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PROTECTIVE EFFECTS OF SELENIUM SUPPLEMENTATION AGAINST HIGH FRUCTOSE CORN SYRUP-INDUCED RETINAL DAMAGE IN RATS THROUGH REDUCTION OF INFLAMMATION AND APOPTOSIS

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Abstract

***Introduction*:** High fructose corn syrup (HFCS) consumption is associated with metabolic complications such as retinopathy. This study aimed to investigate the potential protective effects of selenium (Se) against HFCS-induced retinal damage.

Methods: Forty Wistar albino rats were divided into four groups (n=7 each): (I) control; (II) high fructose corn syrup (HFCS, 20% in diet); (III) HFCS + Se (20% in diet, 0.3 mg/kg orally); and (IV) Se only. After six weeks, retinal damage was thoroughly assessed using histopathological and immunohistochemical analyses. Histopathological assessment focused on retinal thickness measurements, whereas immunohistochemical analyses quantified the expression of tumor necrosis factor-α (TNF-α) and Caspase-3 (Cas-3), key markers of inflammation and apoptosis, respectively. Statistical analysis was performed using one-way ANOVA (Fisher's LSD), with results expressed as mean ± SD, and a p-value of <0.05 was considered statistically significant.

***Results*:** Histopathological findings revealed a significant increase in retinal thickness in the HFCS group (288.6 ± 25.37 µm) compared to that in the control group (84.43 ± 5.79 µm). Notably, the HFCS+Se group exhibited a significantly reduced average retinal thickness (180.1 ± 27.08 µm) compared with the HFCS group ($p<0.0001$). Immunohistochemical analysis showed a significant increase in TNF-α expression in the HFCS group compared to that in the control and Se groups ($p<0.01$), although the decrease in the HFCS+Se group was not statistically significant compared to that in the HFCS group ($p>0.05$). Furthermore, Caspase-3 expression was significantly elevated in the HFCS group compared to that in the control and Se groups ($p<0.001$ for both). Importantly, Caspase-3 expression was significantly decreased in the HFCS+Se group compared to that in the HFCS group ($p<0.01$).

Conclusion: Selenium supplementation partially protects against HFCS-induced retinal damage in rats, primarily by significantly mitigating increased retinal thickness and reducing apoptosis, as evidenced by the decreased Caspase-3 expression. Although TNF-α levels showed a trend of reduction with Se, this change was not significant. These findings highlight the potential therapeutic role of selenium in preventing or ameliorating HFCS-induced ocular complications.

Keywords: High fructose corn syrup, Retinal damage, Selenium, TNF-α, Caspase-3. **Cite This Article:** USTA, Gulsah et al. Selenium Supplementation Attenuates High Fructose Corn Syrup-Induced Retinal Damage in Rats. **International Journal of Retina**, [S.l.], v. 8, n. 2, sep. 2025. ISSN 2614-8536. Available at: <https://www.ijretina.com/index.php/ijretina/article/view/301>. Date accessed: 30 sep. 2025. doi: https://doi.org/10.35479/ijretina.2025.vol008.iss002.301...

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INTRODUCTION

Retinopathy, a condition that can significantly impair visual acuity and arises from microvascular damage associated with Metabolic Syndrome (MetS), is recognized as a component of systemic abnormalities.[1,2] The global rise in the consumption of high fructose corn syrup (HFCS) products has been correlated with an increased prevalence of insulin resistance and diabetes, which are critical components of MetS.[3,4] Research indicates that MetS, which affects approximately 35% of the American population, serves as the primary determinant of diabetes mellitus, a condition associated with alterations in the retinal blood vessels.[5]

Specifically, experimental studies have shown that excessive consumption of HFCS can lead to oxidative stress and inflammation.[6,7] Tumor Necrosis Factor (TNF)-α and caspase (Cas)-3 are essential markers of apoptosis and inflammation that are crucial for understanding the pathophysiological mechanisms underlying the effects of HFCS consumption. Studies have reported that HFCS consumption has been associated with increased expression of TNF-α, a pro-inflammatory cytokine implicated in both the kidney and liver.[8,9] In recent years, studies have reported that HFCS consumption plays a role in apoptosis in the hippocampus and heart because of the activation of Cas-3.[10,11] Moreover, studies have shown that TNF-α levels are elevated in individuals with retinal diseases, including diabetic retinopathy.[12] Retinal pigment epithelial (RPE) cell death is associated with the activation of Cas-3.[13] Interestingly, early retinal findings in rats fed a high-fructose diet were primarily associated with glucose metabolism deregulation.[14] Recently, protective treatment regimens against HFCS-induced retinal damage have been investigated.[15]

Selenium (Se) is an essential trace element known to modulate inflammation and immune responses.[16,17] Furthermore, Se deficiency has been shown to exacerbate inflammatory conditions and impair immune cell function.[18] Previous studies have demonstrated the protective effects of Se; for instance, González de Vega et al. showed that Se supplementation protected RPE cells from glucose-induced damage.[19] Another study found that high doses of Se downregulated VEGF production in the hypoxic retina.[20] Additionally, pretreatment with Se has proven more effective than post-treatment in reducing cell damage and apoptosis in retinal ischemia-reperfusion injuries.[21] However, despite these promising findings, the specific potential protective role of Se against retinal damage directly caused by HFCS consumption has not been fully investigated.

Therefore, this study aimed to comprehensively investigate the protective effect of selenium supplementation on HFCS diet-induced retinal damage by evaluating changes through both histopathological (retinal thickness) and immunohistochemical (TNF-α and Caspase-3 expression) analyses.

METHODS

Chemicals

The HFCS (F55:56% fructose and 37% glucose) used in this study was procured from a local manufacturer (Toposmanoglu, Isparta, Turkey). The Se used for treatment was acquired from Sigma (USA). All chemicals used were of analytical grade.

Animals and ethical approval

Adult female Wistar Albino rats (300-350 g) were housed in a controlled environment (21-22°C; 60±5% humidity) with a 12:12-hour light/dark cycle. Rats were kept in standard cages and provided with a commercially available chow diet (Korkuteli Yem, Antalya, Turkey). Tap water was provided ad libitum and changed daily as needed. The study was approved by the Committee on Animal Research of Suleyman Demirel University, Isparta

(Ethic No. 11/02/2021-01/12) and abided by the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

High Fructose Corn Syrup (HFCS) Model

The groups in the study design were exposed to a diet that would trigger MetS by adding 20% (w/v) HFCS solution to their drinking water, which was prepared daily. Se was administered to the selected groups via oral gavage daily at 0.3 mg/kg.

Forty rats were randomly divided into four groups (n=7 per group):

Control Group: Standard chow and drinking water.

HFCS Group: Standard chow and HFCS diet.

HFCS+Se group: Standard chow, HFCS, and Se diet.

Se Group: Standard chow, drinking water, and Se.

After six weeks, all rats were sacrificed under anesthesia with 50– 80 mg/kg ketamine (Bioveta, Czech Republic) and 8–10 mg/kg xylazine (Doğa İlaç, Turkey). Following enucleation, the eyeballs were fixed in 10% buffered formalin solution until necropsy.

Histopathological Analyses

After enucleation, eyeball samples were removed and fixed in 10% neutral formalin solution. Standard tissue processing was performed (ASP300S, Wetzlar, Germany). The samples were then embedded in paraffin and cut into 4 µm slices using a Leica RM2155 (Leica Microsystems, Wetzlar, Germany). Retinal tissues were stained with hematoxylin and eosin (HE) for morphological assessment. Subsequently, retinal thickness measurements were performed using a Nikon Eclipse Ni microscope.

Immunohistochemical Analyses

Samples were then immunostained with TNF-α [Anti-TNF-α Antibody (ab6671)] and Caspase-3 [Anti Caspase-3 Antibody (31A1067):sc-56053]. All primary and secondary antibodies were purchased from Abcam (Cambridge, UK); however, the Caspase-3 antibody was obtained from Santa Cruz Biotechnology (Santa Cruz, CA, USA). All primary antibodies were used at a 1/100 dilution. The first step in the immunohistochemistry process was incubating the primary antibodies for 60 seconds. The Expose Mouse and Rabbit Specific HRP/DAB Detection IHC Kit (ab80436) was used as the secondary antibody system, with diaminobenzidine (DAB) as the chromogen. The primary antiserum step was excluded from negative controls. For each group, immunopositivity was assessed by evaluating images of 100 cells from ten different fields per section, captured at 40X magnification. The Database Manual Cell Sens Life Science Imaging Software System (Olympus Co., Tokyo, Japan) was used to conduct morphometric analyses. A semiquantitative analysis, as shown in Table 1, was employed to score the staining intensity on a scale of 0–3. Statistical analysis was performed on the output of the image analyzer.

Table 1. Immunohistochemical scores of retinal tissues

Staining Intensity Score	Description
0	Absence of staining
1	Slight staining
2	Medium staining
3	Marked staining

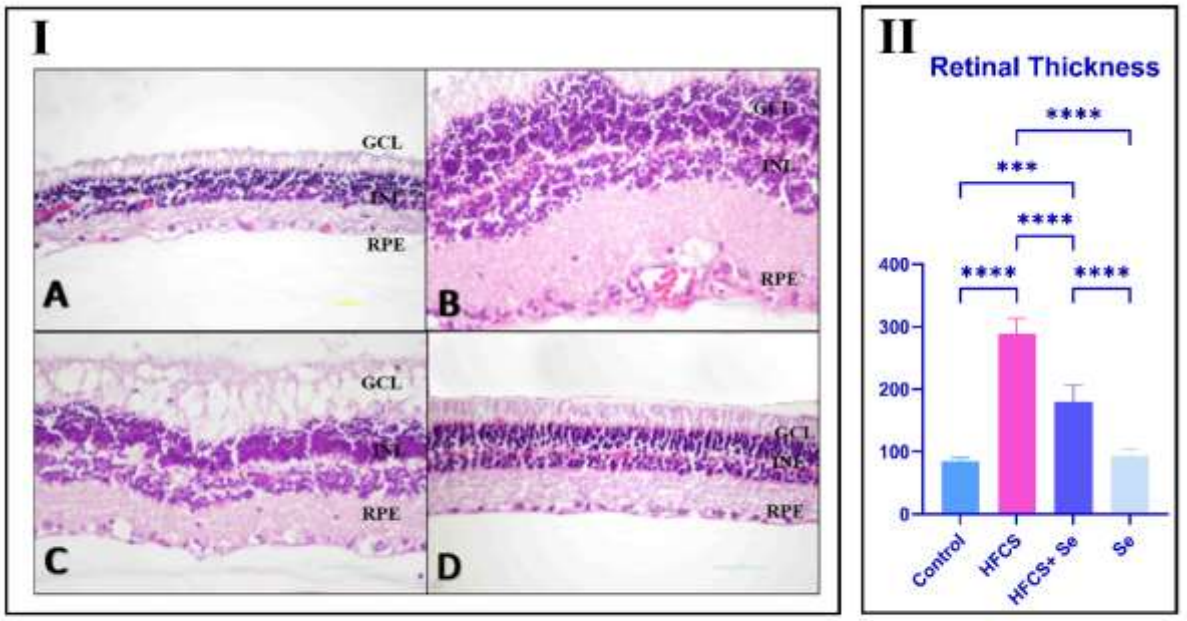
Statistical Analysis

One-way ANOVA (Fisher's LSD) was used to compare the retinal thickness and retinal lesion scores between the experimental groups (GraphPad Prism software). The results are expressed as mean ± SD. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Histopathological finding

As shown in Fig.1, the Control and Se groups exhibited normal retinal tissue architecture. Conversely, the HFCS group showed congestion in retinal vessels and increased vascularity compared to the control group. Notably, these pathological findings were reduced in the HFCS+Se group. Retinal thickness measurements revealed a significant increase in the HFCS group (288.6 ± 25.37 µm) compared to the control group (84.43 ± 5.79 µm) ($p < 0.0001$). Additionally, the HFCS+Se group exhibited a significantly reduced average retinal thickness (180.1 ± 27.08 µm) compared with the HFCS group ($p < 0.0001$). The Se group showed a median retinal thickness (93 ± 11.18 µm) that was not significantly different from that of the control group (p=0.145)



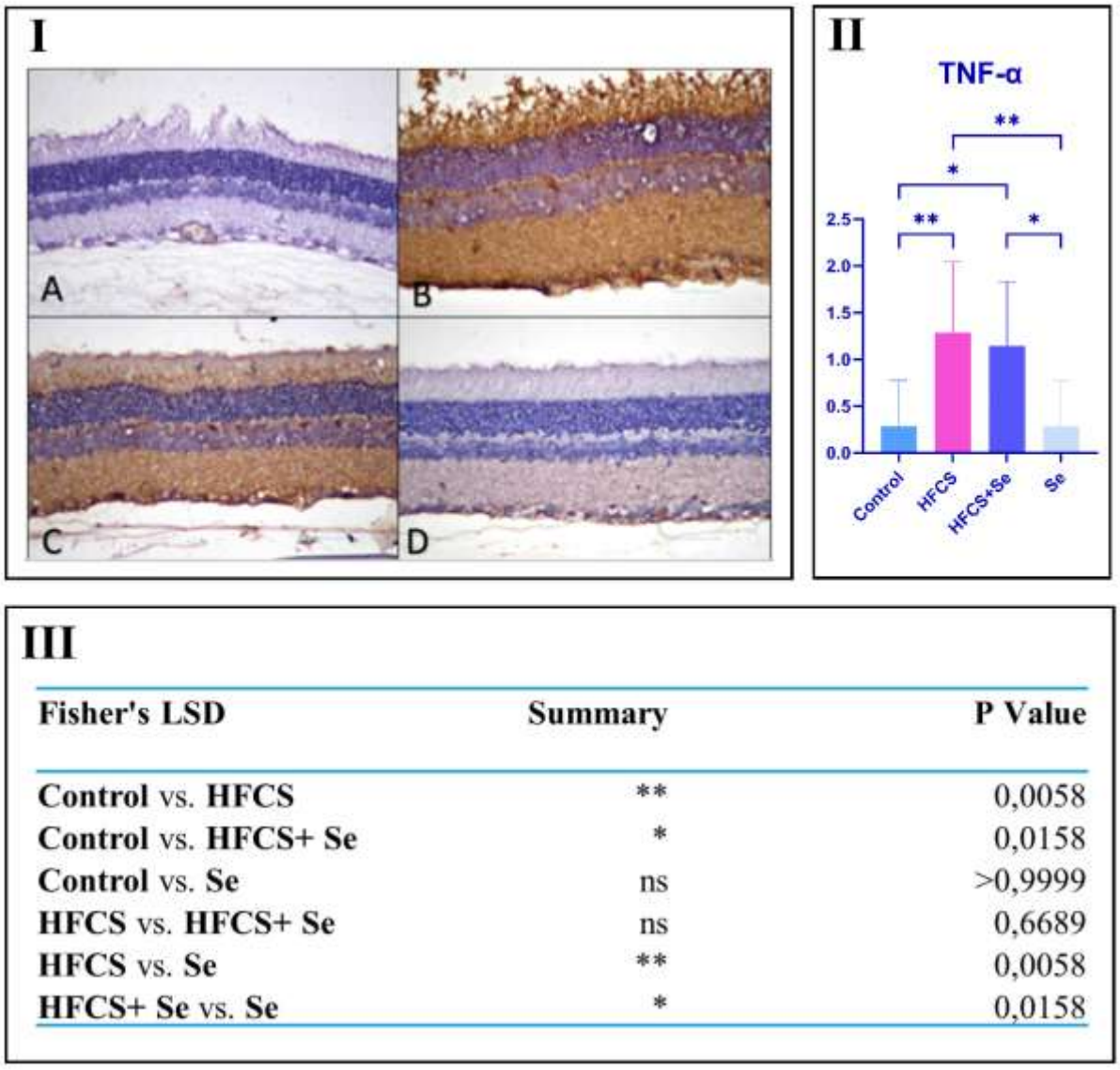
III

Fisher's LSD	Summary	P Value
Control vs. HFCS	****	<0,0001
Control vs. HFCS+ Se	***	0,0001
Control vs. Se	ns	0,1452
HFCS vs. HFCS+ Se	****	<0,0001
HFCS vs. Se	****	<0,0001
HFCS+ Se vs. Se	****	<0,0001

Fig. 1 Histopathological appearance of the retina in the different groups. I. (A) Normal retinal architecture in the control group. (B) Increased congestion in the retinal vascular vessels and vascularity in the HFCS group. (C) Regeneration of epithelial cells in the HFCS+Se group. (D) Normal retinal tissue patterns were observed only in the Se group. HFCS, high fructose corn syrup; Se: Selenium. II. All bars indicate mean values ±SD (n=7 per group). **** represent p<0.0001, *** represent p=0.0001. III. One-way ANOVA (Fisher's LSD) test results of retinal thickness(µm).

Immunohistochemical findings

As shown in Fig. 2, in immunohistochemical analyses, the TNF-α staining score was significantly elevated in the HFCS group compared to the Control and Se groups ($p<0.01$). Although the HFCS+Se group showed a decrease in TNF-α staining score, this reduction was not statistically significant compared to that in the HFCS group ($p=0.668$). The Se group showed no immunostaining, which was not significantly different from that in the control group ($p>0.999$).

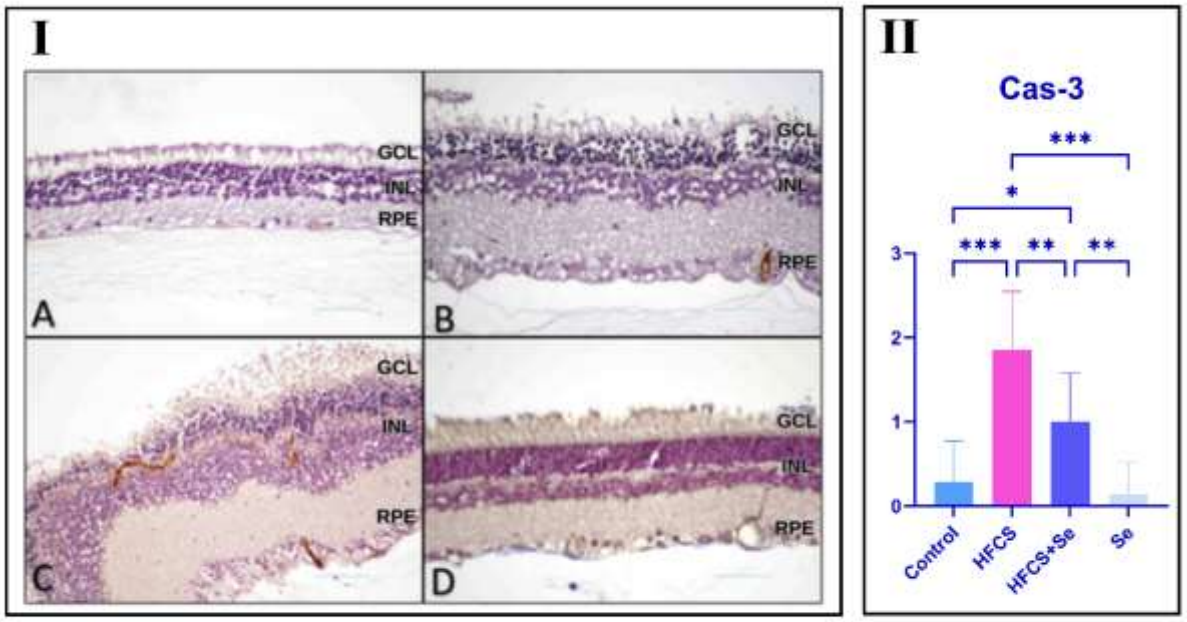


III

Fisher's LSD	Summary	P Value
Control vs. HFCS	**	0,0058
Control vs. HFCS+ Se	*	0,0158
Control vs. Se	ns	>0,9999
HFCS vs. HFCS+ Se	ns	0,6689
HFCS vs. Se	**	0,0058
HFCS+ Se vs. Se	*	0,0158

Fig. 2 TNF-α expression in the different groups. I. A) No TNF-α expression in control group (B) Medium (++) TNF- α immunostaining in HFCS group. (C) Slight (+) TNF-α immunostaining in the HFCS+Se group. (D) No TNF-α expression in the Se group (TNF, DAB, 200X). HFCS, high fructose corn syrup; Se: Selenium. II. All bars indicate the TNF-α expression analysis score (n=7 per group). III. TNF-α expression analysis score of the retina results with Fisher's LSD test ** represent $p<0.01$, * represent $p<0.05$.

As shown in Fig. 3, in immunohistochemical analyses, the Cas-3 staining score was significantly increased in the HFCS group compared to the Control and Se groups ($p<0.001$ for both). This score was significantly decreased in the HFCS+Se group compared to that in the HFCS group ($p<0.005$). The Control, and Se groups exhibited no significant differences in Cas-3 staining scores ($p=0.629$).



III

Fisher's LSD	Summary	P Value
Control vs. HFCS	***	<,001
Control vs. HFCS+ Se	*	,022
Control vs. Se	ns	,629
HFCS vs. HFCS+ Se	**	,007
HFCS vs. Se	***	<,001
HFCS+ Se vs. Se	**	,007

Fig. 3 Caspase-3 expression in the different groups. I. A) No Cas -3 expression in control group. (B) Medium Cas-3 immunostaining in the HFCS group. (C) Slight Cas -3 expression in the HFCS+Se group. (D) No Cas -3 expression in the Se group (CAS-3, DAB, 200X). HFCS, high fructose corn syrup; Se: Selenium. II. All bars indicate the Cas-3 expression analysis score of the retina (n=7 per group). III. Cas -3 expression analysis score of the retina results with Fisher's LSD test. *** represents p<0.001, ** represents p<0.005, * represents p<0.05.

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DISCUSSION

This study aimed to analyze retinal changes due to high blood glucose from HFCS in rats. The results of this study showed increased congestion in the retinal arteries and vascularity, along with increased retinal thickness, in the HFCS group. This confirms the successful establishment of an experimental model demonstrating retinal issues due to a high-fructose diet within 6 weeks.

Over the past 30 years, the increased consumption of HFCS, which is prevalent in processed foods owing to its lower cost, has been linked to various metabolic disorders, including metabolic syndrome, insulin resistance, and organ-specific damage[4]. However, a growing body of evidence has verified the role of inflammation in this state[22,23]. Studies have reported that HFCS consumption increases the expression of TNF-β and Cas-3 in kidney tissue[8]. In another study, it was reported that even a short-term high-fat fructose diet in rats led to the inhibition of hippocampal insulin signaling and activation of Cas-3[10]. Moreover, studies have reported that a high dietary intake of refined carbohydrates, including HFCS,

may contribute to the development of retinal diseases[24]. To our knowledge, no histopathological evaluation has reported the protective effects of selenium against HFCS-induced retinal damage. Therefore, this study evaluated the protective effect of Se against retinal damage caused by HFCS consumption by measuring retinal thickness, as well as inflammatory and apoptotic markers. The results of this study demonstrated that HFCS consumption led to a significantly higher retinal thickness than that in the control group. Moreover, the HFCS+S e group showed significantly reduced retinal thickness compared to the HFCS group, suggesting a protective effect of Se against HFCS-induced retinal damage.

In hyperglycemic conditions, inflammation may directly occur due to altered expression of inflammatory mediators, which results from microenvironmental changes. Studies have reported that Hyperglycemia induces inflammation in aortic endothelial cells, leading to increased expression of inflammatory mediators, especially TNF-α, and endothelial dysfunction[25]. Furthermore, studies have shown that hyperglycemia stimulates the release of pro-inflammatory cytokines, such as TNF-α, which contribute to retinal inflammation and damage[26]. Since the literature indicates the regression of inflammation by anti-TNF agents[27], in the current study, it was preferred to show histopathological changes of inflammation by using TNF-α immunostaining. Indeed, the findings of the immunohistochemical analyses in this study showed that HFCS increased TNF-α production in the retina. However, although there was a slight decrease in TNF-α production in the HFCS+Se group, the difference with the HFCS group was not statistically significant. Moreover, Se alone did not result in TNF-α immunostaining.

Additionally, we investigated the effect of HFCS on Cas-3 expression in the retina. In a study, one of the consequences of microglial activation due to metabolic changes in diabetic retinopathy was increased apoptosis[28]. Similar to that study, in the current study, the results showed moderate immunostaining in the Cas-3 score in the HFCS group, indicating some level of retinal damage and apoptosis. Moreover, the HFCS+Se group showed significantly reduced scores compared to the HFCS group, suggesting that Se also has a protective effect against HFCS-induced apoptosis.

Although this study provides important evidence for the potential protective role of Se in HFCS-induced retinal damage, it has important limitations. First, the six-week study duration, while sufficient to induce detectable retinal damage in the HFCS group, may not fully capture the long-term consequences of HFCS consumption and Se supplementation on retinal health. This study did not examine diabetic retinal findings but investigated supportive treatment that would reduce retinal damage before the underlying pathophysiology develops. Second, although this study provides valuable information through histopathological and immunohistochemical analyses, it does not document the specific molecular mechanisms underlying HFCS-induced retinal damage or Se supplementation. Furthermore, although the findings in this animal model are promising, the translatability of these results to humans is uncertain.

These results suggest that Se supplementation can effectively protect against retinal changes caused by HFCS consumption. Considering the design of this study, further experiments, including detailed analyses, will help to better understand the disease process and identify new treatment targets.

Authors Contributions

GUS: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – original draft. MS: Methodology, Data curation, writing – review and editing. UK: Investigation, Data curation, formal analysis, writing review and editing. DÖ: Data curation, formal analysis, writing – review and editing. NFK: Data curation, formal analysis, writing – review and editing.

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Data Availability

All data are included in the article.

Conflict of interest

The authors declare no conflicts of interest.

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