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Anti-inflammatory action of fluvoxamine in an endotoxin-induced uveitis rat model: Histopathological evidence

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Purpose: To investigate the potential protective effects of fluvoxamine (FVX), a selective serotonin reuptake inhibitor with known anti-inflammatory properties, on corneal, limbal, and retinal tissues in a rat model of endotoxin-induced uveitis (EIU), clinical and histopathologic evaluations were performed.

Methods: Twenty-eight female Wistar Albino rats were divided into four groups: controls, EIU, EIU + FVX, and FVX (n = 7 per group). EIU was induced by a single intraperitoneal injection of lipopolysaccharide (LPS). FVX or normal saline (NS) was administered 30 min before LPS or NS injection. Clinical ocular inflammation was assessed using slit-lamp biomicroscopy 6 h postinjection. Following euthanasia, enucleated eyes were processed for histopathologic analysis of corneal, limbal, and retinal tissues.

Results: Total corneal and epithelial thickness were measured, while limbal and retinal lesions were semiquantitatively graded. The EIU group exhibited significantly increased clinical ocular inflammation scores compared to the control, EIU + FVX, and FVX groups ($p < 0.0001$ for all). At the microscopical analysis, the EIU group showed significant corneal epithelial thickening, cellular changes, edema, hemorrhage, and increased total corneal thickness compared to the control group ($p < 0.001$). In addition, histopathologic analysis revealed retinal hyperemia and edema in the EIU group but not in the EIU + FVX, FVX, or control groups. Histopathologic scores confirmed significant retinal changes in the EIU group compared to the others ($p < 0.001$).

Conclusions: FVX significantly reduced clinical signs of ocular inflammation and mitigated histopathologic damage in the cornea, limbus, and retina.

Uveitis is an inflammatory condition of the uveal tract that can result in significant visual impairment and is frequently associated with systemic autoimmune or infectious diseases [1]. Epidemiologic studies indicate a substantial disease burden, with reported incidence rates ranging from 17 to 52 per 100,000 individuals and prevalence rates varying from 38 to 714 per 100,000, particularly among young adults [2]. Clinically, uveitis presents with blurred vision, ocular pain, photophobia, and floaters. If left untreated, it may lead to sight-threatening complications such as uveitic glaucoma, cystoid macular edema, retinal neovascularization, and retinal ischemia [1,3].

The eye possesses unique immune-regulatory mechanisms, including the blood-retinal barrier, absence of lymphatic drainage, and anterior chamber–associated immune deviation (ACAID), which collectively help maintain ocular immune privilege [4]. Disruption of these mechanisms can lead to uncontrolled inflammation, although the precise pathophysiology of uveitis remains incompletely understood [4]. Animal models, particularly the endotoxin-induced uveitis (EIU) model, have been instrumental in elucidating disease mechanisms and evaluating potential therapeutic interventions. Intraperitoneal administration of lipopolysaccharide (LPS) triggers an acute inflammatory response characterized by the release of proinflammatory cytokines and chemokines, replicating key features of human uveitis [5]. The EIU model effectively mirrors immune pathways observed in human anterior uveitis and provides a reproducible platform for preclinical drug screening [6,7].

Current management of uveitis primarily relies on corticosteroids during acute phases and immunomodulatory agents for chronic control and relapse prevention [1]. However, long-term corticosteroid use is associated with significant ocular and systemic side effects, including cataract formation, glaucoma, and increased susceptibility to infections. Although immunosuppressants reduce relapse rates, they may also compromise systemic immunity [6,8]. These limitations underscore the need for novel therapeutic

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agents with favorable safety profiles and alternative mechanisms of action [9].

Fluvoxamine (FVX), a selective serotonin reuptake inhibitor (SSRI), is commonly used in the treatment of depression and anxiety disorders. Beyond its neurologic effects, emerging evidence suggests that FVX possesses anti-inflammatory and immunomodulatory properties [10]. Experimental studies have demonstrated its potential to attenuate neuroinflammation in conditions such as traumatic brain injury and multiple sclerosis [11,12]. Proposed mechanisms include suppression of proinflammatory cytokine production, inhibition of inflammatory gene expression, and modulation of microglial/macrophage activity [12]. Additionally, FVX has been shown to interact with glucocorticoid receptors, further supporting its potential role in inflammatory regulation. Despite these promising effects, the therapeutic potential of FVX in uveitis remains unexplored.

Given its anti-inflammatory profile, this study aimed to investigate the protective effects of FVX on corneal, limbal, and retinal tissues in a rat model of EIU using clinical and histopathologic assessments.

METHODS

Animals and ethical approval: Twenty-eight adult female Wistar Albino rats (weight range: 300–350 g) were obtained from the Suleyman Demirel University Experimental Animal Laboratory, Isparta, Turkey. This strain was selected based on its well-established use in EIU models and consistent ocular anatomy that facilitates standardized histopathologic evaluation. The rats were housed under controlled environmental conditions (temperature: 21–22 °C, humidity: 60% ± 5%, 12-h light/dark cycle) with ad libitum access to standard laboratory chow and fresh water. The study protocol was approved by the Suleyman Demirel University Animal Research Ethics Committee (Ethic No: 09.05.2024–06/302) and conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. This research was supported by the Scientific Research Projects Coordination Unit of Suleyman Demirel University (project code: TSG-2021–8304).

EIU model and drug administration: The EIU model was established through a single intraperitoneal (i.p.) injection of LPS (*Escherichia coli* 0111: B4, Sigma-Aldrich, Stockholm, Sweden) at a dose of 5 mg/kg dissolved in 0.5 ml normal saline (NS, 0.9% NaCl), as previously described [13]. FVX (Faverine) was prepared at a concentration of 50 mg/kg in 0.5 ml normal saline. All animals received two i.p. injections administered 30 min apart, with the first injection delivered in the left inguinal region and the second in the right inguinal region.

Rats were randomly assigned to four experimental groups (n = 7 per group):

Control Group: Received normal saline in both the left and right inguinal regions.

EIU Group: Received normal saline in the left inguinal region, followed by LPS in the right inguinal region.

EIU + FVX Group: Received FVX in the left inguinal region, followed by LPS in the right inguinal region.

FVX Group: Received FVX in the left inguinal region, followed by normal saline in the right inguinal region.

Six hours after the final injection, the clinical severity of ocular inflammation was assessed using slit-lamp biomicroscopy by an investigator masked to the treatment groups. Evaluation was performed according to the established clinical scoring system presented in Table 1 [14], which grades iris hyperemia, pupil condition, anterior chamber exudate, and hypopyon formation.

Following clinical evaluation, rats were euthanized under deep anesthesia induced by ketamine (50–80 mg/kg; Bioveta, Ivanovice na Hané, Czech Republic) and xylazine (8–10 mg/kg; Doğa İlaç, Istanbul, Turkey). Both eyes were immediately enucleated and fixed in 10% buffered formalin solution for 24 h.

After fixation, the eyes were processed through standard histologic procedures. The globes were sectioned coronally to obtain representative samples containing corneal, limbal, and retinal tissues. Tissues were dehydrated through graded ethanol series, cleared in xylene, and embedded in paraffin blocks. Sections of 5 µm thickness were cut using a microtome and stained with hematoxylin and eosin (H&E) for histologic examination.

Morphometric analyses were performed using an Olympus CX41 light microscope equipped with the CellSens Life Science Imaging Software System (Olympus Corporation, Tokyo, Japan). Total corneal thickness and corneal epithelial thickness were measured at three predetermined points in the central corneal region for each sample, and average values were calculated. Limbal and retinal tissues were evaluated semiquantitatively by a masked pathologist using the grading system shown in Table 2 [15], which assessed hyperemia, edema, and inflammatory cell infiltration.

Statistical analysis: All data are presented as mean ± standard deviation (SD). Statistical comparisons between groups were performed using one-way analysis of variance (ANOVA),

Table 1. Scoring system for clinical evaluation of uveitis.

Clinical signs	Score	Description
Iris hyperemia	0	Absent
	1	Mild
	2	Moderate
	3	Severe
Pupil	0	Normal
	1	Miosis
Exudate in anterior chamber	0	Absent
	1	Small
	2	Large
Hypopyon	0	Absent
	1	Present

followed by Fisher's least significant difference (LSD) post hoc test for multiple comparisons. GraphPad Prism software (version 10.0; GraphPad Software, La Jolla, CA, USA) was used for all statistical analyses. Differences with $p < 0.05$ were considered statistically significant.

RESULTS

Clinical severity of ocular inflammation: The clinical evaluation of ocular inflammation in rats from all experimental groups was performed using slit-lamp biomicroscopy and scored according to established criteria. As shown in Figure 1, the EIU group exhibited significantly higher clinical scores (4.714 ± 1.380) compared to the control group (0.142 ± 0.378), EIU + FVX group (1.714 ± 0.755), and FVX group (0.285 ± 0.488; $p < 0.0001$ for all comparisons).

Corneal histopathologic findings: Histologic examination of corneal tissues revealed distinct morphologic changes among the experimental groups. The control group demonstrated normal corneal architecture with typical stratified squamous epithelium, stroma, and endothelium (Figure 2A). In contrast, the EIU group showed significant pathologic alterations, including markedly thickened corneal epithelium and epithelial sloughing (arrowhead), stromal edema (arrow), and substantially increased overall corneal thickness (Figure 2B). The EIU + FVX group exhibited notably reduced pathologic changes compared to the EIU group (Figure 2C), while the FVX group displayed corneal morphology comparable to the control group (Figure 2D).

Total corneal thickness: Morphometric analysis revealed significant differences in total corneal thickness between groups (Figure 2). The control group showed an average thickness of 145.00 ± 3.36 µm. The EIU group demonstrated a significant increase in thickness (229.90 ± 4.05 µm; $p < 0.001$ compared to control). The EIU + FVX group exhibited substantially reduced thickness (148.90 ± 3.71 µm; $p < 0.001$ compared to the EIU group), which was not significantly different from the control group ($p > 0.05$). The FVX group (142.70 ± 2.69 µm) showed no significant difference from the control group ($p > 0.05$).

Corneal epithelial thickness: Similar patterns were observed in corneal epithelial thickness measurements (Figure 2). The EIU group showed significantly increased epithelial thickness (59.71 ± 2.28 µm) compared to the control group (53.43 ± 2.37 µm; $p < 0.001$). The EIU + FVX group demonstrated significantly reduced epithelial thickness (53.57 ± 1.27 µm; $p < 0.001$ compared to the EIU group), comparable to control levels. The FVX group (54.29 ± 1.70 µm) showed no significant difference from the control group ($p > 0.05$).

Table 2. Histopathological scores of limbal and retinal tissues.

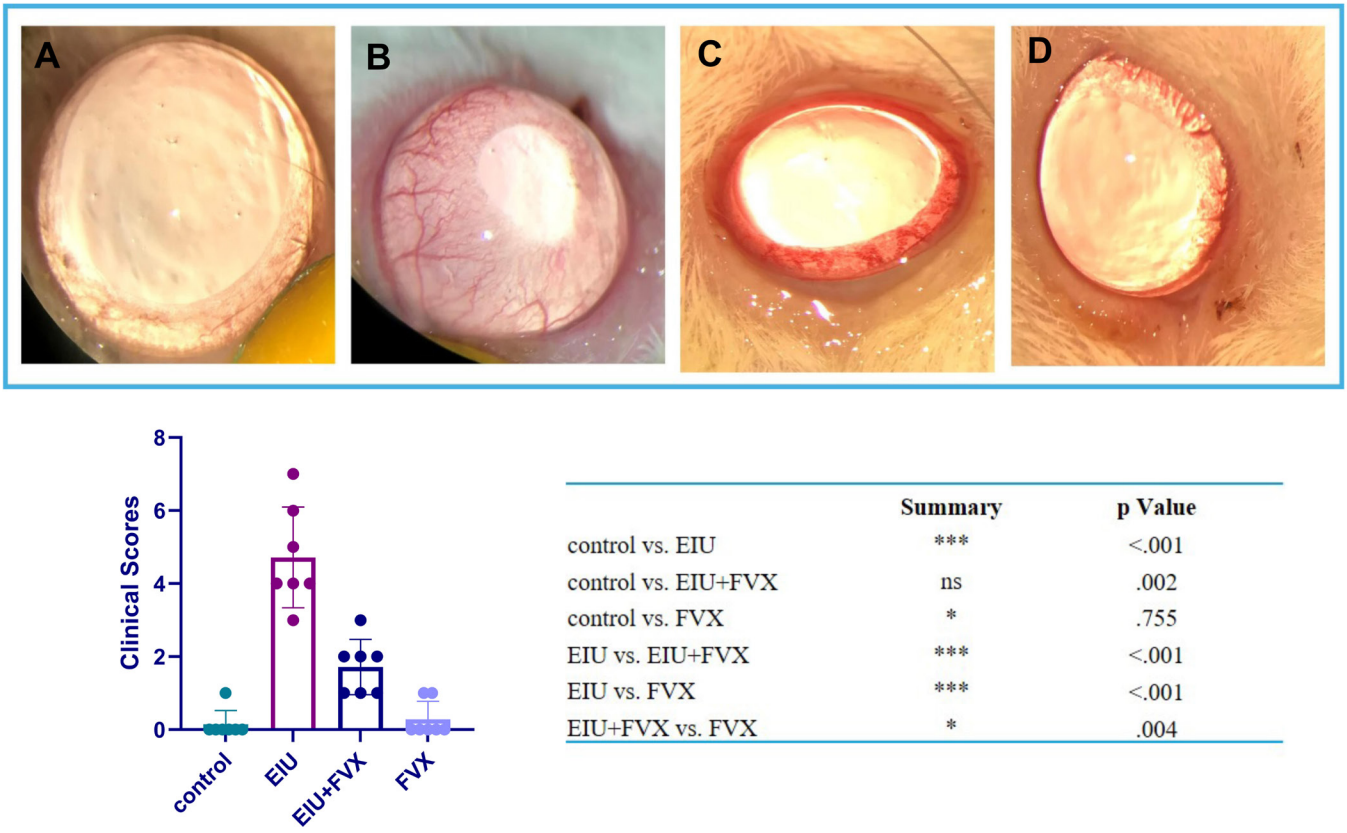
Score	Description
0	Normal tissue histology
1	Slight hyperemia with no edema and inflammation
2	Marked hyperemia
3	Edema, and inflammatory cell infiltrations

Limbal histopathologic findings: Histologic examination of the limbal region revealed normal tissue architecture with no signs of inflammation in both the control and FVX groups (Figure 3A, D). In contrast, the EIU group exhibited severe pathologic changes, including pronounced hyperemia (dilated and congested vessels), stromal edema, and dense inflammatory cell infiltration (arrow; Figure 3B). These alterations were markedly attenuated in the EIU + FVX group, which showed only mild hyperemia and minimal inflammatory changes (Figure 3C).

Semiquantitative scoring of limbal lesions (assessing hyperemia, edema, and inflammatory cell infiltration) demonstrated a statistically significant increase in the EIU group compared to the control group ($p < 0.001$). Both the EIU + FVX and FVX groups exhibited significantly lower scores compared to the EIU group ($p < 0.001$). No significant differences were observed between the control and EIU + FVX groups ($p > 0.05$), the control and FVX groups ($p > 0.05$), or the EIU + FVX and FVX groups ($p > 0.05$; Figure 3).

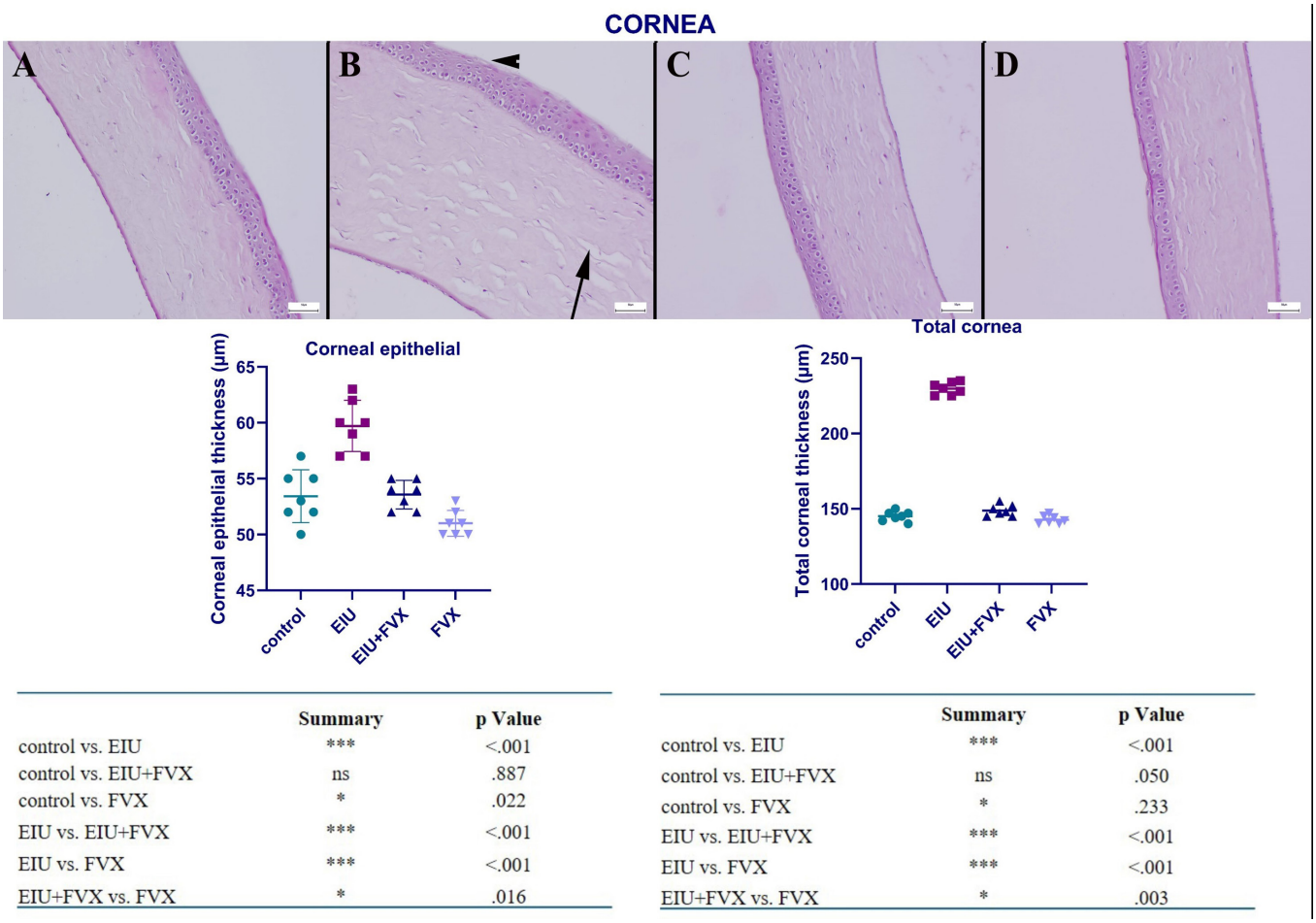
Retinal tissue analysis showed preserved morphology in the control and FVX groups (Figure 4A, D). The EIU group displayed significant retinal hyperemia and edema, with noticeable thickening of the inner plexiform layer (Figure 4B). These pathologic features were substantially reduced in the EIU + FVX group, although mild inner plexiform layer thickening persisted in some specimens (Figure 4C). Additionally, careful examination revealed subtle architectural irregularities in the inner and outer nuclear layers in some FVX group samples, although these changes were inconsistent and did not reach statistical significance.

Semiquantitative evaluation of retinal lesions (hyperemia and edema) revealed a statistically significant increase in the EIU group compared to the control group ($p < 0.001$). Both the EIU + FVX and FVX groups showed significantly improved scores compared to the EIU group ($p < 0.001$), with no significant differences between control, EIU + FVX, and FVX groups ($p > 0.05$; Figure 4).



	Summary	p Value
control vs. EIU	***	<.001
control vs. EIU+FVX	ns	.002
control vs. FVX	*	.755
EIU vs. EIU+FVX	***	<.001
EIU vs. FVX	***	<.001
EIU+FVX vs. FVX	*	.004

Figure 1. FVX attenuates anterior segment inflammation in the EIU model. Slit-lamp biomicroscopy images showing: (**A**) Control group (NS + NS); (**B**) EIU group (NS + LPS); (**C**) EIU+FVX group (FVX + LPS); (D) FVX group (FVX + NS). FVX: fluvoxamine; EIU: endotoxin-induced uveitis; NS: normal saline; LPS: lipopolysaccharide. Scale bars=100 µm. *p<0.001.



	Summary	p Value
control vs. EIU	***	<.001
control vs. EIU+FVX	ns	.887
control vs. FVX	*	.022
EIU vs. EIU+FVX	***	<.001
EIU vs. FVX	***	<.001
EIU+FVX vs. FVX	*	.016

	Summary	p Value
control vs. EIU	***	<.001
control vs. EIU+FVX	ns	.050
control vs. FVX	*	.233
EIU vs. EIU+FVX	***	<.001
EIU vs. FVX	***	<.001
EIU+FVX vs. FVX	*	.003

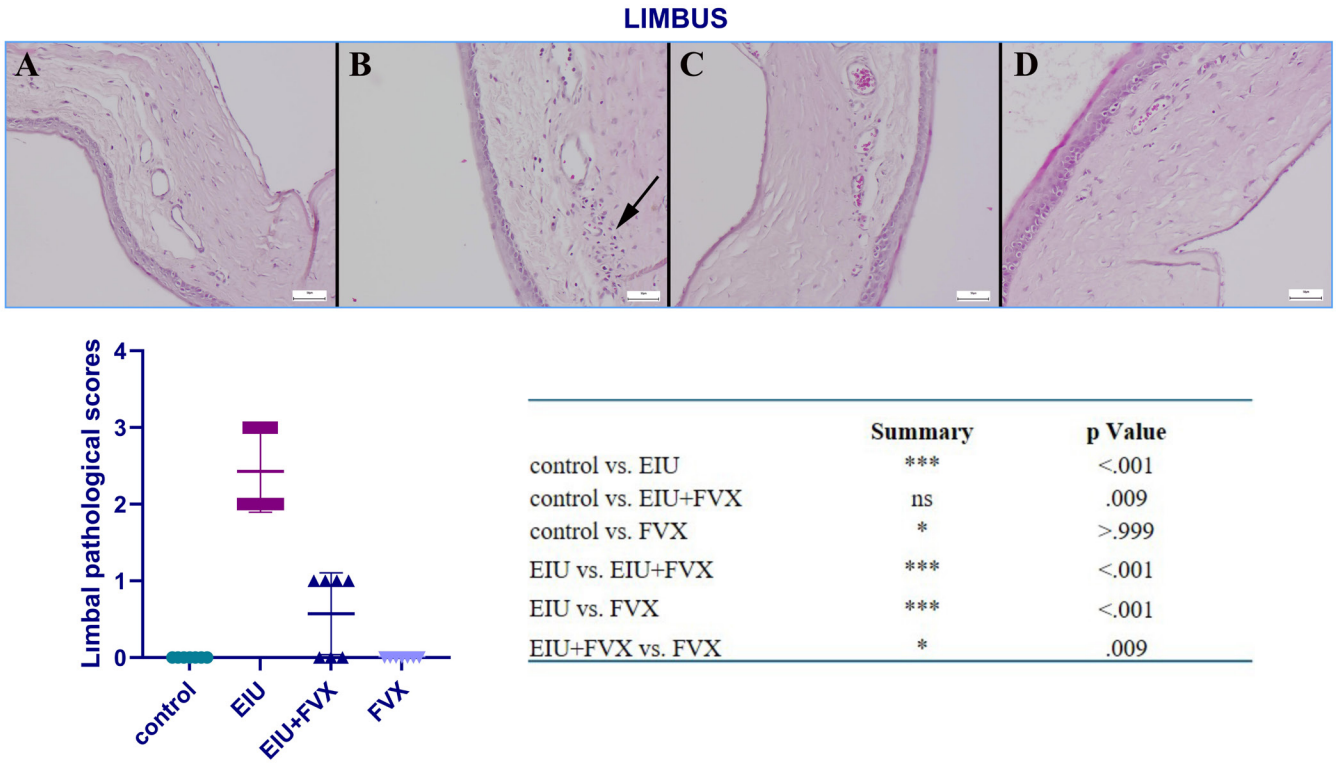
Figure 2. Corneal histopathological findings. **A**: Control group showing normal structure; (**B**) EIU group with epithelial thickening (double arrow), stromal edema and separation (arrow); (**C**) EIU+FVX group with reduced pathology; (**D**) FVX group with normal morphology. Ep: epithelium; St: stroma; En: endothelium. HE staining. Scale bars=50 µm. *p<0.01.

DISCUSSION

Uveitis, a sight-threatening inflammatory condition of the uveal tract, presents significant challenges in both understanding its complex pathogenesis and developing effective treatments [3]. Animal models, particularly the EIU model, have been instrumental in elucidating disease mechanisms and evaluating potential therapeutic agents [16]. Our study used this well-established model, where a single intraperitoneal injection of LPS triggers acute ocular inflammation characterized by leukocyte adhesion to iris microvasculature within 2 h [17] and increased protein leakage into the anterior chamber [18,19], effectively mirroring key aspects of human anterior uveitis [20].

While corticosteroids remain the mainstay of uveitis treatment, their chronic use is associated with significant ocular and systemic side effects, including cataract formation, glaucoma, diabetes, and hypertension [9]. These limitations underscore the urgent need for alternative anti-inflammatory therapies with improved safety profiles.

FVX, primarily known as an SSRI, has recently emerged as a promising anti-inflammatory candidate. The mechanism underlying FVX's immunomodulatory effects appears multifaceted. Human peripheral blood mononuclear cells express serotonin and norepinephrine transporters [19,21], and antidepressants may directly influence these cells [22,23]. Furthermore, serotonin and noradrenaline released from lymphocytes and monocytes can exert immunomodulatory effects through receptors present on immune cells [24]. FVX has been shown to reduce proinflammatory cytokine-induced PGE2 and nitric oxide production [25], both of which are elevated in ocular inflammation [26]. Additionally, FVX demonstrates glucocorticoid receptor activity [27] and suppresses expression of key inflammatory genes, including intercellular adhesion molecule-1 (ICAM-1), vascular cell



	Summary	p Value
control vs. EIU	***	<.001
control vs. EIU+FVX	ns	.009
control vs. FVX	*	>.999
EIU vs. EIU+FVX	***	<.001
EIU vs. FVX	***	<.001
EIU+FVX vs. FVX	*	.009

Figure 3. Limbal histopathological evaluation. **A**: Control with normal architecture; (**B**) EIU group showing inflammatory cell infiltration (arrow); (**C**) EIU+FVX group with mild hyperemia; (**D**) FVX group with normal histology. HE staining. Scale bars=50 µm. *p<0.01.

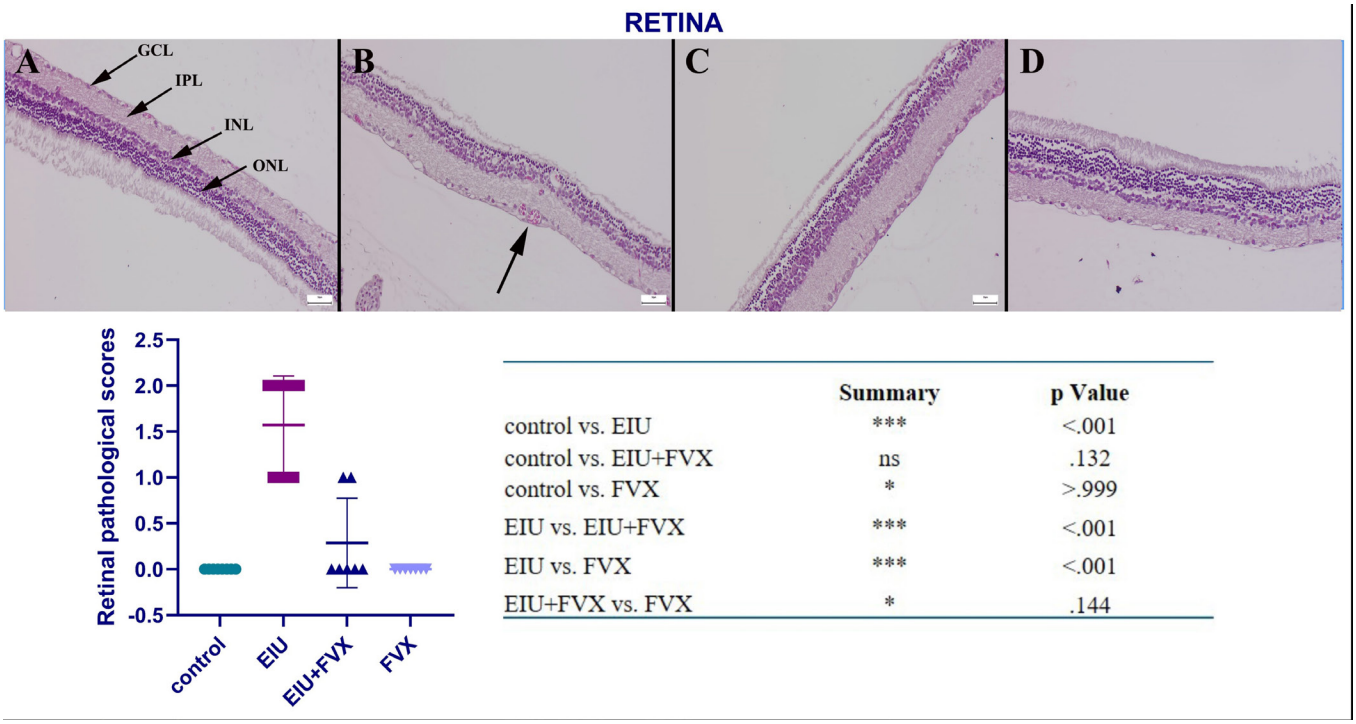
adhesion molecule-1 (VCAM-1), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS), in various experimental models [23,28].

To our knowledge, this study is the first to demonstrate the protective effects of FVX against EIU through comprehensive clinical and histopathologic evaluation. Our findings align with previous research showing FVX's anti-inflammatory properties in diverse contexts. In traumatic brain injury models, FVX inhibited peripheral immune cell infiltration and promoted the polarization of microglia/macrophages toward an anti-inflammatory phenotype [29]. Similarly, in multiple sclerosis models, FVX alleviated inflammation and demyelination [30]. These consistent findings across different disease models strengthen the evidence for FVX's broad anti-inflammatory properties.

Our results demonstrate that FVX pretreatment significantly attenuated clinical signs of ocular inflammation and mitigated histopathologic damage in corneal, limbal, and retinal tissues. Specifically, FVX reduced LPS-induced corneal thickening, epithelial changes, limbal hyperemia, edema, inflammatory cell infiltration, and retinal abnormalities. The therapeutic effects of FVX were evident in both anterior and posterior segment tissues, suggesting a comprehensive protective action against EIU.

Histopathologic examination revealed important morphologic alterations in retinal tissues across experimental groups. The EIU group exhibited significant thickening of the inner plexiform layer in addition to hyperemia and edema. While FVX treatment substantially attenuated these pathologic changes, mild thickening persisted in some EIU + FVX specimens, suggesting either a dose–response relationship or potential need for optimized treatment protocols. Furthermore, careful analysis revealed subtle architectural irregularities in both inner and outer nuclear layers in some FVX group samples, although these changes did not reach statistical significance in our semiquantitative assessment. These observations highlight the importance of further investigating both the therapeutic potential and possible ocular effects of FVX using more sensitive analytical methods.

Despite these promising findings, our study has several limitations that should be addressed in future research. First, we evaluated FVX effects at only a single time point (6 h postinjection). Examination at multiple time points would provide a more comprehensive understanding of the temporal



	Summary	p Value
control vs. EIU	***	<.001
control vs. EIU+FVX	ns	.132
control vs. FVX	*	>.999
EIU vs. EIU+FVX	***	<.001
EIU vs. FVX	***	<.001
EIU+FVX vs. FVX	*	.144

Figure 4. Retinal histopathological analysis. **A**: Control group showing normal retinal architecture with distinct layers: GCL (ganglion cell layer), IPL (inner plexiform layer), INL (inner nuclear layer), ONL (outer nuclear layer); (**B**) EIU group exhibiting marked hyperemia (solid arrow) and edema with noticeable thickening of the inner plexiform layer (dashed arrow); (**C**) EIU+FVX group with attenuated pathological changes; (**D**) FVX group showing largely normal retinal architecture. HE staining. Scale bars=50 µm. *p<0.01.

dynamics of FVX's therapeutic effects. Second, the therapeutic potential of FVX administered after the induction of uveitis (rather than as a pretreatment) remains unknown and represents a crucial area for future investigation. Third, comparative studies evaluating the efficacy of FVX against conventional therapies such as corticosteroid or nonsteroidal anti-inflammatory eye drops would be highly valuable in defining its potential clinical role. Fourth, while no significant toxicity was observed with FVX treatment alone based on our histopathologic scoring, a more meticulous analysis for subtler signs of toxicity (e.g., using electron microscopy or specific apoptotic markers) should be considered in future work to comprehensively establish the safety profile of FVX in ocular tissues. Finally, as our findings are limited to the EIU rat model, further clinical investigations are necessary to determine the potential applicability of FVX in human patients with uveitis.

In conclusion, our study provides compelling evidence that FVX exerts significant protective effects against EIU in rats, reducing both clinical signs of inflammation and histopathologic damage across multiple ocular tissues. These findings support the potential therapeutic value of FVX in uveitis management and warrant further investigation into its mechanisms of action and clinical applications.

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