnut.2025.1650347

[33] Nwozo SO, Oyinloye BE (2011) Hepatoprotective effect of aqueous extract of Aframomum melegueta on ethanol-induced toxicity in rats. Acta Biochim Pol 58 3:355–8

[34] Herzog AG (2006) Menstrual disorders in women with epilepsy. Neurology 66:S23–S28

[35] Amado D, Cavalheiro EA (1998) Hormonal and gestational parameters in female rats submitted to the pilocarpine model of epilepsy. Epilepsy Res 32:266–274

[36] Xavier KNF, Brice DDP, Modeste W-N, Esther NM, Albert K, Pierre K, Pierre W (2019) Preventive effects of Aframomum melegueta extracts on the reproductive complications of propylthiouracil-induced hypothyroidism in male rat. Andrologia 51:

[37] Biney E, Oppong A, Gyampo-Asare K, Adomako N, Mante P (2025) Aframomum melegueta mitigates seizure severity and neuroinflammation via gut-brain axis modulation in PTZ-induced kindling. Clinical Phytoscience. https://doi.org/10.1186/s40816-025-00393-2

[38] Kandratavicius L, Balista P, Lopes Aguiar C, Ruggiero R, Umeoka E, Garcia-Cairasco N, Bueno Junior L, Leite J (2014) Animal models of epilepsy: use and limitations. Neuropsychiatr Dis Treat 10:1693–1705

[39] Puttachary S, Sharma S, Stark S, Thippeswamy T (2015) Seizure-induced oxidative stress in temporal lobe epilepsy. Biomed Res Int. https://doi.org/10.1155/2015/745613

[40] Geronzi U, Lotti F, Grosso S (2018) Oxidative stress in epilepsy. Expert Rev Neurother. https://doi.org/10.1080/14737175.2018.1465410

[41] Fajobi A (2018) Evaluation of Antioxidant, Anti-inflammatory and Phytochemical Constituents of Aframomum melegueta Aqueous Leaf Extract Citation. International Journal of Medicinal Plants and Natural Products 112:888–903

[42] Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A, Gupta S (2012) The effects of oxidative stress on female reproduction: a review. Reproductive Biology and Endocrinology 10:49

[43] Onoja SO, Omeh YN, Ezeja MI, Chukwu MN (2014) Evaluation of the in vitro and in vivo antioxidant potentials of aframomum melegueta methanolic seed extract. J Trop Med. https://doi.org/10.1155/2014/159343

[44] Najafi MR, Ansari B, Zare M, Fatehi F, Sonbolestan A (2012) Effects of antiepileptic drugs on sexual function and reproductive hormones of male epileptic patients.

[45] Svalheim S, Sveberg L, Mochol M, Taubøll E (2015) Interactions between antiepileptic drugs and hormones. Seizure 28:12–1