PROTECTIVE EFFECTS OF FLAVONOIDS AND SAPONINS FROM TIGER NUTS AND DATE FRUITS ON PROSTATE HEALTH IN ALUMINUM-EXPOSED WISTAR RATS.

ABSTRACT

Aim:: To evaluate the histological effects of flavonoid and saponin fractions from *Cyperus esculentus* (tiger nuts) and *Phoenix dactylifera* (date fruits) on the prostate gland of Wistar rats exposed to aluminum chloride, focusing on their potential protective properties against aluminum-induced toxicity.

Study Design: A randomized experimental study involving twenty-five male Wistar rats divided into five groups. Groups were treated with normal saline (control), aluminum chloride, and different combinations of flavonoid and saponin extracts for 28 days.

Place and Duration: Conducted at the animal breeding facility of the College of Medical Sciences, University of Calabar, over a month.

Method: Male Wistar rats were acclimatized for seven days, then assigned to five treatment groups. Flavonoids and saponins were extracted from *Cyperus esculentus* and *Phoenix dactylifera*. The groups received oral administration of extracts and aluminum chloride once daily for 28 days. Prostate tissues were collected post-treatment and processed with hematoxylin and eosin (H&E) for histological evaluation.

Result: Histological analysis showed that the control group had healthy prostate architecture, while the aluminum chloride-treated group presented significant dysplastic changes typical of benign prostatic hyperplasia (BPH). Treatment with flavonoid and saponin fractions resulted in moderate histological improvements. The combination of both extracts exhibited enhanced protective effects, stabilizing prostate architecture and preventing severe stromal hyperplasia.

Conclusion: Flavonoid and saponin fractions from *Cyperus esculentus* and *Phoenix dactylifera* demonstrate protective effects against aluminum chloride-induced histopathological changes in the prostate of Wistar rats, suggesting potential dietary interventions to mitigate environmental toxin impacts on prostate health. Further investigation into their mechanisms and broader applications is warranted.

Keywords: Aluminum Chloride, P*rostate Gland, Flavonoid, Saponins, Histopathology, Wistar Rats*

1. INTRODUCTION

Aluminum chloride ($AlCl_3$) is a widely used chemical in various industries, but its toxicity has raised concerns regarding its impact on human health. Accumulating evidence suggests that aluminum exposure can result in histopathological changes in several organs, including the prostate gland. This is particularly important given the increasing incidence of prostate-related disorders, such as benign prostatic hyperplasia and prostate cancer, which pose significant health risks to males (Igbokwe et al.,

2019; Xu et al., 2017). The prostate, essential for male reproductive health, can suffer from inflammation, cellular damage, and alterations in tissue architecture due to aluminum exposure (Vassal et al., 2021).

Natural compounds, particularly flavonoids and saponins, have garnered attention for their potential health benefits, including antioxidant, anti-inflammatory, and anticancer properties (Ullah et al., 2020). Among the plants rich in these phytochemicals, *Cyperus esculentus* (tiger nuts) and *Phoenix dactylifera* (date fruits) hold significant promise. Tiger nuts have been found to contain high levels of flavonoids and saponins, which may confer various health benefits, including protective effects against oxidative stress and inflammation (Onoharigho et al., 2023; Yu et al., 2022). Similarly, date fruits are known for their rich phytochemical profile, including saponins, which have been associated with protective effects on various biological systems (Fernández-López et al., 2022).

This study aims to evaluate the histological effects of flavonoid and saponin fractions derived from *Cyperus esculentus* and *Phoenix dactylifera*, respectively, on the prostate gland of Wistar rats exposed to aluminum chloride. Understanding these effects can pave the way for potential therapeutic strategies to counteract the negative impacts of aluminum on prostate health.

The increasing prevalence of exposure to environmental toxins has become a pressing public health concern. Aluminum, a common environmental contaminant found in food products and industrial applications, has been implicated in chronic health issues, including neurodegenerative diseases and reproductive disorders (Bondy, 2010). Particularly, aluminum's impact on the prostate gland is an area of growing interest, with studies indicating that exposure can lead to significant alterations in histological structure and function (Lima et al., 2020).

Prostate health is critical to male reproductive function, with a substantial burden of disease linked to prostate conditions. The histopathological consequences of aluminum exposure may exacerbate existing health disparities and contribute to the rising incidence of prostate-related diseases (da Silva et al., 2020). Hence, there is a pressing need for effective interventions that can mitigate the adverse effects of aluminum on prostate health.

Flavonoids and saponins, abundant in *Cyperus esculentus* (tiger nuts) and *Phoenix dactylifera* (dates), respectively, are gaining attention for their beneficial effects in preventing and treating various health conditions. Flavonoids from tiger nuts exhibit strong antioxidant and anti-inflammatory properties, which can help combat oxidative damage and restore normal tissue architecture (Achoribo & Ong, 2017). Similarly, saponins derived from date fruits have been shown to possess protective effects against chemical-induced toxicity, promoting cellular health and function (Sharma et al., 2023).

This study aims to investigate the beneficial histological changes in the prostate gland following treatment with flavonoid fractions from *Cyperus esculentus* and saponin fractions from *Phoenix dactylifera* in Wistar rats exposed to aluminum chloride. By elucidating the protective effects of these natural compounds, this research seeks to provide valuable insights into potential dietary strategies for enhancing prostate health and mitigating the adverse effects of aluminum exposure.

2. MATERIALS AND METHODS

2.1 Breeding of Animals

Twenty-five male Wistar rats weighing 150-180 g were obtained from the animal breeding facility of the college of medical sciences, University of Calabar. They were housed in wooden cages at 27°C-30°C with a 12-hour light/dark cycle and acclimatized for seven days, receiving standard rat chow and water *ad libitum.* After acclimatization, the rats were randomly assigned to five groups of five each.

2.2 Extract Preparation

Cyperus esculentus tubers and *Phoenix dactylifera* fruits were obtained from Bogobiri Street in Calabar, Cross river state. The tubers and fruits were rinsed properly in running tap water to remove dirts and debris. The tubers and fruits were air dried, thereafter grinded into powder with a manual blender (Masterchef, MC-6020).

2.2.1 Extraction of Flavonoids

To extract flavonoids, 100g samples were refluxed in a Soxhlet extractor with ether at 60°C for 8 hours to eliminate oil, then air-dried for 12 hours. After evaporating the ether, the residues were ground and sieved

to select particles between 20-mesh (0.84 mm) and 28-mesh (0.6 mm). These particles were packed into a 400 × 2.5 cm silica gel column. Following the complete absorption of the solution, the column was washed with distilled water to elute the flavonoids. The collected eluate rich in flavonoids was concentrated at 40°C using a rotary evaporator (RE52A, Shanghai Ya Rong Biochemistry Instrument Company, China) until sediment formed. The final vacuum-dried product yielded 62.7g of flavonoids from Cyperus Esculentus tubers (Zeb et al., 2014).

2.2.2 Extraction of Saponins

For saponins, 100g of powdered Phoenix Dactylifera fruit was heated for 4 hours at 55°C. The extract was filtered, and the residue re-extracted. The filtrate was concentrated on a water bath until the volume reduced to 200 ml, then mixed with 100 ml diethyl ether in a separating funnel. After vigorous shaking and settling, the aqueous layer was collected, and the diethyl ether layer discarded. Following this, 80 ml of n-butanol was added to the aqueous portion, mixed, and treated with 10 ml of 5% NaCl solution. The resulting solution was concentrated on a water bath, yielding 43.5g of saponin fractional extract (Zeb et al., 2014).

2.3 Administration of Extracts

The treatment groups received the following:

- Group A: Control, 0.5 ml normal saline.

- Group B: 0.5 mg/kg aluminum chloride.

- Group C: 0.5 mg/kg aluminum chloride + 500 mg/kg *C. esculentus* extract.

- Group D: 0.5 mg/kg aluminum chloride + 500 mg/kg *P. dactylifera* extract.

- Group E: 0.5 mg/kg aluminum chloride + 500 mg/kg each of *C. esculentus* and *P. dactylifera* extracts.

All treatments were administered orally once/day for 28 days, after which the rats were sacrificed.

2.4 Sample Collection

Post-sacrifice using chloroform inhalation, organs including the prostate gland and seminal vesicles were collected and fixed in Bouin's fluid for further processing.

2.5 Tissue Processing

Tissue processing involved fixation in Bouin's fluid, dehydration through increasing alcohol concentrations, clearing in xylene, infiltration with paraffin wax, and embedding in molds. Tissue sections were then mounted on slides.

2.6 Staining Procedure

The sections were subjected to H&E staining, which included fixation of tissue sections, dehydration, staining in hematoxylin, differentiation, blueing in tap water, counterstaining with eosin, and final dehydration and mounting. The stained slides were examined under a microscope, and photomicrographs were captured.

3. **RESULTS** AND DISCUSSION

3.1 Result

3.1.1 Histological Observations

The histological evaluation of prostate tissue from the normal control group reveals a healthy architecture with no signs of dysplasia or hyperplasia. The luminal cells are uniformly arranged, displaying normal morphology without any significant loss of cells. Their nuclei maintain consistent size and shape, showing smooth chromatin patterns and well-defined nucleoli, indicating proper cellular function. Additionally, the basal cell layer remains intact and organized, with a normal distribution of basal cells that exhibit no evidence of hyperplasia. This preservation suggests adequate support for the epithelial cells. The stromal composition is also characteristic of a stable environment, with a healthy balance of fibrous tissue and

smooth muscle fibers, devoid of significant collagen deposition or increased fibroblast activity. Importantly, there are no signs of inflammation or other pathological changes within the tissue.

The histological evaluation of the prostate tissue reveals significant findings consistent with benign prostatic hyperplasia (BPH) accompanied by marked dysplastic changes in the glandular architecture in Aluminum Chloride Treated Group (Group B). Key features observed include dysplasia of luminal cells, characterized by their loss and associated altered cell morphology and nuclear atypia, alongside increased proliferation of basal cells, indicating basal cell hyperplasia. Notably, stromal hyperplasia is evident, with increased fibroblast activity and collagen deposition within the prostatic stroma. The integrity of the basal cell layer is compromised.

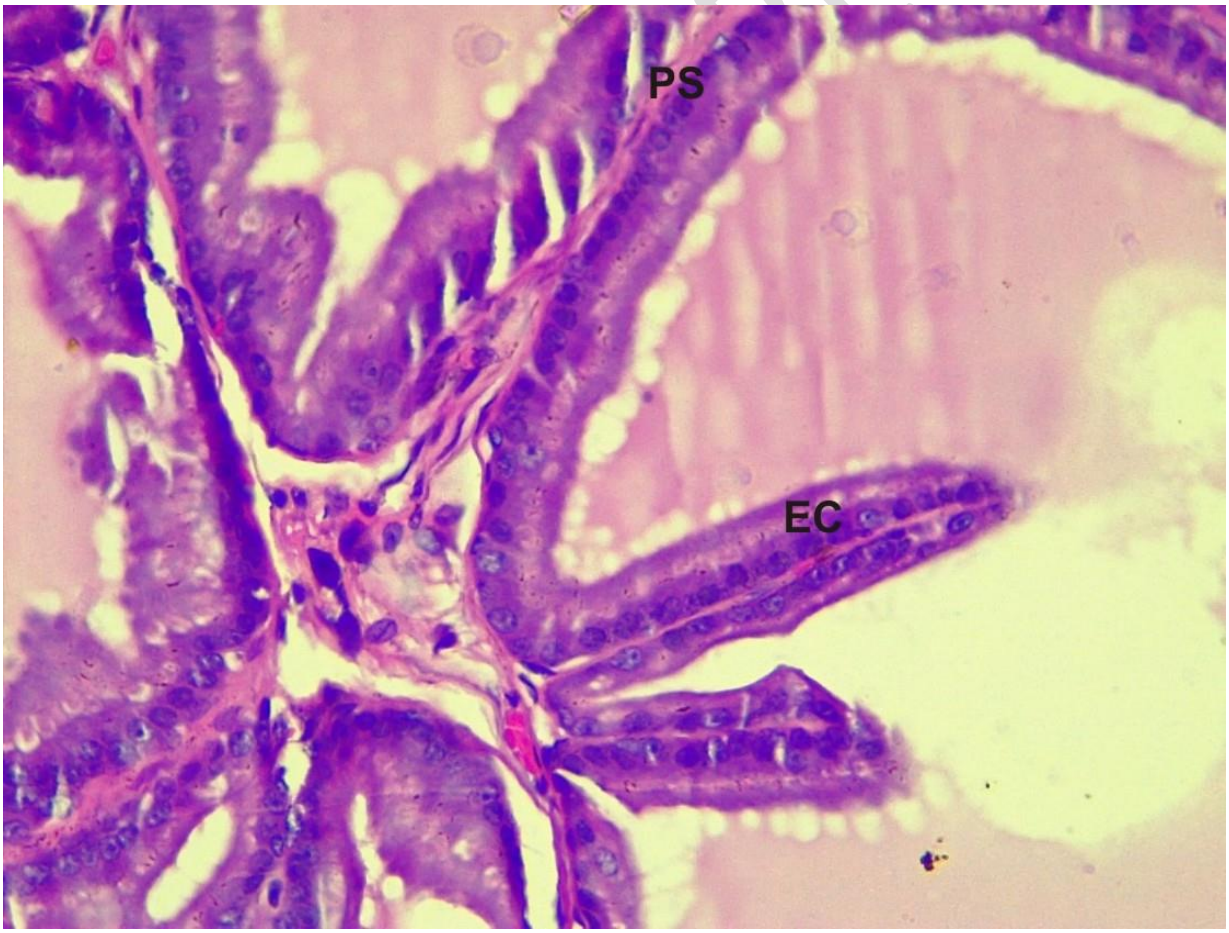
Histological evaluation of prostate tissue from the group treated with flavonoid fractions from *Cyperus esculentus* revealed moderate dysplastic changes compared to the Aluminum Chloride treated group. demonstrated results akin to those observed in the flavonoid-only treatment group. The glandular architecture displayed moderate dysplastic changes, characterized by a persistent loss of luminal cells accompanied by altered morphology and mild nuclear atypia. The basal cell layer exhibited slight disorganization, with evidence of increased cell proliferation, although hyperplastic features were notably less pronounced than in the Aluminum Chloride treated group. Importantly, there was no significant indication of stromal hyperplasia or heightened fibroblast activity.

The histological evaluation of prostate tissue from the group treated with saponin fractions from *Phoenix dactylifera* revealed distinct changes following Aluminum Chloride exposure. The analysis indicated the presence of luminal cells displaying some hyperplastic features, which signifies an adaptive response to the prior dysfunction induced by Aluminum Chloride. While some alterations were noted within the luminal cells, these changes were less pronounced compared to the Aluminum Chloride treated group. Moderate alterations in the morphology of basal cells were observed, suggesting a degree of basal cell hyperplasia. Furthermore, mild changes in the prostatic stroma were present, characterized by slight increases in collagen deposition, but significant stromal hyperplasia and fibroblast activity were not evident.

The histological evaluation of prostate tissue from the group treated with a combination of flavonoid fractions from *Cyperus esculentus* and saponin fractions from *Phoenix dactylifera* demonstrated results akin to those observed in the flavonoid-only treatment group. It revealed moderate dysplastic changes compared to the Aluminum Chloride treated group. The tissue exhibited a persistent loss of luminal cells with altered morphology and mild nuclear atypia, though these changes were less severe than in the aluminum-treated group. Mild disorganization of the basal cell layer was noted, with increased cell proliferation indicating a response to treatment. However, hyperplasia was less pronounced. Notably, there was no evidence of stromal hyperplasia or increased fibroblast activity.

Figure 1: Photomicrographs showing the differences in the histology of the Prostate gland among the experimental groups.

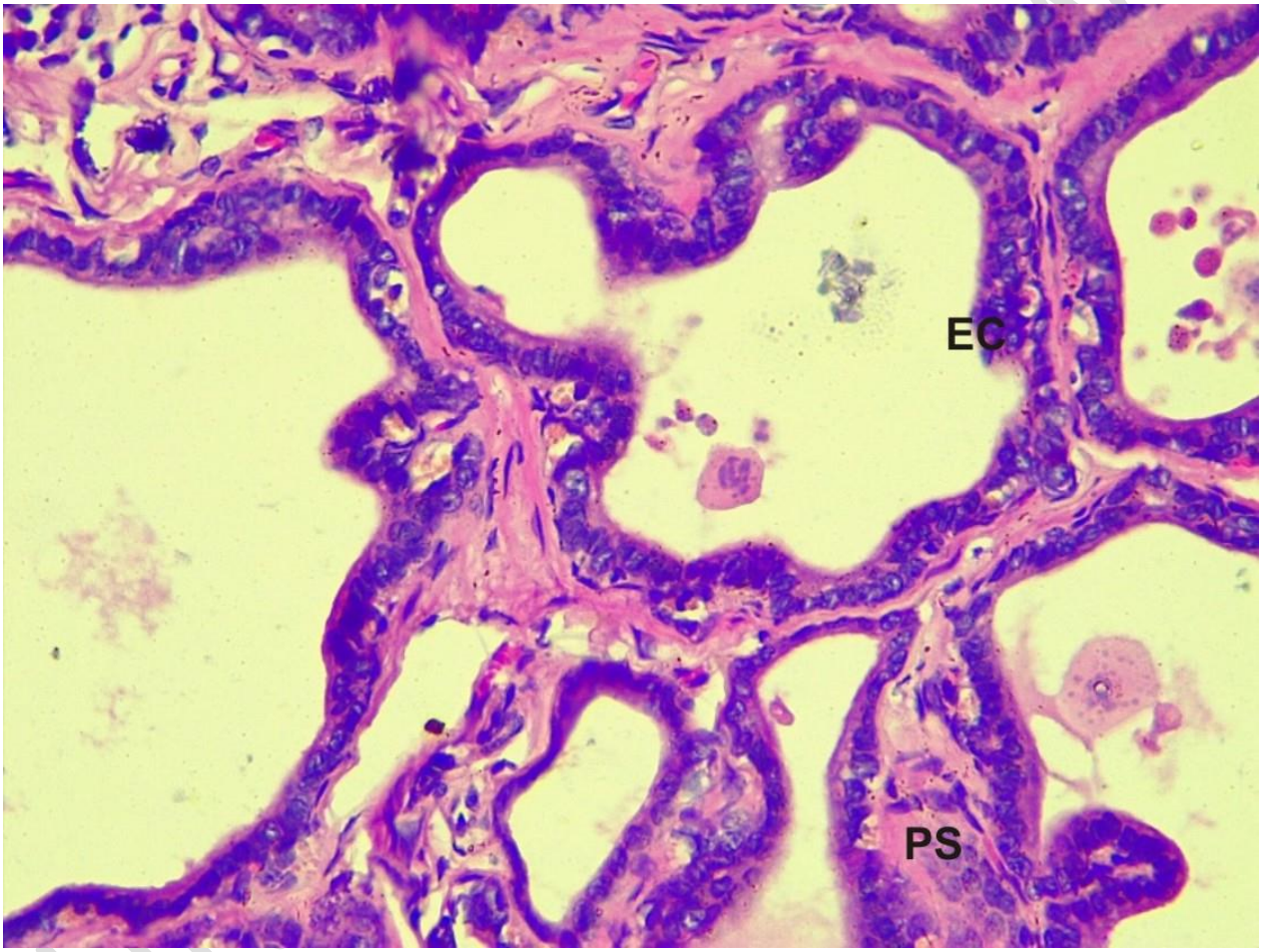
Normal Control group (Group A)



Photomicrograph Analysis (H&E, x100 Magnification)

Section 1: The photomicrograph of prostate tissue from the control group reveals a well-preserved histological architecture characteristic of healthy prostate tissue. The glandular structure is intact, with luminal cells arranged uniformly and exhibiting typical morphology. The epithelial cells (EC) present in the luminal layer have distinct cell borders, and their nuclei are consistent in size and shape, characterized by finely dispersed chromatin and inconspicuous nucleoli. These features indicate normal nuclear structure without signs of atypia. Notably, the basal cell layer remains organized and intact, displaying a continuous layer that provides structural support to the epithelial cells. There is no evidence of hyperplasia or dysplastic changes.

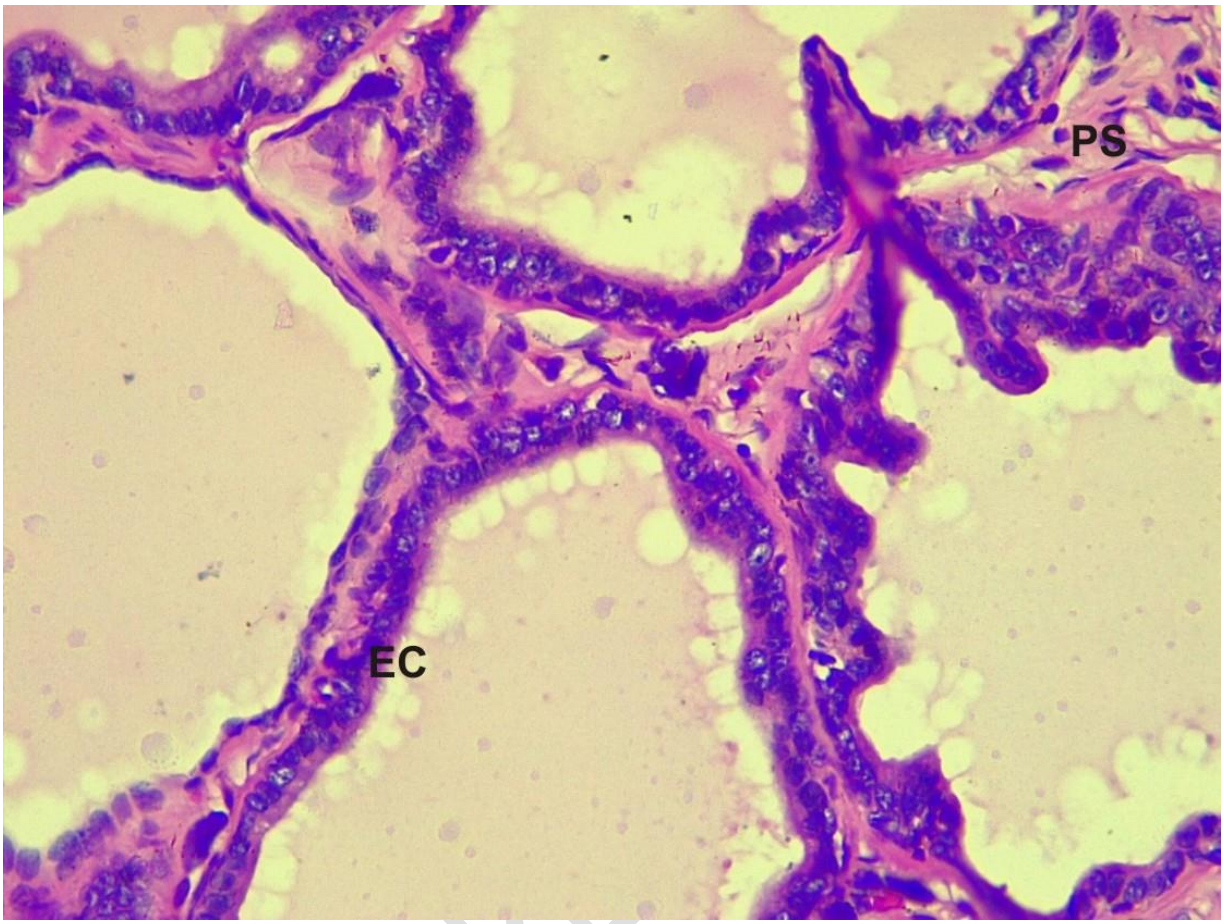
Aluminum Chloride Treated Group (Group B)



Photomicrograph Analysis (H&E, x100 Magnification)

Section 2: This photomicrograph depicts the dysplastic changes in the glandular architecture in in Aluminum Chloride Treated Group (Group B) characteristic of high-grade benign prostatic hyperplasia (BPH). The luminal cells exhibit a noticeable loss, and the remaining epithelial cells (EC) have enlarged nuclei, prominent nucleoli, and a coarse chromatin pattern, indicative of nuclear atypia. The presence of mitotic figures further supports the high activity of dysplastic changes observed in the tissue. Additionally, there is a marked increase in basal cell proliferation.

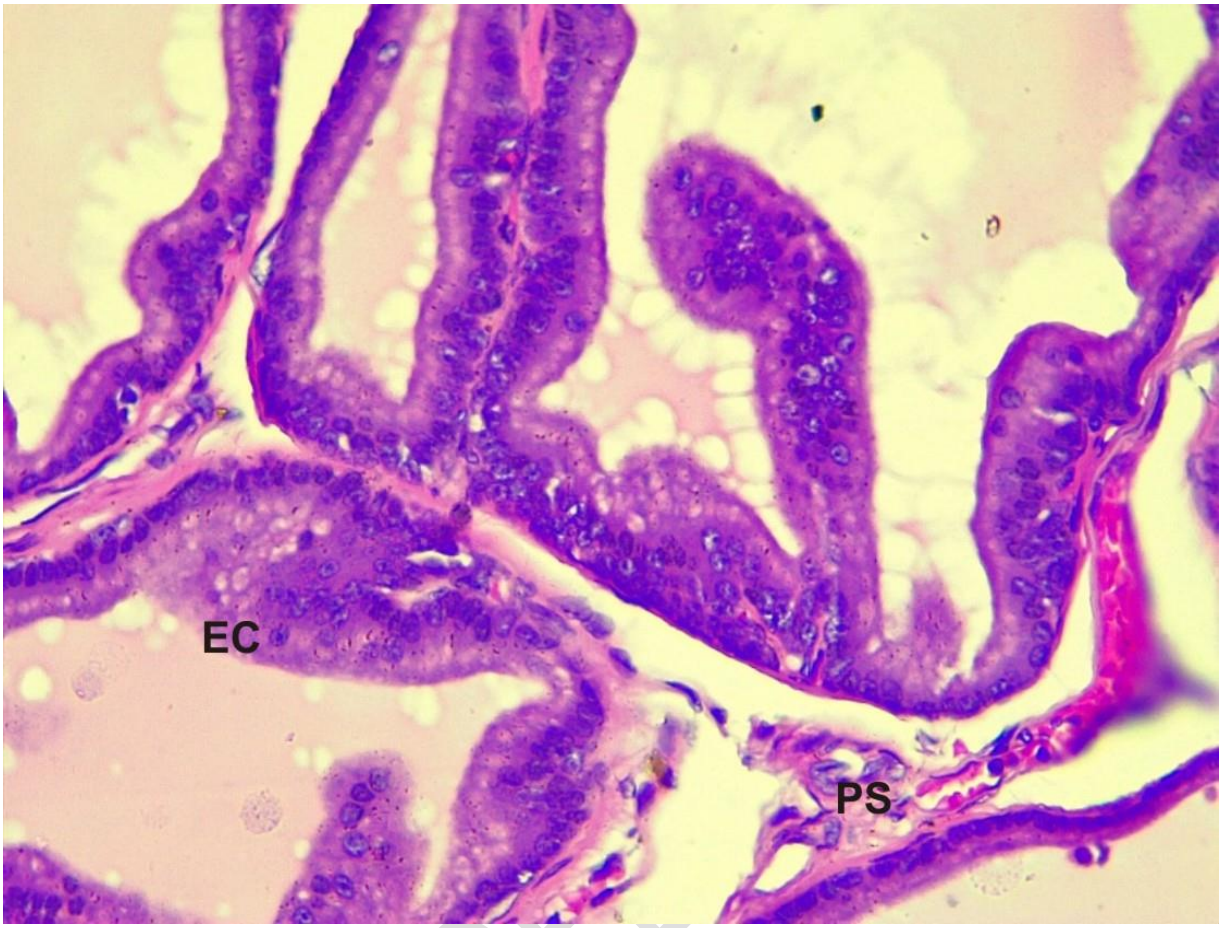
Flavonoid Fractions from Cyperus esculentus Treated Group:



Photomicrograph Analysis (H&E, x100 Magnification)

Section 3: This photomicrograph illustrates moderate dysplastic changes within the glandular architecture of the prostate tissue treated with flavonoid fractions from Cyperus esculentus. The luminal cells show persistent loss and exhibit altered morphology, along with mild nuclear atypia characterized by slightly enlarged nuclei and subtle chromatin irregularities (EC). The degree of dysplasia observed is less severe than that seen in the Aluminum Chloride treated group. Mild disorganization of the basal cell layer is noted, with increased cell proliferation suggesting a responsive adaptation to the treatment. However, the extent of hyperplasia remains less pronounced, and notably, there is no evidence of stromal hyperplasia or elevated fibroblast activity (PS). EC: Epithelial cells, P: Prostatic stroma.

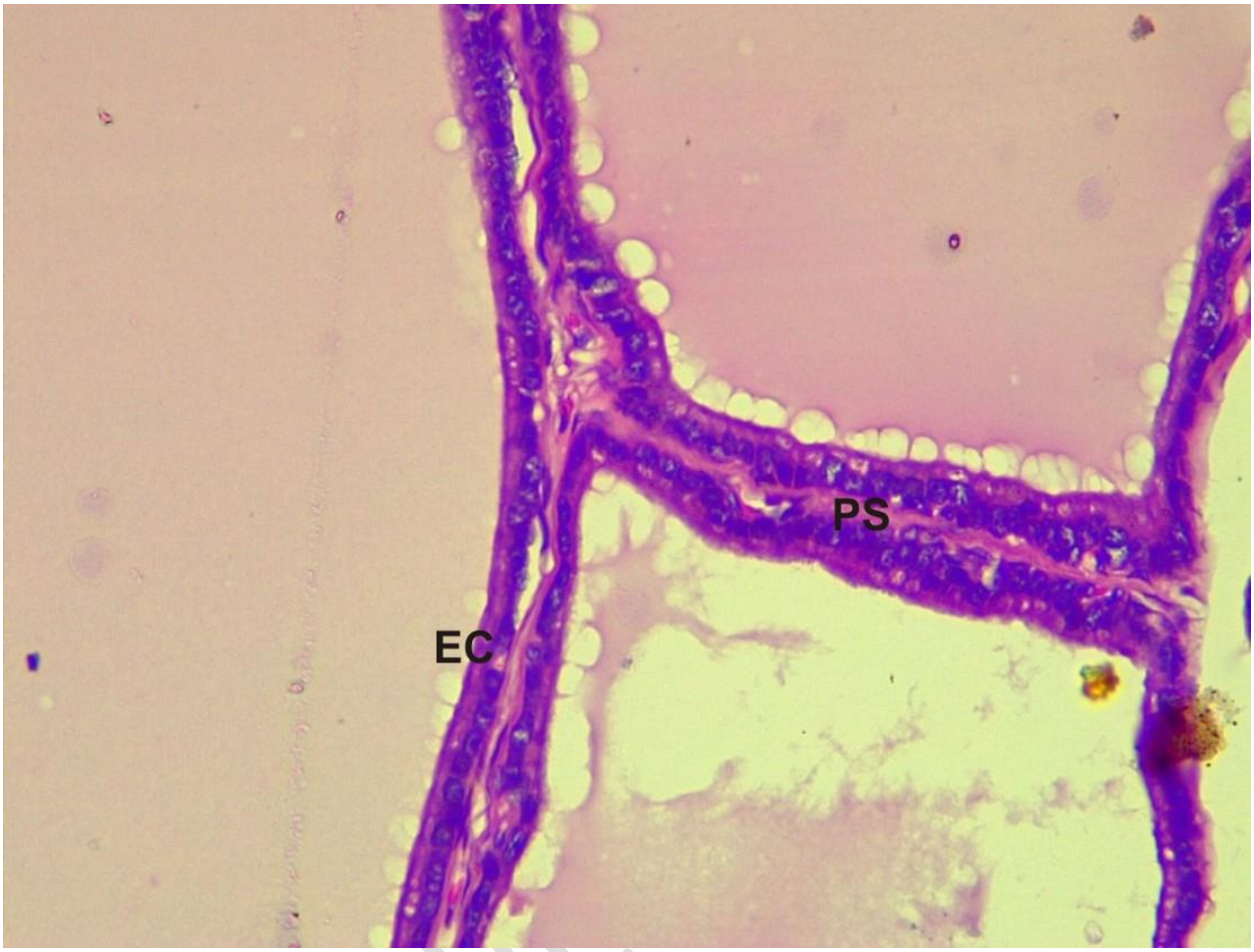
Saponin Fractions from Phoenix dactylifera Treated Group



Photomicrograph Analysis (H&E, x100 Magnification)

Section 3: This photomicrograph displays distinct histological changes in the prostate tissue from the group treated with saponin fractions from Phoenix dactylifera. The luminal cells exhibit some hyperplastic features, indicative of an adaptive response to Aluminum Chloride exposure. Though alterations within the luminal cells are noted (EC), these changes are comparatively minor when juxtaposed with the Aluminum Chloride treated group. Moderate changes in the morphology of basal cells suggest a degree of basal cell hyperplasia. Additionally, mild pathological changes in the prostatic stroma include slight collagen deposition; however, there is no significant evidence of stromal hyperplasia or increased fibroblast activity (PS). EC: Epithelial cells, P: Prostatic stroma.

Combination of Flavonoid and Saponin Treatments



Photomicrograph Analysis (H&E, x100 Magnification)

Section 4: Photomicrograph illustrates the histological evaluation of prostate tissue from the group receiving both flavonoid fractions from Cyperus esculentus and saponin fractions from Phoenix dactylifera. The glandular architecture shows moderate dysplastic changes similar to the flavonoid-only treatment group, emphasizing the persistent loss of luminal cells and accompanying alterations in morphology, characterized by mild nuclear atypia (EC). The basal cell layer exhibits slight disorganization with indications of increased cell proliferation, although the extent of hyperplasia remains notably less than in the Aluminum Chloride treated group. Importantly, there is no significant evidence of stromal hyperplasia or increased fibroblast activity (PS). EC: Epithelial cells, P: Prostatic stroma.

3.2 Discussion

The histological evaluations conducted across the experimental groups provide a comprehensive understanding of the protective effects of flavonoid and saponin fractions from *Cyperus esculentus* (tiger nut) and *Phoenix dactylifera* (date fruit) on prostate health in the context of aluminum chloride-induced toxicity.

In the control group, healthy prostate tissues displayed a well-preserved architecture, indicating normal functional capacity (McNeal, 1988). The luminal cells exhibited consistent morphology with intact nuclear structures, affirming the absence of dysplasia or hyperplasia. This finding underscores the importance of a stable prostatic environment for optimal reproductive health, as the prostate is crucial for producing prostatic fluid which nourishes sperm (Tim Newman, 2023).

Conversely, the Aluminum Chloride treated group (Group B) exhibited pronounced dysplastic changes characteristic of high-grade benign prostatic hyperplasia (BPH). The observed loss of luminal cells, accompanied by nuclear atypia and increased basal cell proliferation, signifies the detrimental impact of aluminum toxicity on prostate architecture (Dermer, 1978; Goncalves et al., 2013). The findings align with previous studies that implicate aluminum in the degradation of reproductive functions, highlighting the metal's association with disrupted cellular integrity and potential carcinogenic pathways (Exley & Mold, 2014, Zhao et al., 2024).

The administration of flavonoid fractions from *Cyperus esculentus* resulted in moderate dysplastic changes compared to the Aluminum Chloride group, reflecting a degree of cytoprotection. Luminal cells in this group demonstrated less severe nuclear atypia and preserved morphology. This observation supports the notion that flavonoids possess antioxidant properties that mitigate oxidative stress, facilitating the stabilization of prostatic tissue (Zahra et al., 2024; Ullah et al., 2020). The plant's phytochemicals, particularly flavonoids like quercetin and kaempferol, are known to exert protective effects against cellular damage, which has been substantiated by previous literature (Panche et al., 2016; Hasnat et al., 2024).

Similarly, the saponin fractions from *Phoenix dactylifera* also revealed distinct histological changes, signifying an adaptive response to Aluminum Chloride exposure. While hyperplastic features were noted, they were relatively mild compared to the Aluminum Chloride treated group. These findings are in line with the literature suggesting that saponins exert protective effects on

reproductive health by stabilizing cellular membranes and modulating oxidative stress responses (Zhang et al., 2021; Cui et al., 2020).

The combination treatment of flavonoid and saponin extracts yielded results comparable to the flavonoid-only group, demonstrating a synergistic effect in mitigating aluminum chloride-induced toxicity. The preservation of prostatic architecture, reflected in the slight disorganization and increased cell proliferation, highlights the potential of using natural compounds in conjunction to enhance prostate health (Fontana et al., 2020; Isamoh et al., 2024; Reddy et al., 2024, Umoh et al. 2024).

The absence of significant stromal hyperplasia or increased fibroblast activity across all treated groups indicates that both single and combination treatments effectively stabilize the prostatic environment, potentially mitigating the risk of BPH progression (Lepor, 2011; Ng et al., 2024). This protective mechanism of action emphasizes the importance of identifying antioxidants derived from natural sources as promising therapeutic agents for prostate health (Moriasi et al., 2024; Rago & Agostino, 2023).

4. CONCLUSION

In summary, the findings of this study are consistent with the objectives set forth in the introduction, reaffirming the role of flavonoid and saponin fractions from *Cyperus esculentus* and *Phoenix dactylifera* in protecting against aluminum chloride-induced prostate toxicity. The study highlights the necessity for more extensive research to validate these results and to explore the mechanisms by which these phytochemicals exert their protective effects on prostate health. The implications of this research contribute significantly to the understanding of natural compounds in managing prostate disorders, particularly as concerns over chemical exposures continue to rise in discussions regarding male reproductive health.

Ethical Approval

Ethical approval for the study was granted by the Faculty Animal Research Ethics Committee of the Faculty of Basic Medical Sciences, University of Calabar, under approval number 241ANA2723.

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