Check for updates

Original Research Article

Preventive Effects of Tomatidine Against Sodium Selenite-induced Oxidative Damage and Cataractogenesis in Rats via Activating Nrf-2 Pathway

Pharmacognosy Magazine
22(4) 1497–1507, 2026
© The Author(s) 2026
Article reuse guidelines:
in.sagepub.com/journals-permissions-india
DOI: 10.1177/09731296261447608
journals.sagepub.com/home/phm
Sage

Liang Bai[1] and Shiju Zhu[1]

Abstract

Background: Cataracts, characterized by the gradual opacification of the crystalline lens, represent a primary cause of vision impairment worldwide, placing a considerable burden on individuals and healthcare systems. Understanding the precise mechanisms behind cataract formation is essential to developing targeted preventive and treatment approaches.
Objectives: The current study was performed to investigate the preventive mechanisms of tomatidine against selenite-induced cataractogenesis in a rat pup model.
Materials and Methods: Cataracts were experimentally induced in rat pups by administering sodium selenite, followed by administration of tomatidine at dosages of 10 and 20 mg/kg, respectively. The lens opacification level, oxidative stress biomarker levels, calcium, and ascorbic acid concentrations in the lens tissues of rat pups were assessed. The concentrations of antioxidants, inflammatory cytokines, nuclear factor erythroid 2-related factor 2 (Nrf-2), nuclear factor-κB (NF-κB), and cyclooxygenase-2 (COX-2) were evaluated in the lenses of rat pups using kits.
Results: The results of this study indicate that tomatidine administration significantly diminished lens opacification level, calcium, oxidative stress biomarkers, and increased ascorbic acid and antioxidant levels in the lens tissues of cataract-induced rat pups. Moreover, the tomatidine treatment significantly reduced the inflammatory cytokine levels, elevated antioxidant concentrations, reduced COX-2 and NF-κB levels, and enhanced Nrf-2 levels in the lens tissues of cataract-induced rat pups.
Conclusion: The findings of this study suggested that tomatidine may be effective in preventing the formation of selenite-induced cataract in rat pups. These outcomes highlight that tomatidine shows promise as a potential therapeutic agent for cataracts.

Keywords

Antioxidants, lens opacification, matrix metalloproteinase, nuclear factor erythroid 2-related factor 2 pathway, tomatidine, inflammation

Received 21 July 2025; **revised** 13 November 2025; **accepted** 10 December 2025

Introduction

Cataract, a significant contributor to visual impairment worldwide, remains a prominent global health concern despite advancements in surgical techniques. A cataract is defined by the opacification of the crystalline lens, which significantly impairs vision and diminishes the quality of life for millions. While cataract surgery has become increasingly effective, offering rapid visual recovery in many cases, it is crucial to acknowledge that it is still the only available treatment (Delbarre & Froussart-Maille, 2020). The prevalence of cataracts is particularly high in developing countries, where access to surgical intervention is often limited by economic constraints and inadequate healthcare infrastructure. The challenges extend beyond the surgical realm, emphasizing the need for preventive methods and safer therapeutic options to mitigate the growing burden of this disease (Burton et al., 2020; Mencucci et al., 2023). Cataracts are considered the primary cause of preventable blindness globally, highlighting

[1]Department of Ophthalmology, Enshi Aier Eye Hospital, Enshi, Hubei, China
Corresponding author:
Liang Bai, Department of Ophthalmology, Enshi Aier Eye Hospital, Enshi, Hubei 445000, China.
E-mail: bailiang38670243@outlook.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-Commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

the critical importance of early detection, timely intervention, and accessible treatment options (Wong et al., 2025). While age-standardized blindness rates have shown a decline in certain regions, the absolute numbers of individuals with vision loss are projected to increase, indicating that the overall burden of cataract remains a significant public health challenge (Pesudovs et al., 2021).

The etiopathogenesis of cataracts is multifactorial, involving a complex interplay of oxidative stress, protein aggregation, and disruption of lens homeostasis. Oxidative stress plays an imperative role in cataract development. Reactive oxygen species (ROS) can damage lens proteins and lipids, resulting in the formation of insoluble aggregates that scatter light and impair lens transparency. Furthermore, changes in the lens epithelial cells, which are responsible for maintaining lens structure and function, contribute to cataract formation (He et al., 2017). The lens undergoes notable structural, light transmission, metabolic, and enzymatic activity alterations as it ages. While the exact mechanisms are not fully elucidated, disruptions in calcium homeostasis, growth factor signaling, and chaperone protein function have also been implicated in cataractogenesis. External risk factors such as sunlight exposure, smoking, diabetes, steroid use, and ionizing radiation exposure can also contribute to cataract formation. The anatomical classification of cataracts encompasses nuclear, cortical, posterior subcapsular, and mixed types, each characterized by distinct pathological features and progression patterns (Ranaei Pirmardan et al., 2023).

Current therapeutic strategies for cataracts primarily revolve around surgical removal of the opacified lens followed by the implantation of an artificial intraocular lens to restore vision. Phacoemulsification, a technique involving the use of ultrasound to break up the cataract and aspirate the fragments, has become the standard of care for cataract surgery (Heruye et al., 2020). Despite the high success rates of cataract surgery, several challenges and potential complications remain. These include posterior capsule opacification, endophthalmitis, cystoid macular edema, and refractive errors (Bolletta et al., 2021; Lee & Afshari, 2023). The need for safer, alternative therapies for cataracts is driven by the limitations and potential complications associated with current surgical interventions, as well as the desire to address the underlying mechanisms of cataract development. Tomatidine is a naturally occurring steroidal alkaloid present in tomato plants, especially in the leaves and unripe green tomatoes. Several previous studies have already mentioned that tomatidine has several biological effects, including anti-osteoarthritic (Chu et al., 2020), anti-inflammatory (Huang et al., 2021), anti-viral activity against SARS-CoV-2 (Zrieq et al., 2021), hepatoprotective (Wu et al., 2021), and anti-cancer (Mukherjee et al., 2023) effects. Furthermore, tomatidine relieved neuronal damage (Wang et al., 2024), ameliorated diabetes-induced cognitive impairments (Zhang et al., 2025), and showed anti-depressant-like activity (Deyama et al., 2024) in the experimental models. However, there is no previous evidence for the anti-cataractogenic activity of tomatidine. Therefore, the current study was performed to assess the preventive mechanisms of tomatidine against selenite-induced cataractogenesis in a rat pup model.

Materials and Methods

Experimental Animals

Nine-day-old Sprague–Dawley rat pups were acquired from the institutional animal facility. Each cage included 10 pups with their mother, maintained under standard laboratory conditions. The relative humidity in the animal chamber was sustained at 55% ± 5%, with a temperature of 25°C ± 2°C. These pups were utilized in compliance with institutional protocols and the Association for Research in Vision and Ophthalmology's Statement on Animal Use in Research. The pups were allocated into one control group and three treatment groups, with each group consisting of 12 pups.

Treatment Groups

Group I was administered only saline and served as a control. Group II was administered with selenite alone, and Groups III and IV were administered selenite and tomatidine. Each pup in Groups II–IV was administered a single subcutaneous administration of sodium selenite (2.46 mg/kg) on postpartum day 10. Pups in Groups III and IV were administered intraperitoneal injections of tomatidine at 10 and 20 mg/kg concentrations, respectively. The initial dosage of tomatidine was given one day before the selenite injection, followed by daily tomatidine injections for seven consecutive days. The choral hydrate was utilized to anesthetize the pups on postpartum day 24 and evaluated for cataractogenesis. Subsequent to an investigation of cataractogenesis, the pups were sacrificed and placed in a CO_2 chamber. Lens tissue samples were collected and preserved at −70°C for future evaluations.

Analysis of Lens Opacification

The cataract phases were classified utilizing a scale of 0–6. Grade 0 represented a clear lens; Grade 1 indicated the initial presence of nuclear opacity characterized by minute scatterings; Grade 2 denoted a slight nuclear opacity; Grade 3 described a diffuse nuclear opacity with cortical scattering; Grade 4 signified a partial nuclear opacity; Grade 5 referred to a nuclear opacity that did not involve the lens cortex; Grade 6 indicated a mature dense opacity encompassing the entire lens. All evaluations were conducted by two observers who had no prior awareness of the research groups.

Analysis of Biochemical Marker Levels

The levels of total protein, nitric oxide (NO), hydrogen peroxide (H_2O_2), carbonyl protein, and malondialdehyde (MDA)

were evaluated in the rat lens samples utilizing commercially available test kits. The tests were conducted according to the manufacturer's guidelines (Abcam, USA). The levels of advanced glycation end products (AGEs) and matrix metalloproteinase-2 (MMP-2) in the rat lens samples were investigated utilizing kits. The assays were performed according to the manufacturer's protocols (CusaBio, USA). The calcium and ascorbic acid levels in the rat lens samples were quantified utilizing standard test kits. The tests were performed as per the manufacturer's specifications (Abcam, USA).

Analysis of Antioxidant Marker Levels

The levels of glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione-*S*-transferase (GST), and glutathione reductase (GR) in the rat lens tissue samples were assessed using the relevant test kits. All tests were performed in triplicate as per the manufacturer's specification (Abcam, USA).

Analysis of Inflammatory Cytokine Levels

The levels of interleukin (IL)-6, IL-1β, and TNF-α in the experimental rats were assessed utilizing commercial test kits. The tests were performed with three duplicates according to the instructions supplied by the manufacturer (Elabscience, USA).

Analysis of Nuclear Factor-κB, Nuclear Factor Erythroid 2-related Factor 2, and Cyclooxygenase-2 Levels

The levels of nuclear factor erythroid 2-related factor 2 (Nrf-2), cyclooxygenase-2 (COX-2), and nuclear factor-κB (NF-κB) in the lens tissues of experimental rats were assessed utilizing assay kits. The studies were performed with three replicates using the manufacturer's specified guidelines (MyBioSource, USA).

Statistical Analysis

Statistical tests were conducted using GraphPad Prism, and the findings from each experiment were portrayed as the mean ± SD of triplicates. The values were assessed using one-way ANOVA and Tukey's *post hoc* test, with significance set at $p < .05$.

Results

Effect of Tomatidine on the Lens Opacification in Experimental Rats

Figure 1(A) depicts the level of lens opacification in the experimental rat pups. The present findings illustrated an elevation in the lens opacification level in the selenite-induced rat pups when compared with the control. Interestingly, the administration of tomatidine (10 and 20 mg/kg) reduced the lens opacification in the selenite-induced animals. The results indicate that tomatidine administration may be beneficial in reducing cataract formation in rats.

Effect of Tomatidine on the Biochemical Markers in Experimental Rats

The effect of tomatidine on the levels of biochemical markers in the lens tissues of the experimental rat pups was assessed, with results depicted in Figure 1B–1F. The rat pups with selenite-induced cataract had increased MDA, NO, H_2O_2, and carbonyl protein levels along with reduced total protein level in their lens tissues compared to the control group. Nonetheless, tomatidine administration at dosages of 10 and 20 mg/kg substantially decreased the MDA, NO, H_2O_2, and carbonyl protein levels while elevating the total protein level in the lens tissues of the selenite-induced rat pups.

Effect of Tomatidine on the Antioxidant Levels in Experimental Rats

The current results demonstrated that rat pups induced with selenite showed a significant reduction in antioxidant levels, that is, GSH, SOD, CAT, GPx, GST, and GR levels in their lens tissues relative to the control (Figure 2). Fascinatingly, the administration of tomatidine at dosages of 10 and 20 mg/kg elevated the antioxidant concentrations in the lens tissues of selenite-induced rat pups, demonstrating its antioxidant properties.

Effect of Tomatidine on the Advanced Glycation End Products and Matrix Metalloproteinase-2 Levels in Experimental Rats

Figure 3A and 3B depicts the concentrations of MMP-2 and AGEs in the lens tissue samples of the experimental rat pups. An elevation in MMP-2 and AGEs levels was seen in the lens tissue samples of selenite-treated rat pups when compared with controls. The treatment of tomatidine at dosages of 10 and 20 mg/kg markedly decreased the levels of both AGEs and MMP-2 in the lens of selenite-induced rat pups.

Effect of Tomatidine on the Inflammatory Cytokines in Experimental Rats

Figure 3C–3E illustrates the inflammatory cytokine levels in the experimental rat pups. A notable elevation in the IL-6, IL-1β, and TNF-α levels was observed in the selenite-induced rats compared with the control group. Interestingly, tomatidine treatment at doses of 10 and 20 mg/kg substantially decreased the concentrations of IL-6, IL-1β, and TNF-α in selenite-induced rat pups, which proves its anti-inflammatory property.

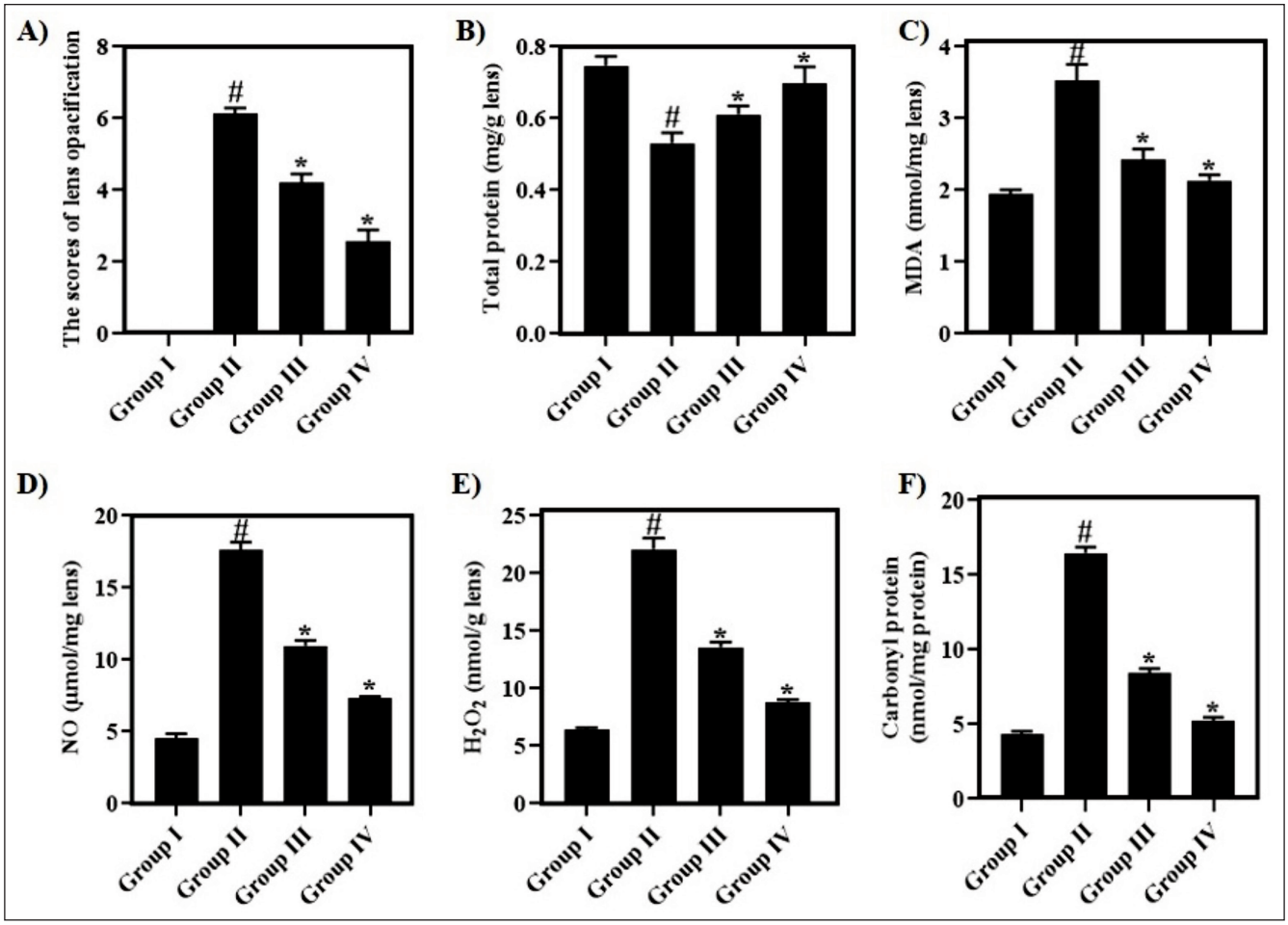


Figure 1. Effect of Tomatidine on the Lens Opacification and Biochemical Marker Levels in the Experimental Rats.

Notes: The values are given as a mean ± SD from the triplicates. The data undergo statistical analysis by one-way analysis of variance (ANOVA) and Tukey's *post hoc* tests utilizing GraphPad Prism software. A symbol "#" indicates that the values are significant at $p < .01$ relative to the control group; "*" indicates that the values are significant at $p < .05$ relative to the selenite-induced group.

Effect of Tomatidine on the Ascorbic Acid and Calcium Levels in Experimental Rats

Figure 4A and 4B shows the levels of calcium and ascorbic acid in the lens tissues of the experimental rat pups. In the lens tissues of rat pups with selenite-induced cataract, there was a markedly increased level of calcium, accompanied by a subsequent decrease in ascorbic acid levels, compared to the control. However, the 10 and 20 mg/kg doses of tomatidine elevated the ascorbic acid level and decreased calcium levels in the lens of selenite-induced rat pups.

Effect of Tomatidine on the Nuclear Factor Erythroid 2-related Factor 2, Nuclear Factor-κB, and Cyclooxygenase-2 Levels in the Experimental Rats

The present findings indicated that rat pups with selenite-induced cataracts exhibited an elevation in NF-κB and COX-2 levels, while reducing the Nrf-2 level in their lenses compared with the control group (Figure 4C–4E). Captivatingly, the tomatidine treatment (10 and 20 mg/kg) demonstrated a reduction in NF-κB and COX-2 levels and elevated the Nrf-2 levels in the lens tissues of selenite-induced rat pups.

Discussion

Cataracts, characterized by the progressive opacification of the crystalline lens, stand as a primary cause of visual impairment globally, imposing a significant burden on individuals and healthcare systems. The prevalence of cataracts exhibits a strong correlation with age, with the risk escalating notably after the age of 40, thereby underscoring the importance of geriatric eye care. Despite advancements in surgical techniques and accessibility, cataracts continue to pose a substantial public health challenge, particularly in developing countries where barriers to treatment persist (GBD 2019

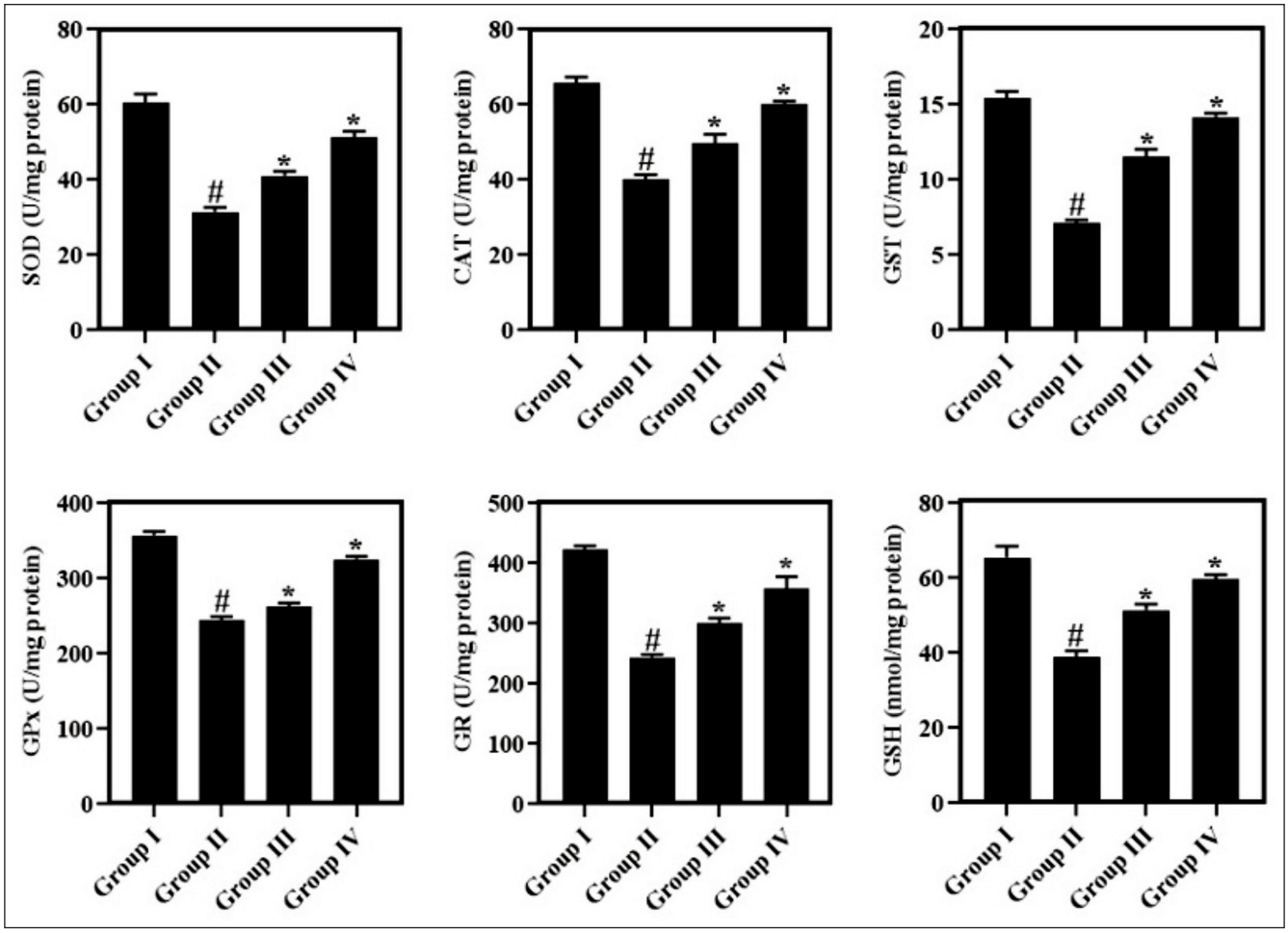


Figure 2. Effect of Tomatidine on the Antioxidant Levels in the Experimental Rats.

Notes: The values are given as a mean ± SD from the triplicates. The data undergo statistical analysis by one-way analysis of variance (ANOVA) and Tukey's *post hoc* tests utilizing GraphPad Prism software. A symbol "#" indicates that the values are significant at $p < .01$ relative to the control group; "*" indicates that the values are significant at $p < .05$ relative to the selenite-induced group.

Blindness and Vision Impairment Collaborators, 2021). The etiology of cataracts is multifactorial, encompassing a complex interplay of genetic predisposition, environmental influences, and metabolic derangements. These factors can initiate a cascade of biochemical events within the lens, culminating in protein aggregation, oxidative damage, and disruption of lens architecture (Richardson et al., 2020). Understanding the specific mechanisms driving cataract formation is essential for developing targeted preventative and therapeutic methods. Cataract surgery is generally safe and effective, it is not without potential complications, including infection, inflammation, retinal detachment, and posterior capsule opacification. Moreover, access to cataract surgery remains a significant challenge in many parts of the world, particularly in low-resource settings, where cost, infrastructure limitations, and a shortage of trained ophthalmologists impede timely intervention (Jolley et al., 2022). These barriers contribute to a significant backlog of cataract cases, resulting in preventable blindness. Therefore, there is a compelling need for safer, more accessible, and cost-effective alternative therapies that can prevent, delay, or even reverse cataract progression, particularly in populations with limited access to surgical care (Kyari, 2019).

Oxidative stress has emerged as a pivotal cause in the pathogenesis of various types of cataracts. The lens, a highly specialized and metabolically active tissue, is especially susceptible to oxidative damage due to its exposure to ultraviolet radiation, high oxygen tension, and limited regenerative capacity. Understanding the relationship between oxidative stress and the development of cataracts necessitates a comprehensive investigation into the roles of specific oxidative stress biomarkers in the pathogenesis of the disease (Thompson et al., 2022). Oxidative stress arises from multiple sources, both endogenous and exogenous, leading to the generation of a diverse array of ROS. These reactive species can inflict damage on crucial lens components, culminating

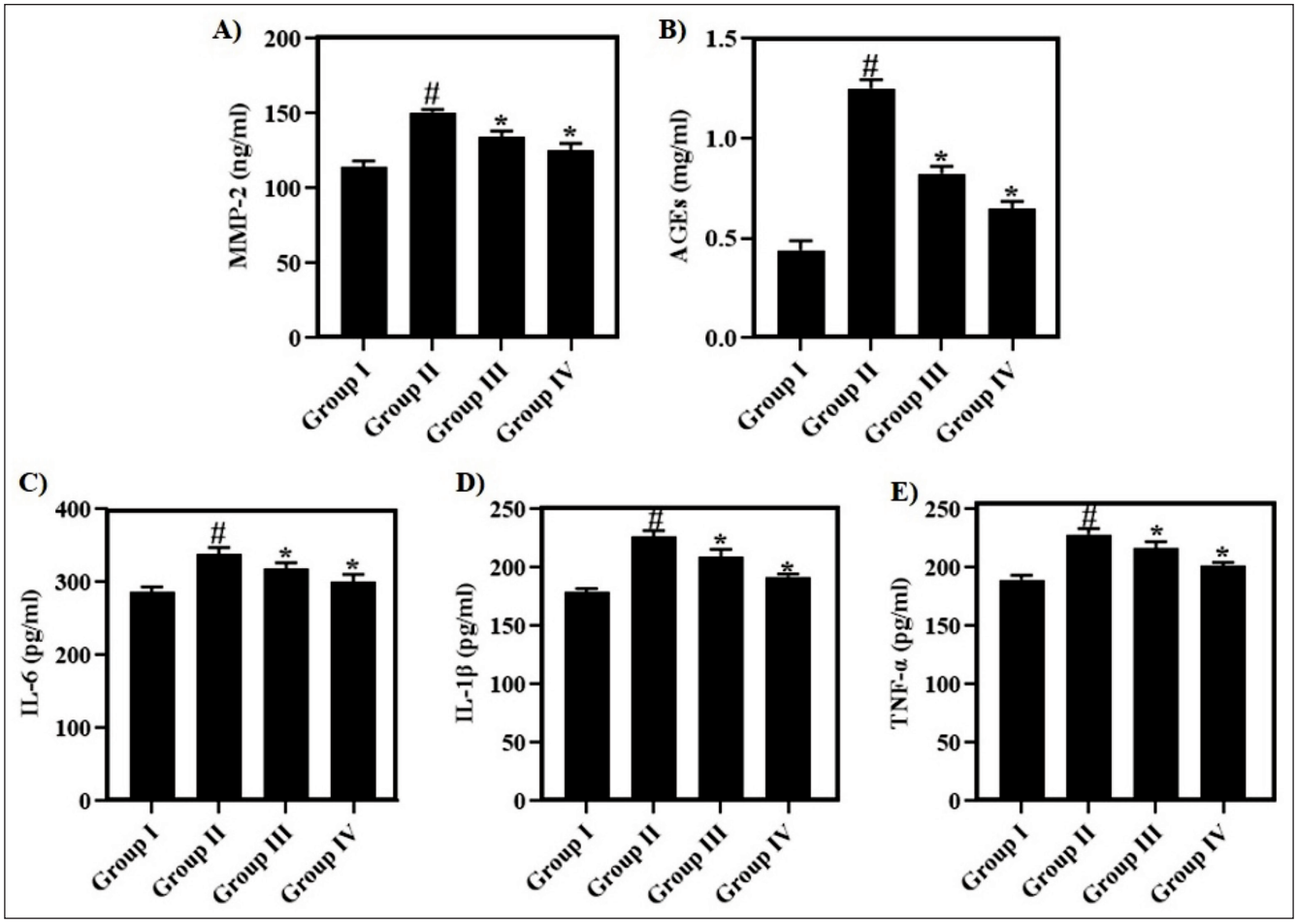


Figure 3. Effect of Tomatidine on the Advanced Glycation End Products (AGEs), Matrix Metalloproteinase-2 (MMP-2), and Inflammatory Cytokine Levels in the Experimental Rats.

Notes: The values are given as a mean ± SD from the triplicates. The data undergo statistical analysis by one-way analysis of variance (ANOVA) and Tukey's *post hoc* tests utilizing GraphPad Prism software. A symbol "#" indicates that the values are significant at $p < .01$ relative to the control group; "*" indicates that the values are significant at $p < .05$ relative to the selenite-induced group.

in lens opacification. Elevated levels of ROS can overwhelm the lens's endogenous antioxidant defenses, leading to oxidative injury and cataractogenesis (Fan et al., 2022). MDA, a lipid peroxidation product, serves as a widely recognized biomarker of oxidative stress-induced damage. NO, a multifaceted signaling molecule, plays a dual role in oxidative stress depending on its concentration and the cellular context (Ateş et al., 2004). H_2O_2, another key ROS, can directly oxidize cellular components or be converted into more reactive radicals, contributing to oxidative damage. Carbonyl protein, a product of protein oxidation, reflects the extent of oxidative damage to lens proteins, which can disrupt their structure and function (Nita & Grzybowski, 2016).

GSH plays a crucial role in counteracting ROS and maintaining redox balance in the lens. SOD catalyzes the dismutation of superoxide radicals into H_2O_2 and O_2, while CAT and GPx facilitate the reduction of H_2O_2 into water and oxygen (Lee et al., 2024). GST conjugates GSH to electrophilic compounds, leading to their detoxification and elimination from the lens. GR regenerates reduced glutathione from its oxidized form, ensuring a continuous supply of this critical antioxidant. In conditions of oxidative stress, the balance between ROS generation and antioxidant mechanisms is dysregulated. The study of these biomarkers provides valuable insights into the mechanisms underlying oxidative stress-mediated cataract formation (Hsueh et al., 2022). By examining the changes in these biomarkers during cataract development, researchers can elucidate the specific pathways involved and identify potential therapeutic targets for preventing or delaying cataract progression (Lu et al., 2018). In this study, we observed that the rat pups with selenite-induced cataract showed elevated MDA, NO, H_2O_2, and carbonyl protein levels along with antioxidant GSH, SOD, CAT, GPx, GST, and GR levels in their lens tissues. Captivatingly, the tomatidine treatment markedly reduced the oxidative stress markers and augmented the antioxidant concentrations in the

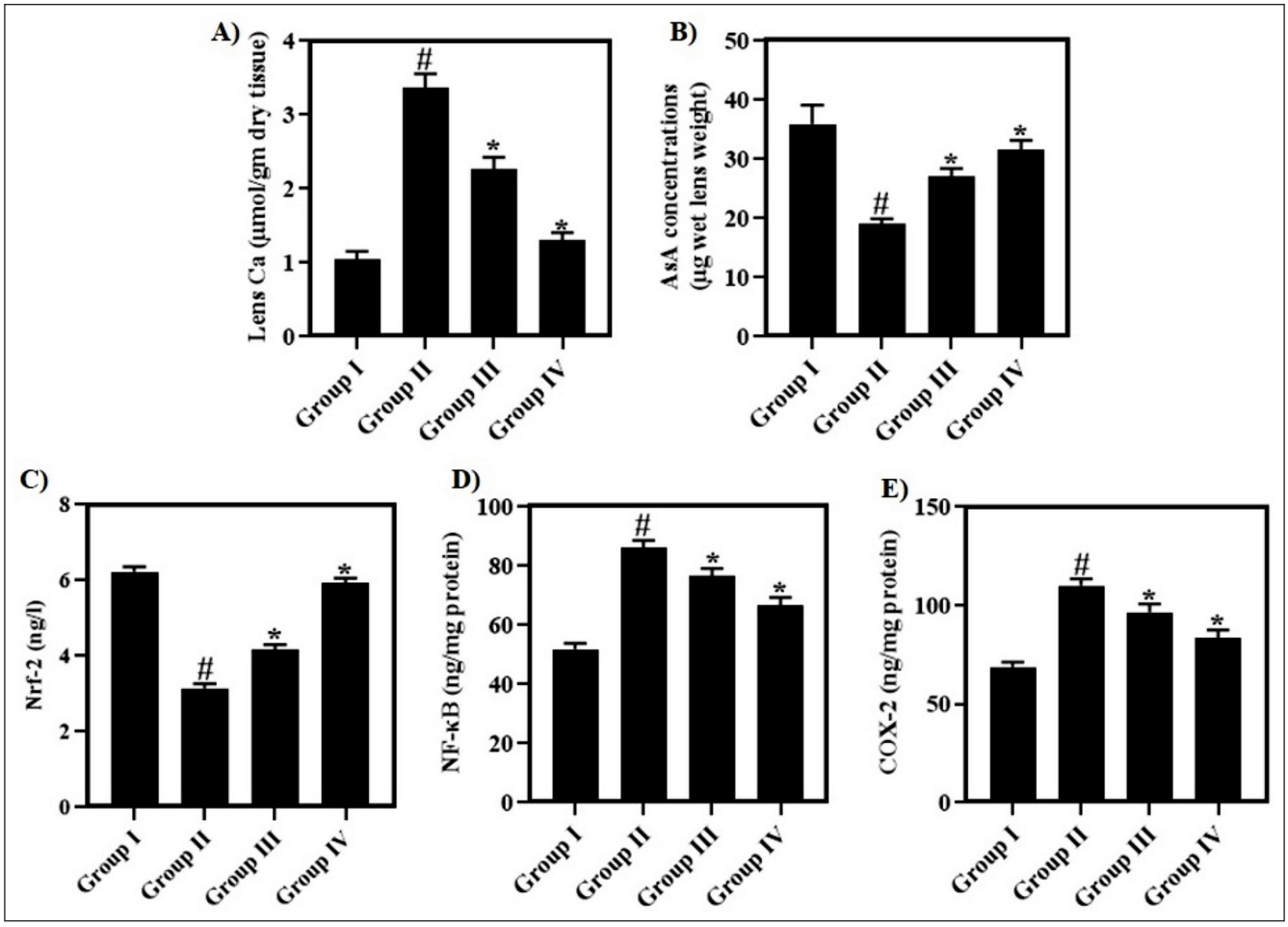


Figure 4. Effect of Tomatidine on the Ascorbic Acid, Calcium, Nuclear Factor Erythroid 2-related Factor 2 (Nrf-2), Nuclear Factor-κB (NF-κB), and Cyclooxygenase-2 (COX-2) Levels in the Experimental Rats.

Notes: The values are given as a mean ± SD from the triplicates. The data undergo statistical analysis by one-way analysis of variance (ANOVA) and Tukey's *post hoc* tests utilizing GraphPad Prism software. A symbol "#" indicates that the values are significant at $p < .01$ relative to the control group; "*" indicates that the values are significant at $p < .05$ relative to the selenite-induced group.

lens tissues of selenite-induced rat pups, which suggests its antioxidant capacity.

AGEs and MMP-2 are implicated in the complex pathophysiology of cataracts. The formation of AGEs leads to protein crosslinking, conformational changes, and impaired protein function, contributing to lens opacification (Glenn et al., 2009). AGEs can modify lens proteins, leading to their aggregation and insolubilization, which contributes to the scattering of light and reduced lens transparency. AGEs contribute to the yellowing and opacification of the lens nucleus in nuclear cataracts (Ott et al., 2014). MMP-2 plays a crucial role in the degradation of collagen, a primary component of the lens capsule and basement membrane. MMP-2 is involved in the breakdown of the lens capsule and basement membrane, which can compromise lens integrity and contribute to cataract formation (Jiang et al., 2021). Imbalances in MMP activity can disrupt the delicate equilibrium of ECM turnover, leading to pathological conditions like cataract development. The dysregulation of MMP-2 activity has been implicated in several ocular diseases, including cataracts, where it contributes to the lens structural protein degradation and the disruption of lens architecture (Shimizu et al., 2013). Overall, the interplay between AGEs and MMP-2 contributes to the multifaceted pathophysiology of cataracts. Chronic accumulation of AGEs in tissues is responsible for collagen crosslinking and tissue stiffening. The generation of AGEs can initiate signaling cascades that exacerbate oxidative stress and inflammation, further promoting lens damage. Targeting AGE formation and MMP-2 activity, along with mitigating oxidative stress, holds promise to develop novel therapeutic methods to prevent or delay cataract progression (Cooksley et al., 2024). The present findings showed the elevated MMP-2 and AGEs levels in the lens tissue samples of selenite-treated rat pups. Interestingly, the tomatidine treatment markedly decreased the levels of both AGEs and MMP-2 in the lens of selenite-induced rat pups.

The pathogenesis of cataract is increasingly recognized to involve inflammatory mechanisms, with inflammatory cytokines playing significant roles. Cataracts are frequently linked to oxidative damage, and inflammation can exacerbate this damage, leading to cortical and nuclear cataracts. Inflammatory cytokines, including TNF-α, IL-1β, and IL-6, are key mediators in this inflammatory cascade, influencing various cellular processes within the lens. These cytokines are not only indicators of inflammation but also active participants in the molecular events that drive cataract formation (Wang & Tao, 2021). TNF-α, a pleiotropic cytokine, participates in the regulation of apoptosis, inflammation, and immunity. TNF-α can trigger oxidative stress in lens epithelial cells, resulting in damage and apoptosis, which are critical events in cataract development. Elevated levels of TNF-α can disrupt lens homeostasis by interfering with the normal function of lens epithelial cells, which are responsible for maintaining lens transparency (Zhu et al., 2016). IL-1β, another pro-inflammatory cytokine, also plays a significant role in cataractogenesis by promoting inflammation within the lens. IL-1β can trigger intracellular pathways that result in the production of ROS, exacerbating oxidative injury to lens components. The cytokine can also stimulate the expression of MMPs, enzymes that degrade the extracellular matrix, leading to the disruption of lens structure and transparency (Klein et al., 2006). IL-6 is involved in regulating immunity, inflammation, and hematopoiesis, and it has been implicated in the onset of several ocular diseases, including cataracts. IL-6 contributes to cataract development by promoting inflammation and stimulating the accumulation of other pro-inflammatory markers (Kessel et al., 2014). Understanding the specific roles of inflammatory cytokines in cataracts can aid in the development of targeted therapies. The present findings evidenced that IL-6, IL-1β, and TNF-α were considerably augmented in the selenite-induced rat pups. However, the tomatidine treatment remarkably diminished the concentrations of these cytokines in the selenite-induced rat pups, which witnesses its anti-inflammatory activity.

Cataract development is a multifactorial process influenced by a complex interplay of molecular mechanisms, with oxidative stress emerging as a central player. The lens is especially susceptible to oxidative damage, as it relies on antioxidant defense systems to neutralize ROS. Among the key regulators of cellular defense against oxidative stress, Nrf-2 stands out as a crucial transcription factor (Liu et al., 2017). Nrf-2 orchestrates the expression of a battery of antioxidant genes, which collectively scavenge free radicals and detoxify harmful electrophiles. In the context of cataractogenesis, a decline in Nrf-2 activity or impaired Nrf-2 signaling can compromise the lens's capacity to counteract oxidative insults, leading to the accumulation of oxidized proteins, lipids, and DNA, ultimately contributing to lens opacification (Yang et al., 2015). Conversely, NF-κB, a ubiquitous transcription factor that participated in inflammation and immune responses, has also been implicated in the pathogenesis of cataracts. NF-κB activation can be triggered by oxidative stress, inflammatory cytokines, and other cellular stressors, leading to the worsening of inflammation. In the lens, excessive NF-κB activation can promote chronic inflammation, disrupt cellular homeostasis, and contribute to the onset of cataracts (Ku et al., 2022). The sustained activation of NF-κB can also impair lens epithelial cell differentiation and promote their abnormal proliferation, further disrupting lens architecture and transparency. Inflammation can trigger oxidative stress by promoting the ROS accumulation from activated leukocytes and resident cells. The complex interplay between Nrf-2 and NF-κB pathways, in response to stress, involves intricate molecular mechanisms (Chung et al., 2017).

COX-2, an inducible enzyme responsible for the synthesis of prostaglandins from arachidonic acid, has also been linked to cataract formation. While COX-2 is typically expressed at low levels in normal tissues, its expression can be markedly upregulated in response to several stimuli. The prostaglandins produced by COX-2 can exert a variety of effects on ocular tissues, including promoting inflammation, increasing vascular permeability, and stimulating angiogenesis (Song et al., 2020). In the lens, elevated COX-2 expression and prostaglandin production can contribute to the development of cataracts by disrupting lens epithelial cell function, promoting oxidative stress, and inducing inflammatory responses. Given the role of COX-2 in inflammation, it is plausible that its modulation could influence the inflammatory component of cataractogenesis (Chandler et al., 2007). In addition to their individual roles, Nrf-2, NF-κB, and COX-2 can interact with each other in complex ways to influence cataract development. For example, Nrf-2 activation can suppress NF-κB signaling by promoting the expression of antioxidant genes that reduce oxidative stress, thereby diminishing the stimuli that activate NF-κB (Li et al., 2024). Conversely, NF-κB activation can inhibit Nrf-2 activity by inducing the expression of genes that target Nrf-2, leading to decreased Nrf-2 protein levels. The inflammatory response mediated by NF-κB could upregulate COX-2 expression, amplifying the inflammatory cascade and contributing to lens damage (Böhm et al., 2023). Therefore, targeting these markers can assist in understanding the molecular mechanisms underlying cataractogenesis and facilitate the development of targeted therapies. The findings of this work demonstrated that selenite-induced rat pups showed increased NF-κB and COX-2 levels, while reducing the Nrf-2 level in their lens tissues. However, the tomatidine treatment revealed a considerable reduction in NF-κB and COX-2 levels and augmented the Nrf-2 levels in the lens tissues of selenite-induced rat pups.

In addition to these findings, the present study has several limitations that should be acknowledged. The translational value of our findings is limited, as the study was conducted in a single animal model, which may not accurately reflect the human condition. Additionally, the reliance on a single animal model restricts the generalizability of our results. Furthermore, the lack of long-term or clinical

validations limits the applicability of our findings to real-world scenarios. The study's scope was also limited to evaluating the preventive effects of tomatidine, and its therapeutic potential in existing cataracts remains unexplored. These limitations notwithstanding, our study provides valuable insights into tomatidine's potential as a therapeutic candidate for cataracts. We acknowledge these limitations and plan to address them in future studies, including evaluating tomatidine's efficacy in multiple animal models, conducting long-term and clinical validations, and exploring its therapeutic potential in existing cataracts. Thereby, we aim to strengthen the translational value of our research and provide more comprehensive evidence of tomatidine's potential benefits.

Conclusion

The findings of this study suggested that tomatidine may be effective in preventing the formation of selenite-induced cataract in rat pups. The tomatidine treatment diminished lens opacification level, decreased oxidative stress markers, and elevated the antioxidant concentrations in the lens tissues of selenite-induced rat pups. Moreover, the tomatidine administration decreased AGEs, MMP-2, and inflammatory cytokine levels. The NF-κB and COX-2 levels were reduced, and the tomatidine treatment increased Nrf-2 levels in the lens tissues of selenite-induced rat pups. The results of this work highlight that tomatidine shows promise as a potential therapeutic agent for cataracts.

Abbreviations

AGEs: Advanced glycation end products; CAT: Catalase; COX-2: Cyclooxygenase-2; GSH: Glutathione; IL: Interleukin; MDA: Malondialdehyde; MMP-2: Matrix metalloproteinase-2; NF-κB: Nuclear factor-κB; NO: Nitric oxide; Nrf-2: Nuclear factor erythroid 2-related factor 2.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This work has been approved by the institutional animal ethical committee of Enshi Aier Eye Hospital, Enshi, Hubei, 445000, China.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Informed Consent

Not applicable.

ORCID iD

Liang Bai https://orcid.org/0009-0007-7088-7072

References

Ateş, N. A., Yildirim, O., Tamer, L., Unlü, A., Ercan, B., Muşlu, N., Kanik, A., Hatungil, R., & Atik, U. (2004). Plasma catalase activity and malondialdehyde level in patients with cataract. *Eye*, *18*(8), 785–788.

Böhm, E. W., Buonfiglio, F., Voigt, A. M., Bachmann, P., Safi, T., Pfeiffer, N., & Gericke, A. (2023). Oxidative stress in the eye and its role in the pathophysiology of ocular diseases. *Redox Biology*, *68*, 102967.

Bolletta, E., Coassin, M., Iannetta, D., Mastrofilippo, V., Aldigeri, R., Invernizzi, A., de Simone, L., Gozzi, F., De Fanti, A., Cappella, M., Adani, C., Neri, A., Moramarco, A., De Maria, M., Salvarani, C., Fontana, L., & Cimino, L. (2021). Cataract surgery with intraocular lens implantation in juvenile idiopathic arthritis-associated uveitis: Outcomes in the era of biological therapy. *Journal of Clinical Medicine*, *10*(11), 2437.

Burton, M. J., Ramke, J., Marques, A. P., Bourne, R. R. A., Congdon, N., Jones, I., Gilbert, C. E., Foster, A., & Faal, H. B. (2020). The lancet global health commission on global eye health: Vision beyond 2020. *Lancet Global Health*, *9*(4), e489–e551.

Chandler, H. L., Barden, C. A., Lu, P., Kusewitt, D. F., & Colitz, C. M. (2007). Prevention of posterior capsular opacification through cyclooxygenase-2 inhibition. *Molecular Vision*, *13*, 677–691.

Chu, X., Yu, T., Huang, X., Xi, Y., Ni, B., Zhang, R., & You, H. (2020). Tomatidine suppresses inflammation in primary articular chondrocytes and attenuates cartilage degradation in osteoarthritic rats. *Aging*, *12*(13), 12799–12811.

Chung, I., Hah, Y. S., Ju, S., Kim, J. H., Yoo, W. S., Cho, H. Y., Yoo, J. M., Seo, S. W., Choi, W. S., & Kim, S. J. (2017). Ultraviolet B radiation stimulates the interaction between nuclear factor of activated T cells 5 (NFAT5) and nuclear factor-kappa B (NF-κB) in human lens epithelial cells. *Current Eye Research*, *42*(7), 987–994.

Cooksley, G., Nam, M. H., Nahomi, R. B., Rankenberg, J., Smith, A. J. O., Wormstone, Y. M., Wormstone, I. M., & Nagaraj, R. H. (2024). Lens capsule advanced glycation end products induce senescence in epithelial cells: Implications for secondary cataracts. *Aging Cell*, *23*, e14249.

Delbarre, M., & Froussart-Maille, F. (2020). Signs, symptoms, and clinical forms of cataract in adults. *Journal Français D'ophtalmologie*, *43*, 653–659.

Deyama, S., Sugie, R., Tabata, M., & Kaneda, K. (2024). Antidepressant-like effects of tomatidine and tomatine, steroidal alkaloids from unripe tomatoes, via activation of mTORC1 in the medial prefrontal cortex in lipopolysaccharide-induced depression model mice. *Nutritional Neuroscience*, *27*(8), 795–808.

Fan, Q., Li, D., Zhao, Z., Jiang, Y., & Lu, Y. (2022). Protective effect of Glutaredoxin 1 against oxidative stress in lens epithelial cells of age-related nuclear cataracts. *Molecular Vision*, *28*, 70–82.

GBD 2019 Blindness and Vision Impairment Collaborators & Vision Loss Expert Group of the Global Burden of Disease Study. (2021). Trends in prevalence of blindness and distance and near vision impairment over 30 years: An analysis for the Global Burden of Disease Study. *Lancet Global Health*, *9*(2), e130–e143.

Glenn, J. V., Mahaffy, H., Wu, K., Smith, G., Nagai, R., Simpson, D.A., Boulton, M. E., & Stitt, A. W. (2009). Advanced glycation end product (AGE) accumulation on Bruch's membrane: Links to age-related RPE dysfunction. *Investigative Ophthalmology & Visual Science*, *50*(1), 441–451.

He, M., Wang, W., & Huang, W. (2017). Variations and trends in health burden of visual impairment due to cataract: a global analysis. *Investigative Ophthalmology & Visual Science*, *58*(10), 4299–4306.

Heruye, S. H., Maffofou Nkenyi, L. N., Singh, N. U., Yalzadeh, D., Ngele, K. K., Njie-Mbye, Y. F., Ohia, S. E., & Opere, C. A. (2020). Current trends in the pharmacotherapy of cataracts. *Pharmaceuticals*, *13*(1), 15. https://doi.org/10.3390/ph13010015. Erratum in: *Pharmaceuticals*, 17(7), 947.

Hsueh, Y. J., Chen, Y. N., Tsao, Y. T., Cheng, C. M., Wu, W. C., & Chen, H. C. (2022). The pathomechanism, antioxidant biomarkers, and treatment of oxidative stress-related eye diseases. *International Journal of Molecular Sciences*, *23*(3), 1255.

Huang, W. C., Wu, S. J., Chen, Y. L., Lin, C. F., & Liou, C. J. (2021). Tomatidine improves pulmonary inflammation in mice with acute lung injury. *Mediators of Inflammation*, 4544294.

Jiang, H., Gao, Y., Chen, Z., & Xu, H. (2021). Association between MMP-2 gene polymorphism and cataract susceptibility: A protocol for systematic review and meta-analysis. *Medicine*, *100*(14), e25392.

Jolley, E., Virendrakumar, B., Pente, V., Baldwin, M., Mailu, E., & Schmidt, E. (2022). Evidence on cataract in low- and middle-income countries: an updated review of reviews using the evidence gap maps approach. *International Health*, *14*(1), i68–i83.

Kessel, L., Tendal, B., Jørgensen, K. J., Erngaard, D., Flesner, P., Andresen, J. L., & Hjortdal, J. (2014). Post-cataract prevention of inflammation and macular edema by steroid and nonsteroidal anti-inflammatory eye drops: A systematic review. *Ophthalmology*, *121*, 1915–1924.

Klein, B. E., Klein, R., Lee, K. E., Knudtson, M. D., & Tsai, M. Y. (2006). Markers of inflammation, vascular endothelial dysfunction, and age-related cataract. *American Journal of Ophthalmology*, *141*(1), 116–122.

Ku, H., Chen, J. J., Hu, M., Tien, P. T., Lin, H. J., Xu, G., Wan, L., & Gan, D. (2022). Myopia development in tree shrew is associated with chronic inflammatory reactions. *Current Issues in Molecular Biology*, *44*, 4303–4313.

Kyari, F. (2019). Managing cataract surgery in patients with glaucoma. *Community Eye Health*, *31*, 88–90.

Lee, B. J., & Afshari, N. A. (2023). Advances in drug therapy and delivery for cataract treatment. *Current Opinion in Ophthalmology*, *34*(1), 3–8.

Lee, B., Afshari, N. A., & Shaw, P. X. (2024). Oxidative stress and antioxidants in cataract development. *Current Opinion in Ophthalmology*, *35*(1), 57–63.

Li, J., Buonfiglio, F., Zeng, Y., Pfeiffer, N., & Gericke, A. (2024). Oxidative stress in cataract formation: Is there a treatment approach on the horizon? *Antioxidants*, *13*(10), 1249.

Liu, X., Hao, J., Xie, T., Malik, T., Lu, C., Liu, C., Shu, C., Lu, C., & Zhou, D. (2017). Nrf2 as a target for prevention of age-related and diabetic cataracts by against oxidative stress. *Aging Cell*, *16*(5), 934–942.

Lu, B., Christensen, I. T., Ma, L. W., Wang, X. L., Jiang, L. F., Wang, C. X., Feng, L., Zhang, J. S., & Yan, Q. C. (2018). miR-24-p53 pathway evoked by oxidative stress promotes lens epithelial cell apoptosis in age-related cataracts. *Molecular Medicine Reports*, *17*(4), 5021–5028.

Mencucci, R., Stefanini, S., Favuzza, E., Cennamo, M., De Vitto, C., & Mossello, E. (2023). Beyond vision: Cataract and health status in old age, a narrative review. *Frontiers in Medicine*, *10*, 1110383.

Mukherjee, D., Chakraborty, S., Bercz, L., D'Alesio, L., Wedig, J., Torok, M. A., Pfau, T., Lathrop, H., Jasani, S., Guenther, A., McGue, J., Adu-Ampratwum, D., Fuchs, J. R., Frankel, T. L., Pietrzak, M., Culp, S., Strohecker, A. M., Skardal, A., & Mace, T. A. (2023). Tomatidine targets ATF4-dependent signaling and induces ferroptosis to limit pancreatic cancer progression. *iScience*, *26*(8), 107408.

Nita, M., & Grzybowski, A. (2016). The role of the reactive oxygen species and oxidative stress in the pathomechanism of the age-related ocular diseases and other pathologies of the anterior and posterior eye segments in adults. *Oxidative Medicine and Cellular Longevity*, *2016*, 3164734.

Ott, C., Jacobs, K., Haucke, E., Navarrete Santos, A., Grune, T., & Simm, A. (2014). Role of advanced glycation end products in cellular signaling. *Redox Biology*, *2*, 411–429.

Pesudovs, K., Lansingh, V. C., Kempen, J. H., Steinmetz, J. D., Briant, P. S., Varma, R., Wang, N., Jonas, J., Resnikoff, S., Taylor, H. R., Braithwaite, T., Cicinelli, M. V., Vos, T., & Bourne, R. R. A. (2021). Cataract-related blindness and vision impairment in 2020 and trends over time in relation to VISION 2020. The right to sight: An analysis for the global burden of disease study. *Investigative Ophthalmology & Visual Science*, *62*, 3523.

Ranaei Pirmardan, E., Zhang, Y., Barakat, A., Naseri, M., Russmann, C., & Hafezi-Moghadam, A. (2023). Pre-hyperglycemia immune cell trafficking underlies subclinical diabetic cataractogenesis. *Journal of Biomedical Science*, *30*(1), 6.

Richardson, R. B., Ainsbury, E. A., Prescott, C. R., & Lovicu, F. J. (2020). Etiology of posterior subcapsular cataracts based on a review of risk factors including aging, diabetes, and ionizing radiation. *International Journal of Radiation Biology*, *96*(11), 1339–1361.

Shimizu, F., Sano, Y., Tominaga, O., Maeda, T., Abe, M. A., & Kanda, T. (2013). Advanced glycation end-products disrupt the blood-brain barrier by stimulating the release of transforming growth factor-β by pericytes and vascular endothelial growth factor and matrix metalloproteinase-2 by endothelial cells *in vitro*. *Neurobiology of Aging*, *34*, 1902–1912.

Song, X. L., Li, M. J., Liu, Q., Hu, Z. X., Xu, Z. Y., Li, J. H., Zheng, W. L., Huang, X. M., Xiao, F., Cui, Y. H., & Pan, H. W. (2020). Cyanidin-3-*O*-glucoside protects lens epithelial cells against high glucose-induced apoptosis and prevents cataract formation via suppressing NF-κB activation and Cox-2 expression. *Journal of Agricultural and Food Chemistry*, *68*(31), 8286–8294.

Thompson, B., Davidson, E. A., Chen, Y., Orlicky, D. J., Thompson, D. C., & Vasiliou, V. (2022). Oxidative stress induces inflammation of lens cells and triggers immune surveillance of ocular tissues. *Chemico-Biological Interactions*, *355*, 109804.

Wang, H., & Tao, Y. (2021). Relationship between the higher inflammatory cytokines level in the aqueous humor of *Fuchs uveitis* syndrome and the presence of cataract. *BMC Ophthalmology*, *21*(1), 108.

Wang, X., Huang, W., Sun, H., Wang, H., Wang, D., & Wang, Y. (2024). Tomatidine relieves neuronal damage in spinal cord

injury by inhibiting the inflammatory responses and apoptosis through blocking the NF-κB/CXCL10 pathway activation. *Frontiers in Pharmacology*, *15*, 1503925.

Wong, Y. L., Aslam, T. M., Chang, D. F., & Erny, B. (2025). Sustaining ophthalmic practices for the future: A high-value care approach to environmental responsibility. *Ophthalmology and Therapy*, *14*(6), 1199–1218.

Wu, S. J., Huang, W. C., Yu, M. C., Chen, Y. L., Shen, S. C., Yeh, K. W., & Liou, C. J. (2021). Tomatidine ameliorates obesity-induced nonalcoholic fatty liver disease in mice. *Journal of Nutritional Biochemistry*, *91*, 108602.

Yang, S. P., Yang, X. Z., & Cao, G. P. (2015). Acetyl-l-carnitine prevents homocysteine-induced suppression of Nrf2/Keap1 mediated antioxidation in human lens epithelial cells. *Molecular Medicine Reports*, *12*(1), 1145–1150.

Zhang, W. G., Ding, J., Wang, L., Wu, C. J., Mao, J. Y., Ding, K., Zhang, C., Hu, Z. B., Li, S., & Wang, L. (2025). Tomatidine ameliorates diabetes-induced cognitive impairment and tau hyperphosphorylation through the AMPK-TFEB pathway. *Journal of Neurochemistry*, *169*(5), e70087.

Zhu, X., Zhang, K., He, W., Yang, J., Sun, X., Jiang, C., Dai, J., & Lu, Y. (2016). Proinflammatory status in the aqueous humor of high myopic cataract eyes. *Experimental Eye Research*, *142*, 13–18.

Zrieq, R., Ahmad, I., Snoussi, M., Noumi, E., Iriti, M., Algahtani, F. D., Patel, H., Saeed, M., Tasleem, M., Sulaiman, S., Aouadi, K., & Kadri, A. (2021). Tomatidine and patchouli alcohol as inhibitors of SARS-CoV-2 enzymes (3CLpro, PLpro and NSP15) by molecular docking and molecular dynamics simulations. *International Journal of Molecular Sciences*, *22*(19), 10693.