

The Effect of High-Dose Paracetamol on Thyroid Gland Morphometry; Animal Experiment

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Abstract

Objective: The present study aimed to investigate the histomorphological alterations induced by high-dose acetaminophen administration on the thyroid gland and trachea in rats, and to comparatively examine the protective efficacy of Vaccinium arctostaphylos (VA) fruit extract versus N-acetylcysteine (NAC).

Materials and Methods: A total of 40 male Wistar albino rats were randomly assigned to five equal groups (n=8/group): Control, Acetaminophen (PCM; 2 g/kg), PCM + N-acetylcysteine (NAC; 140 mg/kg), PCM + Vaccinium arctostaphylos extract (VA; 250 mg/kg), and PCM + VA (500 mg/kg). Treatments were administered via oral gavage. After 24 hours, the thyroid gland and trachea were excised following euthanasia under high-dose anesthesia. Tissue sections (5 µm) were stained with hematoxylin-eosin and evaluated histomorphologically using a semi-quantitative scoring system. Intergroup variations were analyzed using the Kruskal-Wallis test followed by Dunn's post-hoc test with Bonferroni correction (p < 0.05).

Results: High-dose paracetamol (PCM) administration induced severe tissue damage, characterized by widespread disruption of thyroid follicular architecture (2.25 ± 0.43), decreased colloid density, and variable increases in follicular epithelial cell height. Additionally, significant tracheal alterations, including pseudostratified ciliated epithelial desquamation and tracheitis (moderate in 62.5% and severe in 37.5% of rats), were observed. In contrast, the PCM + VA (500 mg/kg) and PCM + NAC groups demonstrated complete preservation of thyroid follicular regular round-oval morphology and tracheal epithelial integrity, showing no significant differences compared to the Control group (p = 1.000, score: 0.00 ± 0.00). However, the lower dose of VA (250 mg/kg) failed to exhibit a significant protective effect, resulting in persistent follicular disruption and moderate tracheitis comparable to the PCM-only group (p = 1.000).

Conclusion: High-dose paracetamol induces concurrent, severe histomorphological damage in both the thyroid gland and trachea, highlighting their vulnerability to systemic toxic stress due to close anatomical proximity. A 500 mg/kg dose of Vaccinium arctostaphylos fruit extract provides histomorphological protection comparable to N-acetylcysteine, whereas the 250 mg/kg dose is insufficient. These findings demonstrate a clear dose-dependent efficacy and suggest that VA extract holds strong therapeutic potential as a natural antioxidant counteracting paracetamol-induced organ toxicity.

Keywords: Acetaminophen, Acetylcysteine, Antioxidants, Rats, Wistar, Thyroid Gland, Trachea, Vaccinium arctostaphylos

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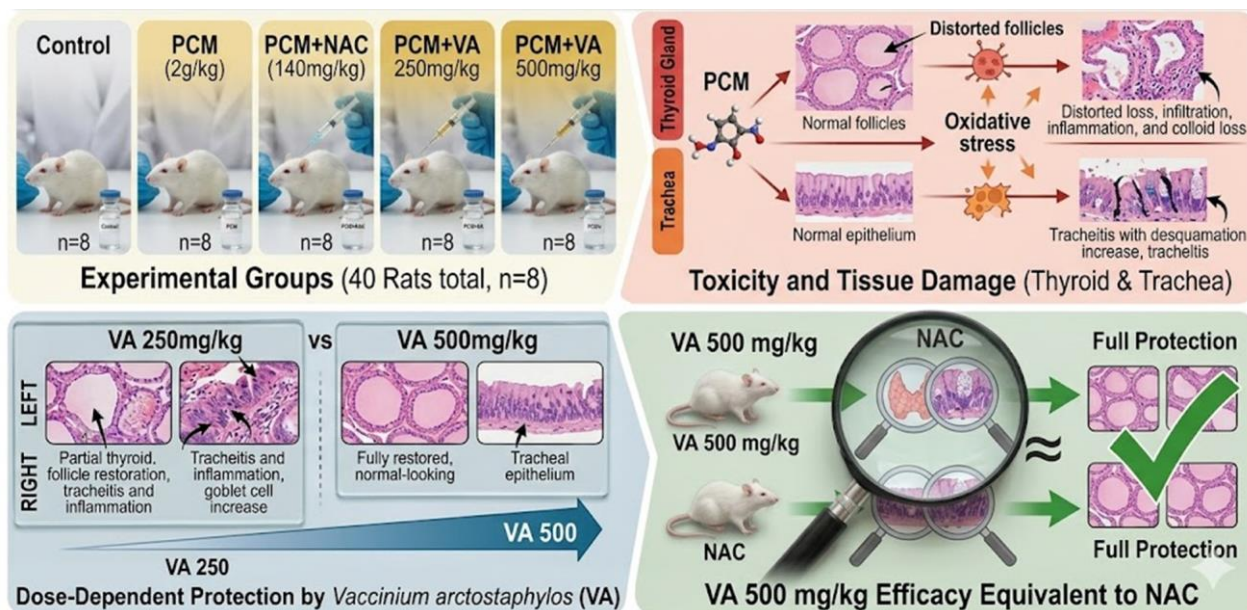
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Graphical Abstract



Highlights

- High-dose paracetamol induces concurrent histopathological damage in both the rat thyroid gland and trachea.
- Acetaminophen toxicity causes thyroid follicular disruption, colloid depletion, and severe tracheitis.
- *Vaccinium arctostaphylos* (VA) fruit extract exhibits a distinct dose-dependent protective effect.
- At 500 mg/kg, VA extract provides tissue preservation comparable to the standard antidote, N-acetylcysteine.
- The lower dose of VA extract (250 mg/kg) is insufficient to prevent paracetamol-induced organ damage.

INTRODUCTION

The thyroid gland is a bilobulated endocrine organ located in the cervical region, positioned between the second and fourth tracheal cartilaginous rings. In humans, the gland weighs approximately 20–30 grams and consists of two lateral lobes connected by an isthmus. Its vascular supply is derived from the superior and inferior thyroid arteries (1,2). Due to its high metabolic activity and the production of endogenous hydrogen peroxide by the follicular epithelium, the thyroid gland is particularly susceptible to oxidative stress, creating substantial demands on its antioxidant defense systems. Histologically, the gland is composed of colloid-containing follicles. Follicular epithelial cells, or thyrocytes, are responsible for the synthesis and storage of thyroid hormones, while parafollicular C cells reside within the interfollicular connective tissue (3). The structural integrity of these follicles—characterized by uniform cuboidal epithelium, dense eosinophilic colloid content, and a balanced interfollicular connective tissue matrix—serves as an indicator of both the functional and anatomical health of the gland. Furthermore, this close topographical relationship with the respiratory tract suggests that pathological processes originating in the thyroid tissue may concurrently alter the structure of the adjacent trachea (4).

Paracetamol (acetaminophen, PCM) is a widely utilized analgesic and antipyretic drug globally. It remains a preferred choice across all age groups due to its over-the-counter availability and established safety profile at therapeutic doses. However, acute or unintentional overdose precipitates severe organ toxicity (5). Previous studies have confirmed that toxic doses of PCM induce significant oxidative stress and subsequent structural damage across various tissues (6,7). N-acetylcysteine (NAC) is effectively utilized as the standard antidote to counteract paracetamol toxicity, and its protective efficacy has been well documented in empirical models (7,8).

Experimental designs evaluating the organ-protective potential of plant-derived antioxidants against PCM-induced toxicity have highlighted the therapeutic value of various natural extracts and bioactive compounds (9,10). *Vaccinium arctostaphylos* (VA), a plant species native to the Eastern Black Sea Region, exhibits potent antioxidant and anti-inflammatory properties (11). These effects are primarily attributed to its rich polyphenolic profile, which includes high concentrations of anthocyanins, flavonoids, and phenolic acids. Since the thyroid gland maintains elevated antioxidant demands to mitigate the hydrogen peroxide generated during hormone synthesis (3), the specific polyphenolic constituents of VA—particularly its anthocyanins and flavonoids—may be uniquely suited to counteract oxidative damage within the thyroid tissue (11). Consequently, this fruit has been integrated into traditional medicine practices across various regions (12–14).

The present study aimed to evaluate the histomorphological alterations occurring in both the thyroid gland and the trachea within an experimental rat model of high-dose PCM toxicity, while comparatively investigating the protective efficacy of VA fruit extract against standard NAC therapy.

MATERIAL and METHODS

Experimental Animals and Groups

Before starting the study, approval was obtained from the Giresun University Local Ethics Committee for Animal Experiments (approval date: 11.12.2025, decision number: 2025/14). In the study, 40 male Wistar albino rats, 10–12 weeks old and weighing 250–300 g, were used. The animals were fed *ad libitum* with standard rat pellet feed and tap water in rooms where the temperature (20–22°C) and humidity (60±5%) were controlled and a 12-hour light/12-hour dark cycle was maintained. After a one-week acclimatization period, the animals were randomly divided into five groups (n=8).

Group I (Control): 2 ml of phosphate-buffered saline (PBS) (containing 1% carboxymethylcellulose (CMC)) was administered via oral gavage.

Group II (PCM): 2 g/kg paracetamol solution was administered via oral gavage (2 ml) (9).

Group III (PCM +NAC): 140 mg/kg NAC was administered orally, followed by 2 g/kg PCM via oral gavage one hour later.

Group IV (PCM +VA 250): 250 mg/kg VA extract was administered orally, followed by 2 g/kg PCM via oral gavage one hour later.

Group V (PCM +VA 500): 500 mg/kg VA extract was administered orally, followed by 2 g/kg PCM via oral gavage one hour later.

Preparation of *Vaccinium arctostaphylos* Extract

VA fruits were obtained from a legal vendor in dried packages. They were ground in appropriate quantities and treated with methanol for 7 days. After removing the solvent in a rotary evaporator, the resulting crude extract was diluted to the desired concentrations in physiological saline and made ready for use (15).

Tissue Collection and Histomorphological-Pathological Preparation

24 hours after all procedures were completed, the animals were sacrificed under high-dose anesthesia (Ketamine 160 mg/kg + Xylazine 30 mg/kg, intraperitoneal). The cervical region was explored, and the thyroid gland and trachea were excised together, preserving their anatomical proximity. They were fixed in 10% buffered formaldehyde solution. The samples were washed in running water for 12 hours and placed in a tissue processing device (Leica TP1020) for routine tissue processing. For this purpose, the samples were passed through 50%, 70%, 80%, 96%, absolute alcohol, and xylene, respectively; they were kept in each solution twice for two hours each time. Following the routine tissue processing, the samples were embedded in paraffin blocks in a tissue embedding device (Leica EG1150H). After the paraffin blocks were left in the refrigerator overnight, 5 µm thick sections were taken onto slides using a microtome (Leica RM 2125 RTS) (16).

Histomorphological-pathological evaluation and scoring

Preparations were evaluated twice at different times by the researcher under a light microscope at 40X, 100X, and 400X magnifications. Histomorphological evaluations were performed in a blinded fashion; the evaluator was masked to the experimental group assignments during tissue examination. Five randomly selected areas were examined from each preparation. For the thyroid gland, follicular architectural integrity, follicular epithelial character, colloid density, and presence of mononuclear inflammatory cell infiltration were evaluated; for the trachea, pseudostratified ciliated epithelial integrity, basal membrane continuity, lamina propria, and submucosal inflammatory cell infiltration were evaluated.

The degree of damage was assessed using a semi-quantitative scoring system (17). In this system, the absence of any observed findings was rated as negative (-), mild changes in limited areas as positive (+), moderately significant changes in wider areas as positive (++), and the presence of widespread to severe changes as positive (+++).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (v25.0; IBM Corp., Armonk, NY, USA) software. Since histomorphological scores are on an ordinal scale, the non-parametric Kruskal-Wallis H test was preferred for intergroup comparisons. In cases where the Kruskal-Wallis test yielded significant results ($p < 0.05$), pairwise comparisons were carried out using the Dunn post-hoc test with Bonferroni correction. Results were expressed as median and mean $\pm$ standard deviation (SD). The statistical significance level was set at $p < 0.05$. The symbol (*) was used for $p < 0.05$, (**) for $p < 0.01$, and (***) for $p < 0.001$.

RESULTS

Control group

Histological examination of the thyroid gland in the control group revealed regular, round-to-oval follicular morphology with lumens well-filled with eosinophilic colloid in six out of eight animals (75%).

The follicular epithelium consistently maintained its single-layered cuboidal character, and the interfollicular connective tissue appeared architecturally normal. Tracheal evaluation showed a luminal surface lined with intact pseudostratified ciliated prismatic epithelium, a continuous basement membrane, and a lamina propria composed of normal loose connective tissue. Additionally, submucosal goblet cell distribution and the C-shaped tracheal cartilage rings remained within physiological limits. While the overall histological architecture of this group was largely unremarkable, mild (+) mononuclear inflammatory cell infiltration was noted within the lamina propria and the immediate tracheal vicinity in two animals (25%). The mean mononuclear inflammatory cell infiltration score for the thyroid gland in the control group was calculated as 0.25 ± 0.43 (Figure 1C).

PCM Group (2 g/kg)

Concomitant evaluation of the thyroid and tracheal histomorphology in the PCM group (2 g/kg) demonstrated significant tissue damage and robust inflammatory alterations in all animals (100%) across both organs. Within the thyroid gland, widespread disruption of the follicular architecture (Mean $\pm$ SD: 2.25 ± 0.43), marked depletion of colloid density, and variable increases in follicular epithelial cell height were observed. Subcapsular edema was detected alongside dense mononuclear inflammatory cell infiltration within the parafollicular and interfollicular connective spaces. Tracheal specimens revealed extensive desquamation and loss of integrity in the pseudostratified ciliated epithelial layer, widespread mononuclear inflammatory cell infiltration in the lamina propria, submucosal edema, a prominent increase in goblet cell count, and dense inflammatory cell accumulation at the perichondrium level. Based on the severity of tracheitis, moderate (++) inflammation was graded in five animals (62.5%), while severe (+++) tracheitis was observed in the remaining three animals (37.5%) (Figure 1A).

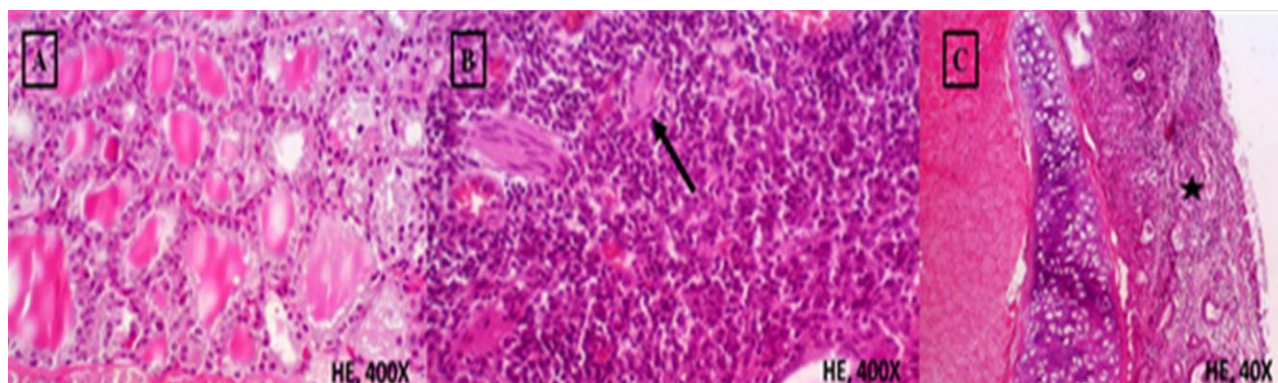


Figure 1. Histomorphological appearance of thyroid gland and trachea tissues. A- Control group; normal healthy thyroid gland, Hematoxylin-Eosin (HE) staining, $\times 400$. B- PCM group; mononuclear inflammatory cell infiltration in trachea (arrow, Tracheitis), HE staining, $\times 400$. C- PCM + VA 250 mg/kg group; mononuclear inflammatory cell infiltration in trachea (asterisk, Tracheitis), HE staining, $\times 40$.

PCM + NAC Group (140 mg/kg)

In the PCM + NAC co-treatment group, the structural integrity of both the thyroid gland and the trachea was fully preserved, presenting a histomorphological appearance indistinguishable from the control group. The thyroid follicles exhibited a regular architecture with dense colloid content, and the cuboidal character of the follicular epithelium was completely retained across all animals (100%). Interfollicular connective tissues showed no signs of mononuclear inflammatory cell infiltration or edema, yielding a mean damage score of 0.00 ± 0.00 . Similarly, the tracheal evaluation confirmed an intact pseudostratified ciliated epithelial layer, a continuous basement membrane, and the complete resolution of submucosal edema and lamina propria inflammation, while the tracheal cartilage rings maintained their normal physiological C-shaped arrangement.

PCM + VA Group (250 mg/kg)

Co-administration of the lower dose of VA extract (250 mg/kg) failed to mitigate tissue injury, resulting in persistent, moderate (++) inflammatory alterations in both organs across all animals (100%; Mean $\pm$ SD: 2.00 ± 0.00). Thyroid specimens displayed prominent follicular epithelial irregularity and substantial mononuclear inflammatory cell infiltration within the interfollicular spaces. Tracheal examination revealed focal zones of epithelial separation within the pseudostratified ciliated layer, accompanied by mucosal edema and mononuclear inflammatory cell infiltration in the lamina propria (**Figure 1B**).

PCM + VA Group (500 mg/kg)

In contrast, co-treatment with the higher dose of VA extract (500 mg/kg) successfully maintained tissue integrity in both organs, showing total alignment with the healthy control architecture. The thyroid follicular architecture remained strictly regular in all animals (100%), featuring intact colloid content and normal cuboidal epithelial morphology, resulting in a mean damage score of 0.00 ± 0.00 . Tracheal specimens demonstrated complete preservation of the pseudostratified ciliated epithelium and basement membrane continuity. No signs of edema or mononuclear inflammatory cell infiltration were detected in the lamina propria or submucosa, goblet cell distribution remained within physiological parameters, and the tracheal cartilage rings retained their normal morphology.

Statistical Findings

The Kruskal-Wallis H test revealed a statistically highly significant difference among the experimental groups regarding thyroid gland histomorphological scores ($H = 36.114$, $p < 0.001$). Pairwise comparisons via Dunn's post-hoc test with Bonferroni correction indicated that the histomorphological damage score of the PCM group was significantly elevated compared to the Control ($p = 0.0026$), PCM + NAC ($p < 0.001$), and PCM + VA 500 ($p < 0.001$) groups. The histomorphological scores of the PCM + VA 250 group did not differ significantly from the PCM group ($p = 1.000$); however, they were significantly higher than those of both the PCM + NAC and PCM + VA 500 groups ($p = 0.0012$). The semi-quantitative histomorphological findings are comprehensively summarized in **Tables 1 and 2**.

Table 1. Summary of histomorphological findings of the thyroid gland and trachea by group.

Group	n	Thyroid Gland	Trachea
Control	8	Normal follicular architecture (75%); mild mononuclear inflammatory cell infiltration + (25%)	Normal epithelium (75%); mild tracheitis+ (25%)
PCM (2 g/kg)	8	mononuclear inflammatory cell infiltration +, follicular structural disruption (100%)	Tracheitis++ (62.5%); Tracheitis+++ (37.5%)
PCM + NAC (140 mg/kg)	8	Normal follicular architecture (100%)	Normal tracheal epithelium (100%)
PCM + VA (250 mg/kg)	8	Follicular disruption, mononuclear inflammatory cell infiltration + (100%)	Tracheitis++ (100%)
PCM + VA (500 mg/kg)	8	Normal follicular architecture (100%)	Normal tracheal epithelium (100%)

Mononuclear inflammatory cell infiltration. (+): Mild, (++) Moderate, (+++): Severe.

Table 2. Summary of thyroid gland histomorphological scores

Group	n	Mean $\pm$ SD	According to Control p	Compared to PCM p
Control	8	0.25 ± 0.43	—	0.0026**
PCM (2 g/kg)	8	2.25 ± 0.43	0.0026**	—
PCM + NAC	8	0.00 ± 0.00	1.000 ns	<0.001***
PCM + VA 250 mg/kg	8	2.00 ± 0.00	0.0108*	1.000 ns
PCM + VA 500 mg/kg	8	0.00 ± 0.00	1.000 ns	<0.001***

Mean: Mean; SD: Standard deviation; ns: Not statistically significant;

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Kruskal-Wallis: $H = 36.114$, $p < 0.001$.

DISCUSSION

In this study, high doses of paracetamol significantly disrupted the follicular architecture of the thyroid gland and the integrity of the tracheal epithelium in rats, while a dose of 500 mg/kg of VA fruit extract prevented this damage to a comparable degree to NAC. In PCM toxicity, NAPQI accumulation leads to the overproduction of reactive oxygen species (ROS) by depleting glutathione reserves (10). This damage mechanism is consistent with the follicular architecture disruption, mononuclear inflammatory cell infiltration, and subcapsular edema findings observed in the PCM group.

The thyroid gland, due to its anatomical location, is the largest endocrine gland in the cervical region and has a direct topographic relationship with the trachea. The gland's rich blood supply, high oxygen consumption, and endogenous hydrogen peroxide produced by the follicular epithelium increase its susceptibility to oxidative stress. These characteristics make the thyroid gland a primary target structure for systemic toxic effects (3,10). In high-dose paracetamol administration, the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI), produced via the cytochrome P450 enzyme system, leads to cellular damage (18,19). Studies investigating the toxic effects of high-dose paracetamol on the thyroid gland have reported cytoplasmic vacuolization in follicular epithelial cells, disruption of follicle and colloid structures, and a significant increase in follicular epithelial height in all PCM groups (20,21). In the present study, the simultaneous observation of follicular architectural disruption, decreased colloid density, increased follicular epithelial cell height, and mononuclear inflammatory cell infiltration findings in the interfollicular space in the PCM group is consistent with the aforementioned literature data. The anatomical proximity of the thyroid and trachea supports the simultaneous involvement of both structures. The simultaneous histomorphological alterations observed in both organs may be attributed to their close anatomical proximity in the cervical region, suggesting that systemic PCM toxicity affects both structures concurrently rather than through direct local spread (22).

VA's rich polyphenolic content is known for its strong free radical scavenging activity (11,15). The fact that VA extract at a dose of 500 mg/kg completely protected the thyroid follicular architecture and tracheal epithelial integrity indicates that this antioxidant capacity is also effective at the histomorphological level. NAC, through its antioxidant mechanism known as glutathione precursor, exhibits a protective effect in many tissues (19,23). Histomorphological scores in both the VA 500 mg/kg and NAC groups were not significantly different from the control group ($p = 1.000$). This indicates that VA at 500 mg/kg provides a protective capacity comparable to that of NAC. The insufficient protective effect of the VA 250 mg/kg dose was demonstrated by the fact that both thyroid gland and tracheal findings were at the same level as the PCM group. This finding suggests that the dose-response relationship is crucial in the protective efficacy of plant antioxidants and is consistent with similar studies (9,24).

Limitations

The study has several main limitations. Quantitative morphometric measurements (follicle diameter, follicular

epithelial height, tracheal epithelial thickness) were not performed using image analysis software. Retrospective morphometric analysis from the available preparations strengthens the anatomical evaluation aspect of the study. In addition, only HE staining was used, and the addition of connective tissue staining and immunohistochemical methods in advanced studies will strengthen the findings. Furthermore, biochemical oxidative stress markers (MDA, SOD, GSH) and thyroid hormone levels (T3, T4, TSH) were not assessed in the present study, which limits the functional interpretation of the histomorphological findings. These parameters should be incorporated in future studies to provide a more comprehensive evaluation.

CONCLUSION

In conclusion, external dacryocystorhinostomy (DCR) remains a highly effective and durable surgical procedure for the management of primary acquired nasolacrimal duct obstruction (PANDO). Evidence from this large-scale cohort of 574 eyes demonstrates that a prior history of dacryocystitis does not adversely influence anatomical or functional success rates, provided that acute inflammation is adequately controlled before surgery. Furthermore, selective rather than routine silicone tube intubation appears sufficient in primary cases, and common systemic comorbidities do not independently increase the risk of failure. From a clinical standpoint, these findings suggest that previous infectious episodes should not be viewed as a negative prognostic indicator, allowing surgeons to proceed with standard surgical planning and optimize patient counseling in routine clinical practice.

Acknowledgement

None.

Conflicts of Interest

None of the authors have any conflict of interest or financial ties to disclose.

Ethical Considerations

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Study was approved by Giresun University Local Ethics Committee for Animal Experiments (approval date: 11.12.2025, decision number: 2025/14).

Authors' Contribution

Conceptualization: AK, ÖAB, İŞ, TA, KF
 Data curation: AK
 Formal analysis: AK
 Funding Acquisition: –
 Investigation: AK, ÖAB, İŞ, TA, KF
 Methodology: AK
 Statistics: AK
 Project administration: AK
 Supervision: AK
 Validation: AK, ÖAB, İŞ, TA, KF
 Visualization: AK, KF
 Writing – original draft: AK, ÖAB, İŞ, TA, KF
 Writing – review & editing: AK

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