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Histomorphological Alterations, Hormonal Fluctuations and Redox Imbalance in Aluminum-Induced Ovarian Toxicity in Adult Wistar Rats; Ameliorating Effect of Herbal Teas

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Abstract:- Heavy metal exposure has raised concerns about increasing female infertility. This research delved into the protective effects of composite teas against aluminum-induced ovarian toxicity in female Wistar rats. The increase in female infertility index due to heavy metal exposure has been reported to have steadily increased over the years. This study investigated the protective effects of composite teas on aluminum-induced ovarian toxicity in adult female wistar rat. Thirty (30) adult female wistar rats (180g - 220g) were divided into 6 groups (n = 5). Group A received feed pellets and distilled water; Group B received 150mg/kg $AlCl_3$; Group C received 150mg/kg $AlCl_3$ and 5ml/kg of Green tea; Group D received 150mg/kg $AlCl_3$ and 5ml/kg of Moringa tea; Group E received 150mg/kg $AlCl_3$ and 5ml/kg of Turmeric tea and Group F received 150mg/kg $AlCl_3$ and 5ml/kg of Lipton black tea. Conversely, composite tea administration notably improved antioxidant levels, hormone profiles, and preserved ovarian structures. This suggests composite teas mitigate oxidative stress-induced negative changes, improving ovarian histology, hormones. Conclusively, Composite teas possess the therapeutic efficacies to significantly limit the degree of oxidative stress-induced negative changes resulting in improved outcome of histological, hormonal and biochemical parameters of the ovary.

Keywords:- *Aluminum, Composite teas, Herbal plant, Histology, Ovary.*

I. INTRODUCTION

Aluminum is ubiquitous in the hearth environment. As a consequence, food is the primary source for aluminum intake under physiological conditions [1]. The widespread presence of aluminum, both in the environment and in foodstuffs, makes it virtually impossible to avoid exposure to this metal ion [2]. In fact, aluminum is a component of many items used daily, including personal hygiene products and medications. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has recently given a scientific opinion on the safety of aluminum from dietary intake [3]. In the JECFA report, the tolerable weekly intake (PTWI) for aluminum was determined and corresponded to 2 mg aluminum per kg of body weight per week. The JECFA affirms in their report that 'The Committee noted that estimates of the contribution to overall mean dietary exposure from all sources (including natural sources, water consumption, food contact materials and food additives) were in the range of 10 – 140 mg/week in adult populations (0.2 – 2.3 mg/kg bw per week as aluminum, assuming a body weight of 60 kg) 'it also noted that children generally have higher food intake than adults when expressed on a body weight basis and therefore represent the highest potential exposure to aluminum per kilogram of body weight' [4] .

Previous researches have shown that $AlCl_3$ caused toxic effects on the reproductive system. Among these researches, most of them focus on the male reproductive system [5-7], while a few reports are about the female reproductive system. In female mice, Al accumulates in the ovary which could damage the ovarian structure [8]. Fu and collaborators [9] reported that $AlCl_3$ disrupted the structure and function of the ovary, in general, by decreasing energy production and possible ovulation which may lead to infertility of female rats.

No effective methods for reducing the concentration of aluminum in food exists, therefore man is constantly exposed to the intake of this metal. However, studies are being undertaken to develop methods of reducing the toxic effect of aluminum on the organism through chelating this metal using nutrients (which reduces its absorption by tissues) or increasing the oxidative capacity of the body (which decreases the possibility of inducing oxidative damage to internal organs) [10]. So far, for instance, thiamine, methionine, glutathione, ascorbic acid, citric acid and zinc have been found to have a positive effect [10]. From a practical nutritional point of view it is important to examine food products containing significant amounts of antioxidant components in order to use them in a daily diet to prevent the

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hazardous effect of toxic metals on the human body. Tea, as the most popular drink in the world apart from water, deserves particular attention [11]. Tea contains a number of substances with an antioxidant effect such as, for example, tannic acid [12], catechins [13] and quercetin [14]. This study aimed at investigating the protective effects of composite teas on adult female wistar rats exposed to aluminum.

II. MATERIALS AND METHOD

A. Chemicals/Reagents

Aluminium Chloride was obtained from Pascal Scientific Limited, opposite Akure south local government, Akure, Ondo state, Nigeria. The ELIZA kits for hormone profiles were bought from Nums Diagnostic Center, Suleija, Niger state. Rat pellete was purchased at an approved store by Federal University of Technology, Akure. All other chemicals used in the study were of analytical grade. The Aluminium chloride solution was prepared by dissolving ten gram (10g) of Aluminium chloride in 400ml of distilled water. The Aluminium chloride solution was administered 150mg/kg body weight of rat.

B. Breeding of the Animal

Thirty (30) adult female wistar rats weighing between 180 g and 220 g were obtained from a breeding stock maintained in the breeding colony of the School of Agriculture and Agricultural Technology, Federal University of Technology Akure (FUTA), Nigeria. The animals were housed in well ventilated wire plastic cages in the animal facility of the Department of Human Anatomy, Federal University of Technology Akure (FUTA), Nigeria. The rats were maintained under standard natural photoperiodic condition of twelve hours of light alternating with twelve hours of darkness (i.e. L:D;12h:12 h photoperiod) at room temperature (25−26 °C) and humidity of 65 ± 5. They were allowed unrestricted access to water and rat chow, they were acclimatized for 14 days before the commencement of the experiment. The processes of protocols using the experimental animals were in accordance to the Guide for the Care and Use of Laboratory Animals and approved by the Health Research Ethics Committee of the College of Medicine, University of Lagos.

C. Experimental Procedure

The animals were randomly divided into 6 experimental Groups (A–F) made up of five rats each. Group A serves as the Control group, received water and rat pellets only; Group B were fed with 150mg/kg body weight of Aluminum chloride only for 2 weeks; Group C were fed with Green tea at a dose of 5ml/kg body weight consecutively with 150mg/kg body weight of Aluminum chloride; Group D were fed with Moringa tea at a dose of 5ml/kg body weight consecutively with 150mg/kg body weight of Aluminum chloride; Group E were fed with Turmeric tea at a dose of 5ml/kg body weight consecutively with 150mg/kg body weight of Aluminum chloride; Group F were fed with Lipton tea at a dose of 5ml/kg body weight consecutively with 150mg/kg body weight of Aluminum chloride. All administration was done through oral gavage using oral cannula once a day at 08:00 h and the whole experiment lasted for 30 days.

D. Anthropometric Measurement

The body weight of the animals was checked throughout the experimental period. The ovaries were removed, weighed, and preserved appropriately in the refrigerator at a regulated temperature of 4 °C. An electronic analytical and precision balance (BA210S, d = 0.0001 g) (Satorius GA, Goettingen, Germany) was used in estimating the BW of the animals.

E. Animal Sacrifice and Tissue Excision

The animals were sacrificed 24 h after last administration. Each rat was anaesthetized in Diethyl-ether which was carried out by skilled personnel. Blood was collected from the heart and the ovaries were excised following abdominal incision. The ovaries were fixed in 10% Paraformaldehyde for histological analysis.

F. Ovarian Histology Preparation

The ovaries of the rats were harvested and fixed in 10% Paraformaldehyde for 24 h before being transferred graded alcohol for dehydration. The tissues passed through 50 %, 70%, 90 % and absolute alcohol and xylene for different durations before being transferred into molten paraffin wax for 1h each in an oven at 65◦C for infiltration. The tissues were embedded and serial sections cut on a rotary microtome set at 5 microns were performed. The tissues were picked up with albumenized slides and allowed to dry on hot plates for 2 min. The slides were dewaxed with xylene and passed through absolute alcohol (two changes), 70 % alcohol, 50 % alcohol, (in that order) and then in water for 5 min. The slides were then stained with Hematoxylin and Eosin, mounted in DPX and photomicrographs were taken at a magnification of 400x on a Leica DM750 microscope [15].

G. Biochemical Assays

- *Lipid Peroxidation (LPO) Assessment*

Lipid peroxidation was determined by measuring the thiobarbituric acid reactive substances (TBARS) produced during lipid peroxidation. This was carried out by the method of Varshney and Kale [16]. The method was based on the reaction between 2-thiobarbituric acid (TBA) and malondialdehyde (MDA). The MDA level was calculated according to the method of Adam-Vizi and Seregi (1982). Lipid peroxidation in units/mg protein was computed with molar extinction coefficient of 1.56 x 105 M-1cm-1.

- *Glutathione Peroxidase (Gpx) Assay*

GPx activity was assayed by the method of Rotruck et al. [17] using H_2O_2 as substrate. The reaction mixture consisted of 1.49 mL phosphate buffer (0.1 M, pH 7.4), 0.1 mL sodium azide (1 mM), 0.05 mL glutathione reductase (1 IU/mL), 0.05 mL GSH (1 mM), 0.1 mL EDTA (1 mM), 0.1 mL NADPH (0.2 mM), 0.01 mL H_2O_2 (0.25 mM), and 0.1 mL 10% homogenate in a total volume of 2 mL. The discoloration of NADPH at 340 nm was recorded at 25 °C. Enzyme activity was calculated as nM NADPH oxidized/min/mg protein using a molar extinction coefficient of 6.22 × 103/M cm.

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➢ *Superoxide Dismutase Assay*

The activity of ovarian superoxide dismutase (SOD) was determined according to the method of Crosti et al. [18]. Briefly, the reaction mixture in a 96-well plate consisted of 15µL of sample, 170µL of 0.1 mM DETAPAC in 50 mM sodium phosphate buffer (pH 7.4), and 20 µL of 1.6 mM 6-hydroxydopamine, which initiated the reaction. The reaction was measured at 490 nm for 4 min at 30 s intervals and SOD activity was expressed as U/mg of protein.

➢ *Hormonal Analysis*

The hormonal levels of Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Estradiol (E2), and Progesterone were measured using available immunoassay (ELISA) kits (Randox Laboratories Ltd, Admore Diamond Road, Crumlin, Co., Antrim, United Kingdom, Qt94QY) according to manufacturer instructions.

➢ *Statistical Analyses*

The data are presented as mean ± SEM and were analyzed using one-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test, which was performed using GraphPad Prism version 8.00 for Windows (GraphPad Software, San Diego, CA, USA). A result of $p<0.05$ was considered statistically significant.

III. RESULTS

A. *Effects of Composite Teas on Body Weight in Aluminum Induced Ovarian Toxicity in Normal and Experimental Rats*

The result revealed that rats treated with $AlCl_3$ only showed significant decrease ($p<0.05$) in body weight compared to the control (Fig. 1). However, the rats administered with $AlCl_3$ + Green tea, $AlCl_3$ + Moringa tea, $AlCl_3$ + Turmeric tea, and $AlCl_3$ + Lipton tea showed significant increase ($p<0.05$) in body weight when compared with the $AlCl_3$ only group (Fig. 1).

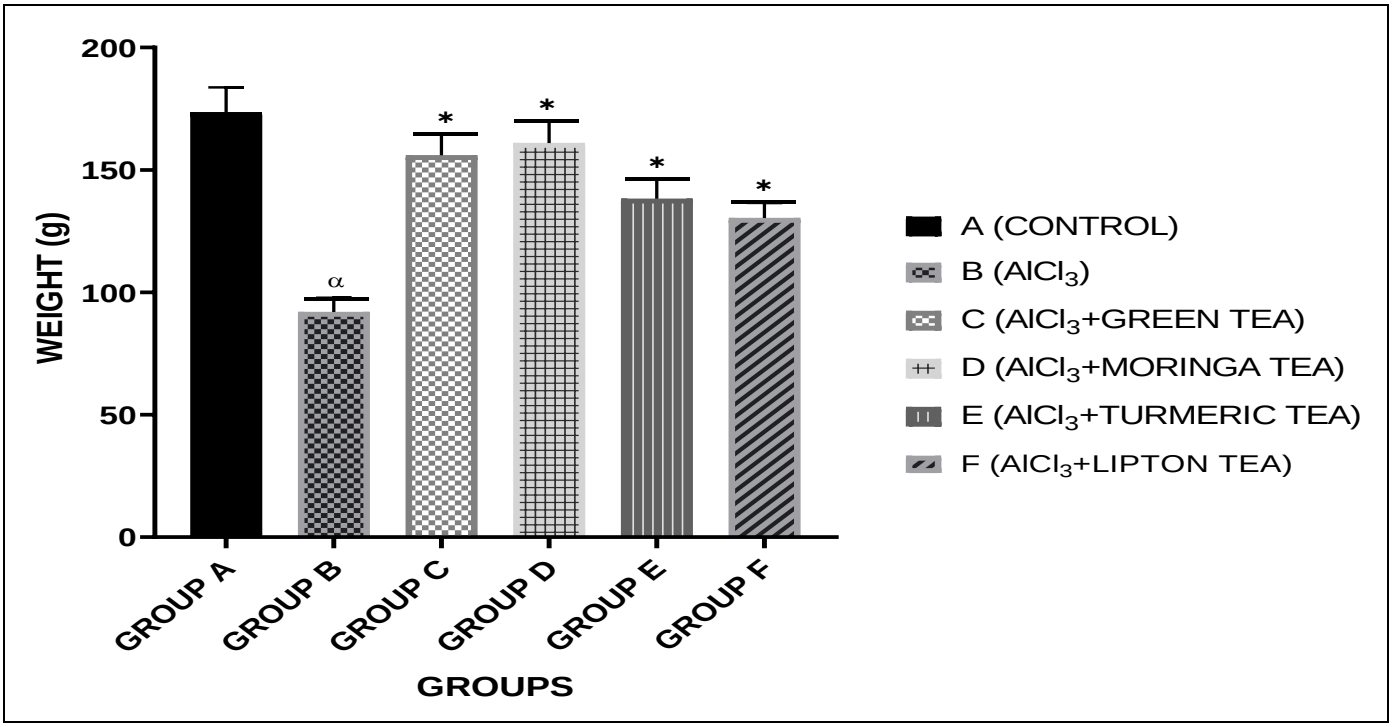

Fig 1: Effects of Composite Teas on Body Weight in Aluminum Induced Ovarian Toxicity in Normal and Experimental Rats (n = 5). * $p<0.05$ as Compared to Group B; α: $p<0.05$ as Compared to Group A.

B. *Biochemical Analysis*

➢ *Effects of Composite Teas on Serum MDA Levels in Aluminum Induced Ovarian Toxicity in Normal and Experimental Rats*

The result revealed that rats treated with $AlCl_3$ only showed a significant increase ($p<0.05$) in MDA level compared to the control (Fig. 2). The level of MDA expressed in $AlCl_3$ + Green tea $AlCl_3$ + Moringa tea, $AlCl_3$ + Turmeric tea and $AlCl_3$ + Lipton tea treated groups significantly decreased compared to $AlCl_3$ only treated group ($p < 0.05$) (Fig. 2).

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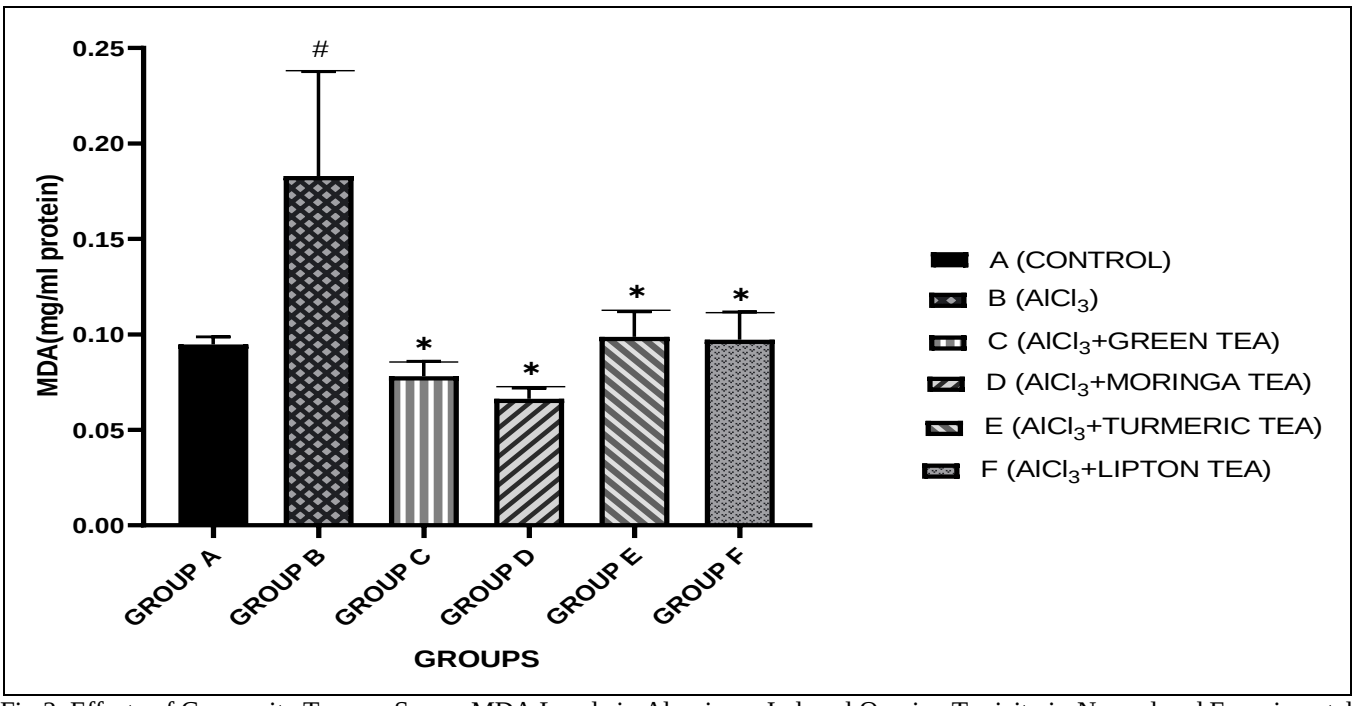

Fig 2: Effects of Composite Teas on Serum MDA Levels in Aluminum Induced Ovarian Toxicity in Normal and Experimental Rats (n = 5). * $p<0.05$ as Compared to Group B; #: $p<0.05$ as Compared to Group A

➢ *Oxidative Stress Markers: SOD and GPx*

The results revealed there was a significant decrease SOD and GPx levels among the animals treated with $AlCl_3$ only (group B) when compared to the control group (group A) ($p<0.05$) (Fig. 3). However, there was an increase in SOD and GPx levels among the animals that received combine administration of $AlCl_3$ + Green tea, $AlCl_3$ + Moringa tea, $AlCl_3$ + Turmeric tea and $AlCl_3$ + Lipton tea (group C, D, E and F) compared with animals treated with $AlCl_3$ only (group B) ($p<0.05$) (Fig. 3). The levels of SOD and GPx expressed in $AlCl_3$ + Green tea, $AlCl_3$ + Moringa tea, $AlCl_3$ + Turmeric tea, and $AlCl_3$ + Lipton tea groups when compared with the control group did not vary significantly.

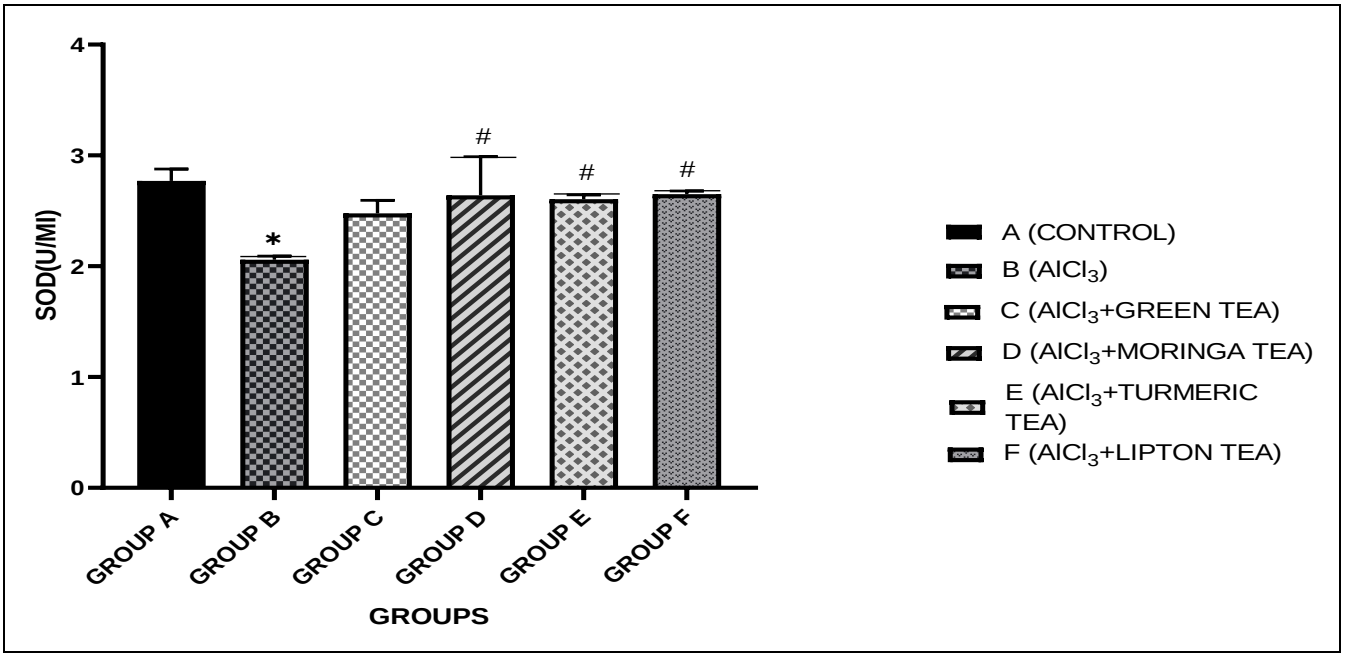

Fig 3(A)

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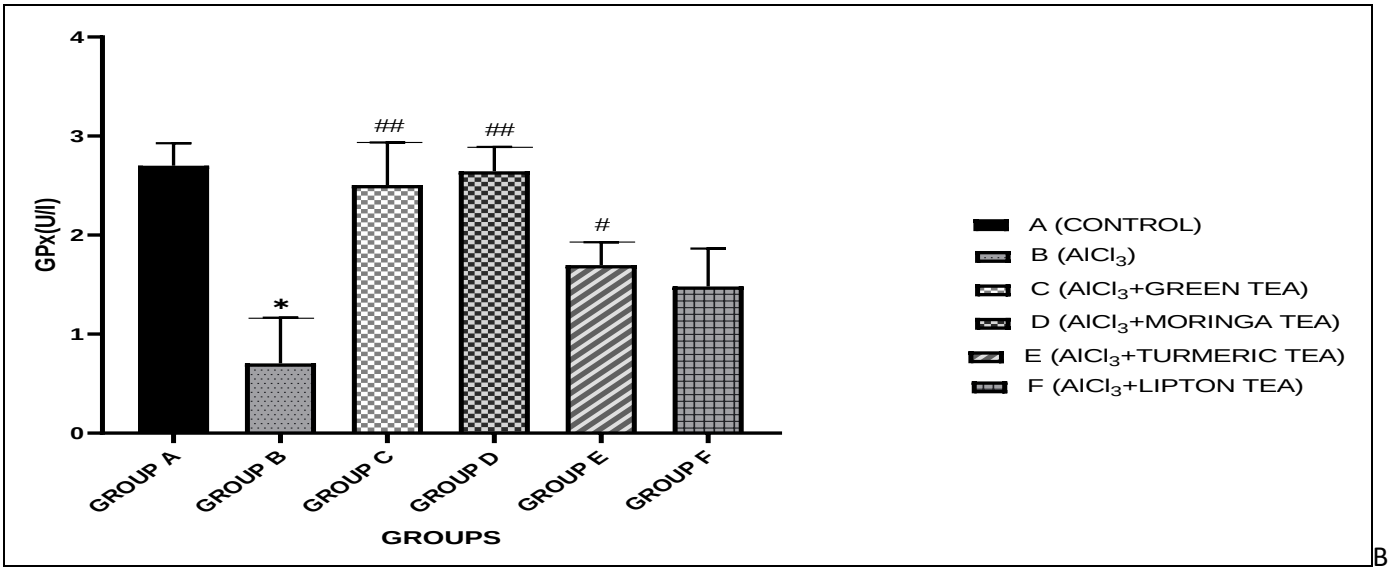

B

Fig 3B

Effects of Composite Teas on Antioxidant Levels (SOD, GPx) in $AlCl_3$ Induced Ovarian Toxicity in Normal and Experimental Rats (n = 5). * p<0.05 as Compared to Group A; #: p<0.05 as Compared to Group B; ##: p<0.05 as Compared to Group B.

C. Hormonal Analysis

- *Effects of Composite Teas on Estradiol in Aluminum Induced Ovarian Toxicity in Normal and Experimental Rats*

There was a significant decrease in E2 serum levels in animals that were treated with $AlCl_3$ only (group B) when compared to the control group (group A) (p<0.05) (Fig.4). However, there was a significant increase in E2 serum levels among the animals that received combine administration of $AlCl_3$ and composite teas (group C, D, E and F) compared with animals treated with $AlCl_3$ only (group B) (p<0.05) (Fig. 4). Although, a significant increase was observed in the serum levels of E2 among animals that received $AlCl_3$ + Moringa tea (group D) compared to $AlCl_3$ + Green tea (group C) (p<0.05) (Fig. 4), while $AlCl_3$ + Lipton tea (group F) showed significantly decrease level of E2 compared to $AlCl_3$ + Green tea (group C) (p<0.05) (Fig. 4). $AlCl_3$ + Turmeric tea (group E) and $AlCl_3$ + Lipton tea (group F) showed significantly decrease level of E2 when compared to $AlCl_3$ + Moringa tea (group D) (p<0.05) (Fig. 4).

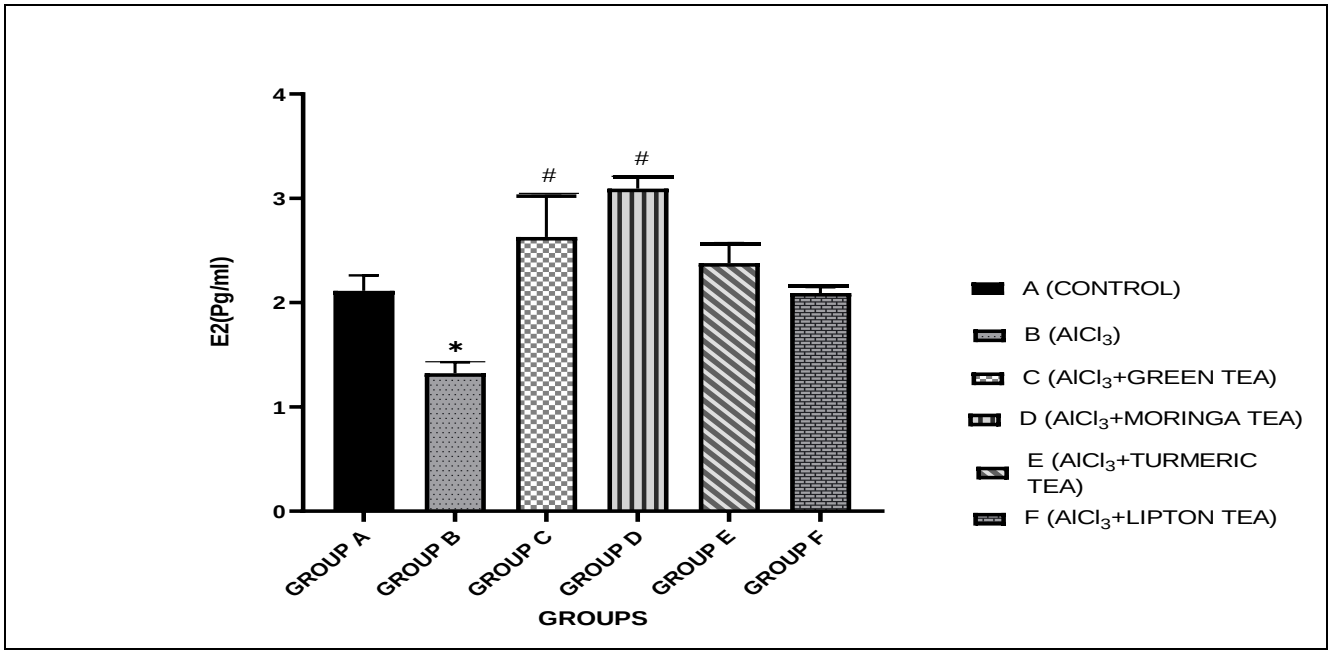

Fig 4: Effects of Composite Teas on Serum E2 Levels in Aluminum Induced Ovarian Toxicity in Normal and Experimental Rats (n = 5). * p<0.05 as Significantly Decrease Compared to Group A; #: p<0.05 as Significantly Increase Compared to Group A

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➢ *Effects of Composite Teas on Progesterone in Aluminum Induced Ovarian Toxicity in Normal and Experimental Rats*

There was a significant decrease in progesterone serum levels in animals that were treated with $AlCl_3$ only (group F) when compared to the control group (group A) ($p<0.05$) (Fig.5). However, there was a significant increase in progesterone serum levels among the animals that received combine administration of $AlCl_3$ and composite teas (group B, C, D, and E) compared with animals treated with $AlCl_3$ only (group F) ($p<0.05$) (Fig. 5). A significant increase was observed in the serum levels of progesterone among animals that received $AlCl_3$ + Green tea (group B) compared to $AlCl_3$ + Turmeric tea (group C) ($p<0.05$) (Fig. 5), while $AlCl_3$ + Lipton tea (group E) showed significantly decrease level of progesterone compared to $AlCl_3$ + Moringa tea (group D) ($p<0.05$) (Fig. 5). $AlCl_3$ + Turmeric tea (group C) and $AlCl_3$ + Moringa tea (group D) showed significantly decrease level of progesterone when compared to $AlCl_3$ + Green tea (group B) ($p<0.05$) (Fig. 5).

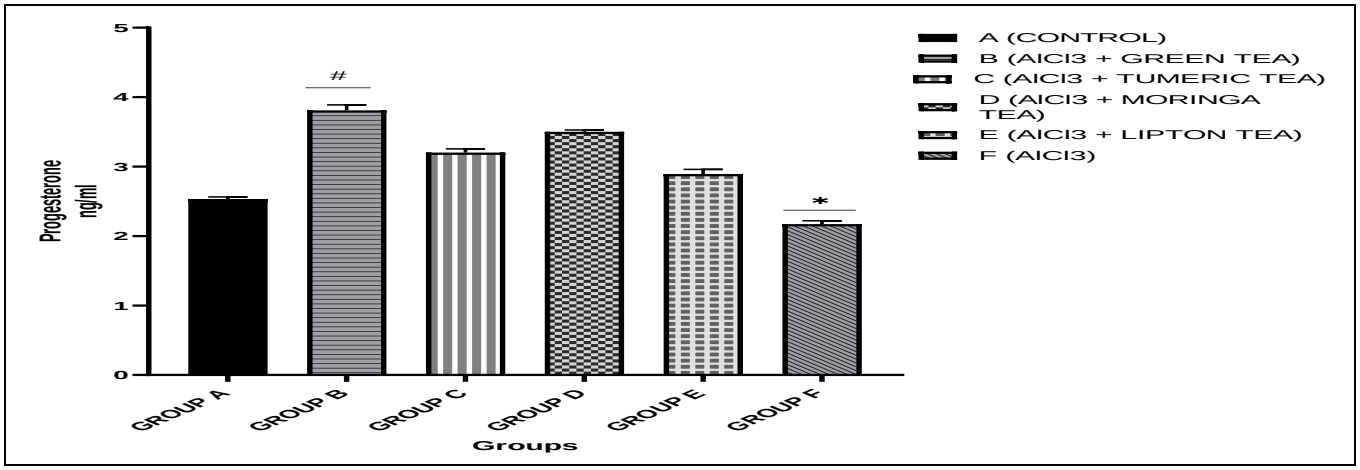

Fig 5: Effects of Composite Teas on Serum Progesterone Levels in Aluminum Induced Ovarian Toxicity in Normal and Experimental Rats (n = 5). *: $p<0.05$ as Significantly Decrease Compared to Group A; #: $p<0.05$ as Significantly Increase Compared to Group A

➢ *Effects of Composite Teas on Luteinizing Hormone in Aluminum Induced Ovarian Toxicity in Normal and Experimental Rats*

There was a significant decrease in LH serum levels in animals that were treated with $AlCl_3$ only (group B) when compared to the control group (group A) ($p<0.05$) (Fig.6). However, there was a significant increase in LH serum levels among the animals that received combine administration of $AlCl_3$ and composite teas (group C, D, E and F) compared with animals treated with $AlCl_3$ only (group B) ($p<0.05$) (Fig. 6).

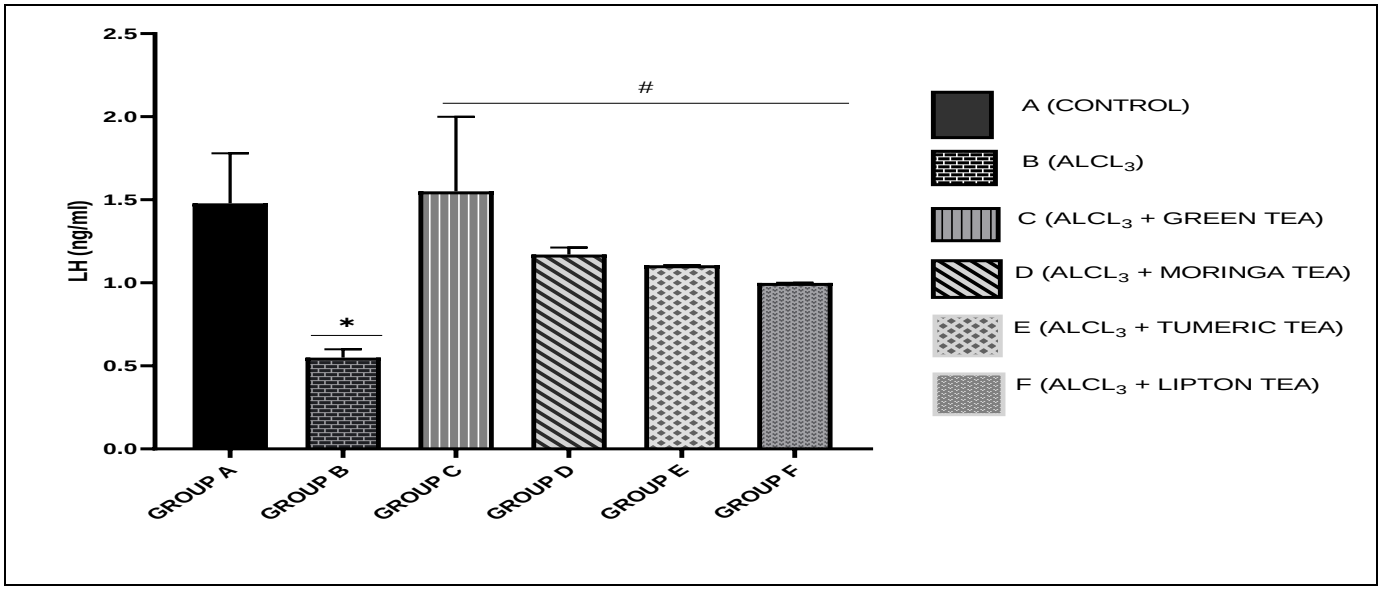

Fig 6: Effects of Composite Teas on Serum LH levels in Aluminum Induced Ovarian Toxicity in Normal and Experimental Rats (n = 5). *:$p<0.05$ as Significantly Decrease Compared to Group A; #: $p<0.05$ as Significantly Increase Compared to Group A

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➢ *Effects of Composite Teas on Follicle Stimulating Hormone Hormone in Aluminum Induced Ovarian Toxicity in Normal and Experimental Rats*

There was a significant decrease in FSH serum levels in animals that were treated with $AlCl_3$ only (group B) when compared to the control group (group A) ($p<0.05$) (Fig.7). However, there was a significant increase in FSH serum levels among the animals that received combine administration of $AlCl_3$ and composite teas (group C, D, E and F) compared with animals treated with $AlCl_3$ only (group B) ($p<0.05$) (Fig. 7).

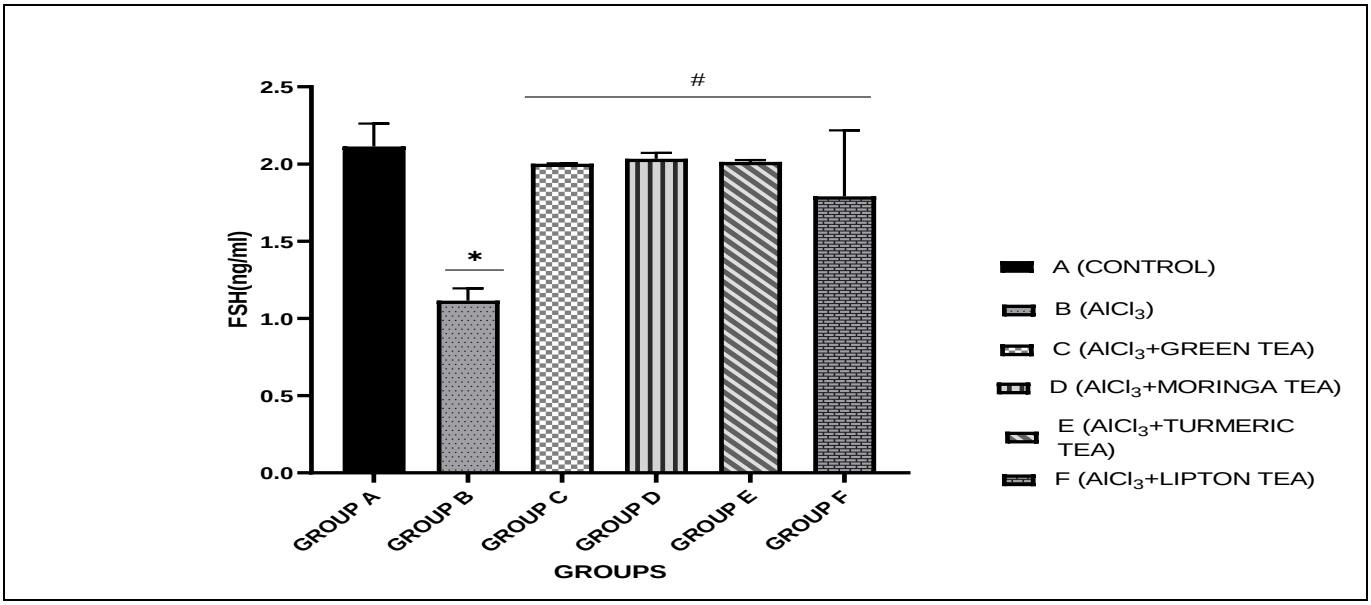

Fig 7 (A)

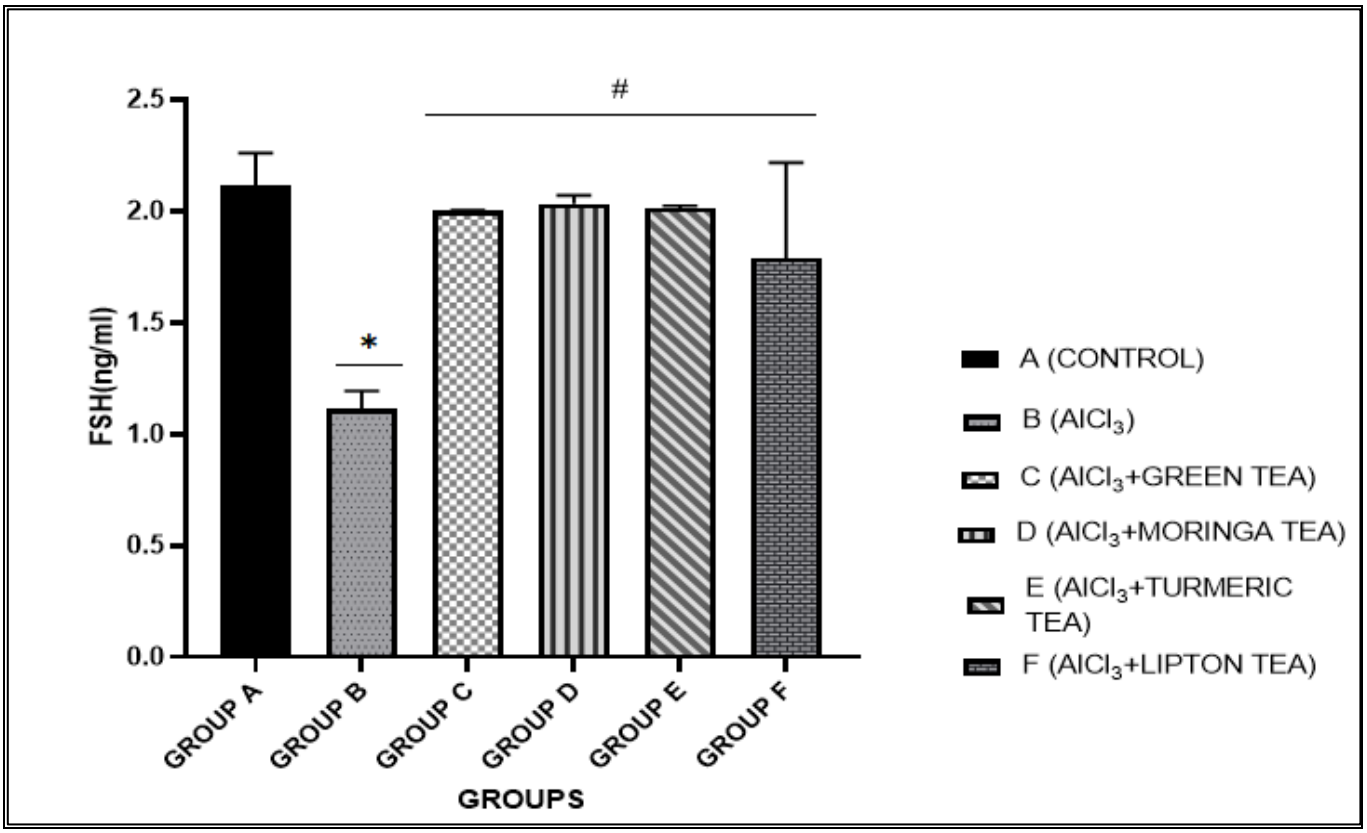

Fig 7 (B)

Effects of Composite Teas on Serum FSH Levels in Aluminum Induced Ovarian Toxicity in Normal and Experimental Rats (n = 5). *:$p<0.05$ as Significantly Decrease Compared to Group A; #: $p<0.05$ as Significantly Increase Compared to Group A

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IV. OVARIAN HISTOLOGY

The photomicrograph of the ovarian histomorphology of the animals in the $AlCl_3$ only (group B) showed apparent alteration in the ovaries, where it induced marked degeneration and necrosis of follicular cells in the ovarian cortex, and as well showed highly congested blood vessels throughout the ovary, with a large number of atretic follicles at different stages of development when compared with the control (group A) (Fig. 8). However, ovarian photomicrograph of the control section had similar characteristics with the composite teas groups showing normal ovarian histology. An enlarged portion of the cortex diameter reveals normal ovarian follicles in different developmental stages, corpus luteum as well as the simple squamous mesothelium, germinal epithelium. Blood vessels are observable in the medulla, primordial follicles are found at the edges of the cortex, and primary follicles with enlarged nuclei are observable too. The ovarian section of the group that received combined administration of $AlCl_3$ and composite teas (group C, D, E, and F) showed restored cyto-architecture of the ovarian morphology.

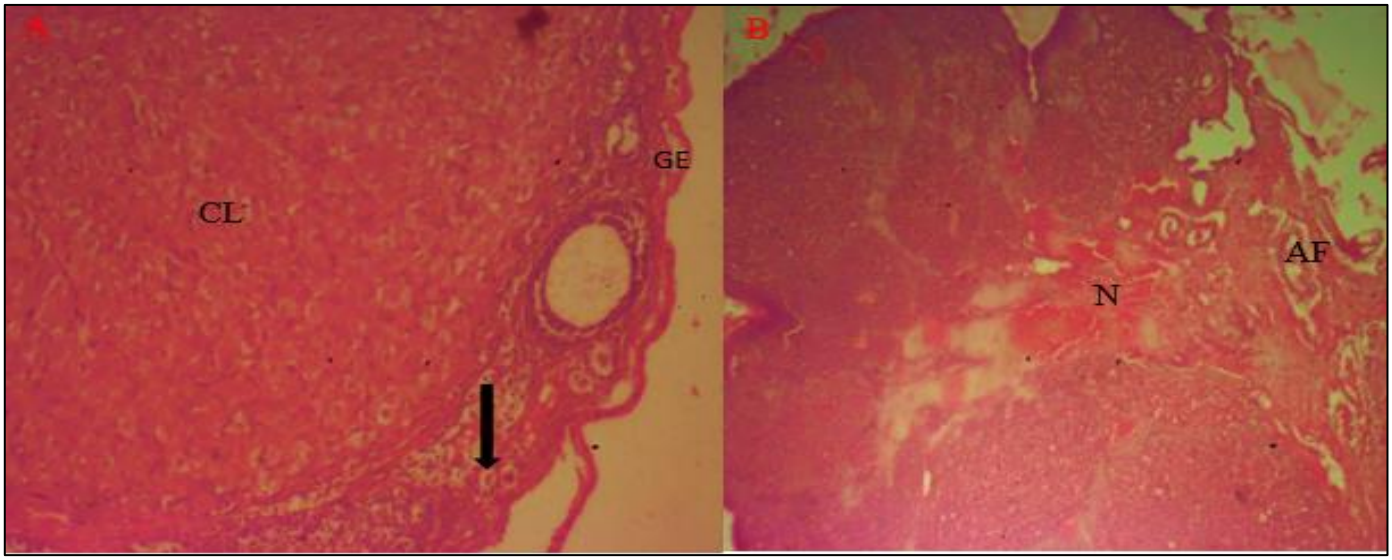

Fig 8: A, B. Ovarian Photomicrographs Showing the Effects of Composite teas on Aluminum Induced Ovarian Toxicity in Normal and Experimental Rats (n = 5). A. Group A [control]: showing normal ovarian microarchitecture characterized with simple squamous mesothelium, Germinal Epithelium (GE), prominent primordial follicles (arrow) and corpus luteum (CL). Group B [$AlCl_3$ only]: showing an abnormal ovarian microarchitecture characterized with necrosis (N) of follicular cells in the ovarian cortex and large number of atretic follicles (AF) at different stages of development. Stains: Haematoxylin and Eosin. Mg X100.

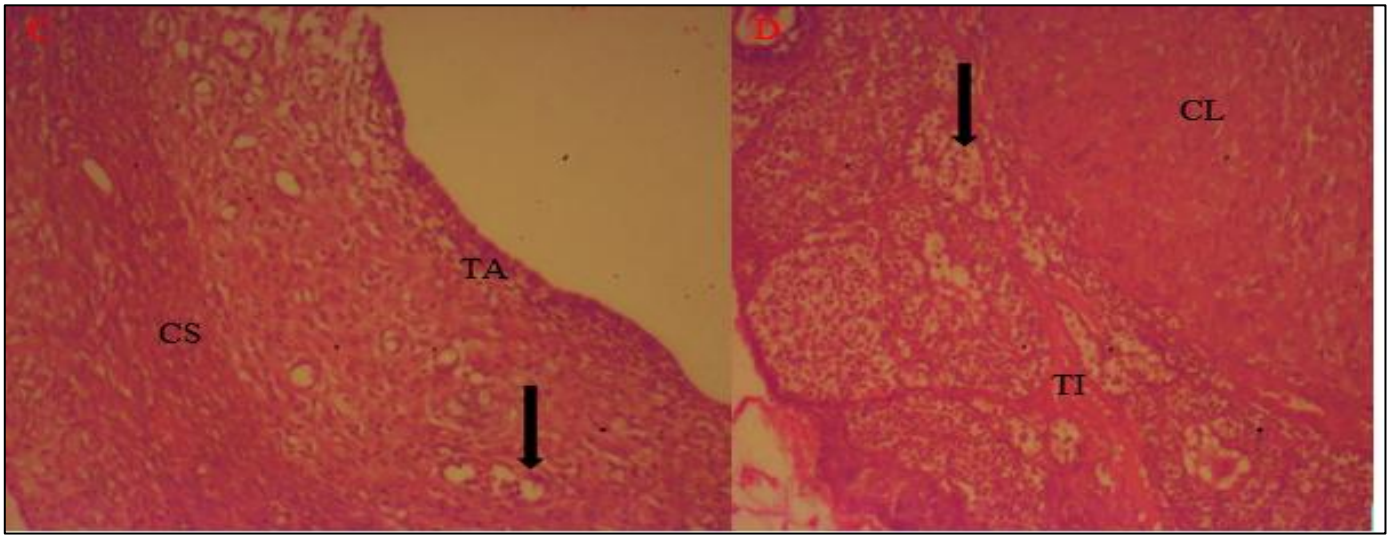

Fig 8: C, D. Group C [$AlCl_3$ and Green tea]: showing restored microarchitecture of ovarian morphology characterized with well-defined cortical stromal (CS), tunica albuginea (TA) and abundant follicular cells (arrow); D. Group D [$AlCl_3$ and Moringa tea]: showing hyperplasia and hypertrophy of stromal interstitial cells with visible Theca Interna (TI) and Corpus Luteum (CL). Stains: Haematoxylin and Eosin. Mg X100.

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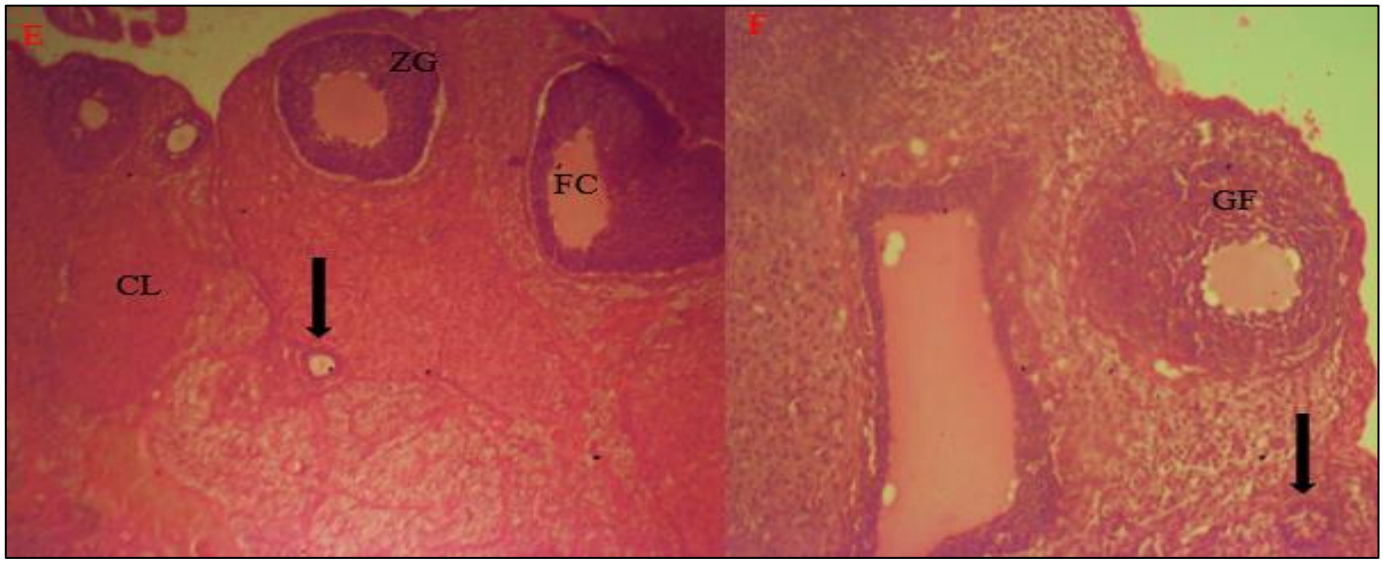

Fig 8: E, F. Group E [AlCl3 and Turmeric tea]: showing mild degeneration in many ovarian follicles at differential stages and atretic follicles. Fluid- filled cyst cavities (FC) are seen within the follicles and the surrounding zona granulosa (ZG) is attenuated. Group F [AlCl3 and Lipton tea]: showing partially restored cortical region with visible Growing follicles (GF), and cyst formation within a corpus luteum. Stains: Haematoxylin and Eosin. Mg X100.

V. DISCUSSION

The present study was undertaken to determine whether composite teas can prevent and/or reduce $AlCl_3$ induced ovarian damage by examining the body weight, different biochemical, hormonal and histological parameters related to ovary function of intoxicated and treated rats. Findings clearly showed significant alterations in ovarian function in histopathological status after $AlCl_3$ exposure associated with increased ovarian oxidative stress and inflammation suggesting the strong pro-oxidant activity of $AlCl_3$ in spite of its non-redox status [19]. However, composite teas co-treatment with $AlCl_3$ showed significant improvement in all biochemical and histological parameters related to ovarian function and structure. This data shows that composite teas are able to ameliorate $AlCl_3$ induced ovarian toxicity by improving levels of endogenous antioxidants, restored hormonal assessments and preserved ovarian structures.

Previous studies have shown that aluminum chloride exposure resulted into significant weight loss in wistar rats [20-22]. Our study accords with the results of previous studies that the ovarian and body weights were significantly decreased by $AlCl_3$ treatment (despite the unlimited access to food). In this study, ovarian sections of the $AlCl_3$ only treated group showed apparent alteration in the ovaries, where it induced marked degeneration and necrosis of follicular cells in the ovarian cortex, and as well showed highly congested blood vessels throughout the ovary, with a large number of atretic follicles at different stages of development when compared to the control group. The histological changes in ovaries of rats administered $AlCl_3$ are in agreement with Mohammed and collaborators [23], and Fu and collaborators [9] who noted a disruption of the rat ovary structure after 64, 128, and 256 mg/kg aluminum intake.

Also, $AlCl_3$ resulted in significant reduction in the levels of serum estradiol concentration compared to control. This support previous finding that high concentration of $AlCl_3$ in humans result in decline in estradiol levels [24-25].

Aluminum chloride toxicity appears to be mediated, in part, by free-radical generation. To date, evidence has shown that the toxic effects associated with $AlCl_3$ are due to the generation of ROS, which in turns results in the oxidative deterioration of cellular lipids, proteins, and DNA [26]. It was demonstrated that Al may alter the activity and levels of a number of components of the tissue antioxidant defense system, such as GSH, SOD leading to enhance production of free radicals especially ROS and development of lipid peroxidation [27]. Lipid peroxidation of biological membranes leads to a loss of membrane fluidity, changes in membrane potential, and an increase in membrane permeability and alterations in receptor functions [28]. In the same line, MDA levels as a marker of lipid peroxidation were significantly increased with a concomitant decrease in the levels of activities of SOD and GPx in the ovary homogenates of intoxicated rat. Although Al is not a transition metal, and therefore, cannot initiate peroxidation, many studies have searched for mechanisms between aluminum Al and oxidative damage in tissues [28].

In this study, there is significant increase in the body and ovarian weights of rats in $AlCl_3$ and composite teas treated groups when compared to $AlCl_3$ only treated group. The increase in weight is one of the major pointers that tea extracts has a nutritive and therapeutic value. Administration of composite teas to AlCl3 treated rats effectively improved ovarian function, as concluded from 1) attenuated histological changes characteristic of $AlCl_3$ ovarian toxicity 2) ameliorated oxidative stress and 3) Improved serum hormonal profile. Previously, it was reported that, the use of tea infusion reduced the toxic effect of lead and cadium on the body by reducing their absorption by tissues and

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increasing the oxidative capacity of the body which decreases the possibility of inducing oxidative damage to internal organs [29].

This study aimed that the main mechanism by which composite teas act in ameliorating $AlCl_3$ induced ovarian toxicity is due to their antioxidant effects. However, most of the previous studies accord with our findings as they have shown that green tea leaf extracts reduced $AlCl_3$ neurotoxicity via its antioxidant effect [30]. Also, Ebrahim et al., [31] reported that curcumin (the most active ingredient in turmeric tea) ameliorated oxidative stress in $AlCl_3$ treated rats via its antioxidant property by scavenging free radicals and chelating metals as well as regeneration of endogenous antioxidant.

VI. CONCLUSION

The present study has provided supportive evidence that the oral administration of $AlCl_3$ in female rats at a dose of 150 mg/kg body weight daily for a period of 28 days induces ovarian dysfunction as evidenced in significant alterations in some biochemical, hormonal and histological parameters. In conclusion, oral administration of AlCl3 in female rats induces ovarian dysfunction. However, composite teas co-administered with AlCl3 mitigate some harmful effects. Thus, supplementation with composite teas may serve as protective therapy against AlCl3-induced ovarian effects.

AUTHOR'S CONTRIBUTION

- Conceptualization and design: OTS; Formal analysis, Investigation: AGT, Experimentation, data collection, data analysis, and data interpretation: AAM, Draft manuscript: FRA; Vetting and approval of the manuscript for submission: OTS
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