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Original Article

Hederagenin Shows Protective Effects Against Sodium Selenite-Induced Oxidative Stress and Cataractogenesis in Rats via Activation of Nrf2/HO-1 Pathway

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ABSTRACT

Background: Cataracts, a pervasive ocular condition, are defined by the progressive opacification of the crystalline lens, leading to a gradual decline in visual acuity and overall quality of life. This lens clouding obstructs the passage of light to the retina, resulting in blurred or distorted vision. **Objectives:** The current study was performed to investigate the protective mechanisms of hederagenin against sodium selenite-induced cataract formation in rat pups. **Materials and Methods:** Experimental cataract in rat pups were induced using sodium selenite, and they were treated with hederagenin at dosages of 10 and 20 mg/kg, respectively. The lens opacification, oxidative stress markers, Calcium (Ca), and Ascorbic Acid (ASA) levels were evaluated in the lens of the experimental rat pups. The levels of antioxidants, inflammatory biomarkers, and Nrf-2, HO-1, and NQO-1 were assessed in the lens of the rat pups using kits. **Results:** The current findings of this study shown that hederagenin treatment effectively decreased the lens opacification level, oxidative stress markers, Ca levels, and elevated the ASA levels in the lens of cataract-induced rat pups. Furthermore, the hederagenin treatment effectively increased the antioxidant concentrations, decreased the COX-2 and NF-κB levels, and increased the HO-1 and Nrf-2 levels in the lens of the cataract-induced rat pups. **Conclusion:** This work indicated that hederagenin effectively protected the progression of sodium selenite-induced cataractogenesis in rat pups. The findings of this work indicate that hederagenin may serve as a viable treatment option for cataract and warrants further investigation in clinical trials.

Keywords: Nrf-2/HO-1 pathway, Cataractogenesis, Cyclooxygenase-2, Hederagenin, Lens opacification.

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INTRODUCTION

Cataract, a primary cause of visual impairment and blindness globally, is responsible for more than fifty percent of global blindness cases, highlighting its significant effect on public health. Cataracts, marked by the opacification of the crystalline lens, obstruct light transmission to the retina, leading to impaired vision and reduced visual acuity. While cataract surgery stands as one of the primary treatment options, the accessibility and quality of these services remain unevenly distributed, particularly in low-resource settings, thus perpetuating the burden of cataract-related blindness.[1] The causes of cataracts is multifaceted, encompassing age-related changes, genetic predispositions, environmental factors such as ultraviolet radiation exposure, metabolic disorders like diabetes, and lifestyle choices including smoking and alcohol consumption. The implications of cataracts extend beyond mere visual impairment, encompassing a spectrum of socioeconomic and psychological consequences, including reduced productivity, increased risk of falls and injuries, diminished quality of life, and heightened dependence on caregivers.[2] The prevalence of cataracts exhibits considerable geographic variation, with higher rates observed in low- and middle-income countries, attributable to factors such as limited access to eye care services, increased exposure to risk factors, and disparities in healthcare infrastructure. Addressing the global burden of cataracts necessitates a multifaceted approach, encompassing preventive strategies, early detection, improved access to affordable and high-quality surgical services, and comprehensive rehabilitation programs to mitigate the impact of visual impairment on individuals and communities.[3]

The predictions suggest that the number of people affected by blindness will continue to rise, exceeding 40 million by 2025, underscoring the necessity for improvements in eye care systems and vision loss prevention.[4] Despite advancements in surgical techniques and technologies, the growing global population and

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increasing life expectancy are expected to drive a substantial elevation in the individual numbers affected by cataracts in the coming decades. Consequently, there is an imperative need for continued research to elucidate the underlying mechanisms of cataract formation, identify novel preventive strategies, and develop more effective and accessible treatment modalities to combat this pervasive condition.[5] The pathogenesis of cataracts encompasses a complex interplay of biochemical, cellular, and molecular events that disrupt the normal structure and function of the crystalline lens. Oxidative stress, defined by a disproportion of ROS generation and the antioxidant mechanisms, plays a central role in cataract development leading to lipid peroxidation and DNA injury within the lens.[6] Additionally, advanced glycation end products accumulate in the lens and contribute to protein cross-linking, lens opacification, and impaired lens transparency. The exploration of modifiable risk factors, including smoking, alcohol consumption, and dietary habits, has opened avenues for therapies focused at decreasing the incidence and progression of cataracts.[7]

Current therapeutic interventions for cataracts primarily involve surgical extraction of the opacified lens, followed by the implantation of an artificial intraocular lens to restore visual acuity. Despite the efficacy of cataract surgery, which includes techniques like phacoemulsification and small incision cataract surgery, several challenges persist.[8] Accessibility to cataract surgery remains a significant hurdle, particularly in developing countries and underserved populations, contributing to a substantial global burden of visual impairment and blindness. Furthermore, the aging global population and increasing prevalence of diabetes, a major risk factor for cataract development, are expected to drive a surge in cataract cases, placing greater demands on healthcare systems and resources.[9] Plant bioactive compounds represent a promising avenue for cataract treatment due to their inherent antioxidant, anti-inflammatory, and anti-glycative effects, offering a multi-faceted approach to mitigating cataractogenesis.[10] Hederagenin is a pentacyclic triterpenoid compound mainly present in the seeds of Hedera helix plant. The various biological properties of the hederagenin was already well reported, including its anti-inflammatory,[11] anti-leishmanial,[12] antidepressant,[13] anti-atherosclerosis,[14] anti-osteoporosis,[15] anticancer,[16] nephroprotective,[17] and neuroprotective[18] activities. Apart from these potential biological activities, there are no study have examined the preventive mechanisms of hederagenin on the cataractogenesis. Therefore, the current work was performed to investigate the preventive mechanisms of hederagenin against sodium selenite-induced cataract formation in rat pups.

MATERIALS AND METHODS

Experimental animals

The present study utilized the Sprague-Dawley rat pups acquired from Institutional Animal Facility. The 6-day-old rat pups, weighing 16-19 g, were housed with their mothers in a standard conditions with temperature of 25±1°C and 12:12 hr light-dark series. Animals were given a conventional food and unrestricted access to water. This work was conducted in strict compliance with the ARRIVE Guidelines for the Use of Animals in Research, and the experiments received approval from the Institutional Animal Ethics Committee.

Experimental groups

The rat pups were arbitrarily allocated into four groups, each comprising 6 pups in each. Group I was considered as the control. To produce cataracts in the lenses, a single subcutaneous administration of sodium selenite (2.46 mg/kg) were given to the pups in Groups II-IV on the Postpartum Day (PD) 12. Following selenite administration, Group II was considered as the disease control group. Furthermore, Groups III and IV were administered hederagenin intraperitoneally at dosages of 10 and 20 mg/kg, respectively, from 11th to the 17th day. On 12th day, the pups in Groups III and IV were administered hederagenin 1 hr before the selenite administration. On PD 24, the pups were sedated with chloral hydrate and assessed for cataract development. Following an evaluation of cataract development, pups were killed and located in a CO2 chamber. Lens samples were extracted and preserved at -70°C for subsequent examination.

Evaluation of lens opacification

On the last day, the lens opacification was assessed using a scale from 0 to 6, as per the previously established methodology.[19] Stage 0: transparent lens; stage 1: minimal light scattering, detectable solely with a white slight lamp; stage 2: visible light scattering and enlarged fibers; stage 3: diffuse nuclear opacity perceptible to bare eye; stage 4: partial nuclear opacity; stage 5: pronounced nuclear opacity; stage 6: dense mature opacity.

Analysis of biochemical marker levels

The concentrations of Nitric Oxide (NO), Malondialdehyde (MDA), and total sulfhydryl/total thiol (-SH) content were assessed in rat lens samples using commercially available assay kits. The examination was performed as per the manufacturer's protocols (Elabscience, USA). The levels of Ascorbic Acid (ASA) and Calcium (Ca) in the rat lens samples were measured using commercial test kits. The tests were conducted as per the manufacturer's specifications (MyBioSource, USA).

Analysis of antioxidant marker levels

Commercially procured test kits were utilized to assess the quantities of antioxidant markers, comprising Catalase (CAT), Superoxide Dismutase (SOD), Glutathione (GSH), Glutathione-S-Transferase (GST), Glutathione Peroxidase (GPx), and Glutathione Reductase (GR) in the rat lens samples. The manufacturer's specified methods were followed to conduct the assays in triplicate (Abcam, USA).

Analysis of nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1), and NAD(P)H:quinone oxidoreductase 1 (NQO1) levels

The concentrations of Nrf2, HO-1, and NQO-1 in the lens tissue samples of experimental rats were assessed using commercial test kits (MyBioSource, USA). The assays were performed using three replicates in accordance with the manufacturer's recommended procedures.

Analysis of inflammatory biomarker levels

The concentrations of inducible Nitric Oxide Synthase (iNOS), Cyclooxygenase-2 (COX-2), and nuclear factor-κB (NF-κB) in the lens tissue samples of experimental rats were evaluated using commercial kits (MyBioSource, USA). The experiments were conducted with three replicates using the manufacturer's prescribed protocols.

Statistical analysis

The data were portrayed as Mean±SD of triplicates. The data are analyzed using GraphPad Prism. The discrepancies in the data of experimental groups were analyzed utilizing a one-way ANOVA and Duncan's Multiple Range Test (DMRT). A significance of $p<0.05$ was used for comparisons among experimental groups.

RESULTS

Effect of hederagenin on the lens opacification levels in experimental rat pups

The current study observed elevated lens opacification levels in the selenite-induced rat pups with cataract relative to other groups. In contrast, the treatment of hederagenin at 10 and 20 mg/kg concentrations illustrated a substantial reduction in the lens opacification, as depicted in Figure 1. These results suggest that hederagenin treatment may be advantageous for mitigating cataract development in the rats.

Effect of hederagenin on MDA, NO, and sulfhydryl levels in experimental rat pups

Figure 2 demonstrates a notable increase in the concentrations of MDA and NO, and decrease in the sulfhydryl contents in the lens samples of the selenite-induced rat pups, contrasting with the values recorded in the control. However, the hederagenin treatment at doses of 10 and 20 mg/kg effectively diminished the MDA and NO concentrations, subsequently elevated the sulfhydryl concentrations in the lens tissues of sodium selenite-induced rat pups with cataract.

Effect of hederagenin on lens ASA and Ca levels in the experimental rat pups

The current findings demonstrated that rat pups with sodium selenite-induced cataract revealed a marked elevation in Ca level and subsequent reduction in ASA levels in their lens compared with control. Whereas, the hederagenin treatment at dosages of 10 and 20 mg/kg showed a considerable diminution in Ca levels and elevation in ASA concentrations in the lens of the sodium selenite-induced rat pups (Figure 3).

Effect of hederagenin on the antioxidant levels in the experimental rat pups

Figure 4 depicts the concentrations of antioxidants in the lens of the experimental rat pups. The rat pups with sodium selenite-induced cataract exhibited a notable decrease in CAT, SOD, GSH, GPx, GST, and GR concentrations in their lens compared with control. Interestingly, the hederagenin treatment (10 and 20 mg/kg) displayed a considerable elevation in the levels of antioxidants in the lens of sodium selenite-induced rat pups. These findings supports the antioxidants properties of the hederagenin.

Effect of hederagenin on the Nrf-2, HO-1, and NQO-1 levels in the experimental rat pups

The rat pups with sodium selenite-induced cataract demonstrated a significant increase in NQO-1 and subsequent decrease in both HO-1 and Nrf-2 levels in their lens samples in comparison to control. Whereas, the 10 and 20 mg/kg of hederagenin markedly diminished the levels of NQO-1 and subsequently elevated the HO-1 and Nrf-2 levels in the lens samples of the sodium selenite-induced pups (Figure 5).

Effect of hederagenin on the inflammatory biomarker levels in the experimental rat pups

Figure 6 illustrates the effect of hederagenin on the inflammatory biomarker levels in the lens of cataract-induced rat pups. The results indicated that the rat pups with sodium selenite-induced cataract exhibited notable increase in COX-2 and NF-κB concentrations and subsequent reduction in iNOS levels in their lens samples compared to the control group. However, the 10 and 20 mg/kg of hederagenin treatment effectively reduced the COX-2 and NF-κB levels and increased the iNOS levels in the lens of sodium selenite-induced rat pups.

DISCUSSION

Cataract, a prominent global health concern and the leading cause of blindness, significantly impacts individuals worldwide. The condition is characterized by the opacification of lens, leading to a gradual decrease in visual acuteness and overall quality of life.[20] The increasing global burden of cataracts highlights the importance of addressing this issue with effective strategies, particularly in regions with lower socioeconomic development. While cataract surgery has become highly effective, safe, and efficient, it is essential to acknowledge that barriers to accessing surgery remain prevalent in many parts of the world.[21] The pathogenesis of cataract encompasses a complex interplay of biochemical, genetic, and environmental causes that disrupt the

normal transparency of the lens. The lens, primarily composed of water and proteins, maintains its clarity through a highly organized structure. Over time, oxidative stress, ultraviolet radiation exposure, metabolic disorders, and aging-related processes can lead to protein aggregation, cross-linking, and denaturation within the lens.[22] These changes cause light to scatter as it passes through the lens, resulting in blurred or distorted vision. Despite significant advancements in surgical techniques, including the evolution from extracapsular cataract extraction to phacoemulsification and micro-incisional cataract surgery, cataract remains a substantial public health challenge.[23] Therefore, addressing cataract is not only a matter of individual health but also a critical component of global public health.

The pathophysiology of cataract is a multifactorial process influenced by a complex interplay of biochemical and environmental causes. The disruption of redox homeostasis and the consequent oxidative stress have been increasingly recognized as significant contributors to various ocular pathologies.[24] Specifically in the retina, oxidative stress has showed hypothetical role in the development of retinal diseases, which highlights the importance of antioxidants as potential therapeutic agents. Furthermore, the intricate balance between pro-oxidant and antioxidant mechanisms is critical for lens transparency, and any disturbance in this equilibrium can activate a series of events leading to cataract formation.[25] Lipid peroxidation, a chain reaction initiated by free radicals, leads to the formation of MDA, which can modify proteins and DNA, disrupting cellular function. MDA, a marker of lipid peroxidation, shows the degree of oxidative injury to cell membranes. Elevated levels of MDA have been found in the lenses of cataract patients, highlighting its participation in the onset of the disease.[26] These modifications can induce protein aggregation and trigger microanatomical changes that affect tissue structure and function. In the context of cataract formation, the accumulation of oxidatively modified proteins can contribute to lens opacification, ultimately impairing vision. Oxidative damage to lipids results in the creation of lipid aldehydes and lipid peroxides, leading to alterations in membrane fluidity and permeability. Such modifications compromise cellular integrity and contribute to the structural changes observed in cataractous lenses.[27]

NO, a versatile signaling molecule, exhibits a dual role in the context of cataract development, with its effects largely dependent on its concentration and the specific cellular environment. iNOS, an enzyme induced by inflammatory stimuli, generates large amounts of NO. Elevated levels of NO, particularly in the presence of superoxide radicals, can lead to the development of peroxynitrite, a potent oxidant that can damage lens proteins and participate in onset of cataract.[28] Total sulfhydryl groups, essential components of proteins and antioxidant molecules play a critical role in preserving lens transparency and defending against oxidative damage. These groups are susceptible to oxidation by ROS, leading to the formation of disulfide bonds and other modifications that can alter protein structure and function. The oxidation of sulfhydryl groups in lens proteins can promote protein aggregation and insolubilization, contributing to lens opacification.[29] The present results witnessed the increased concentrations of MDA and NO, and decreased iNOS and sulfhydryl contents in the lens of sodium selenite-induced

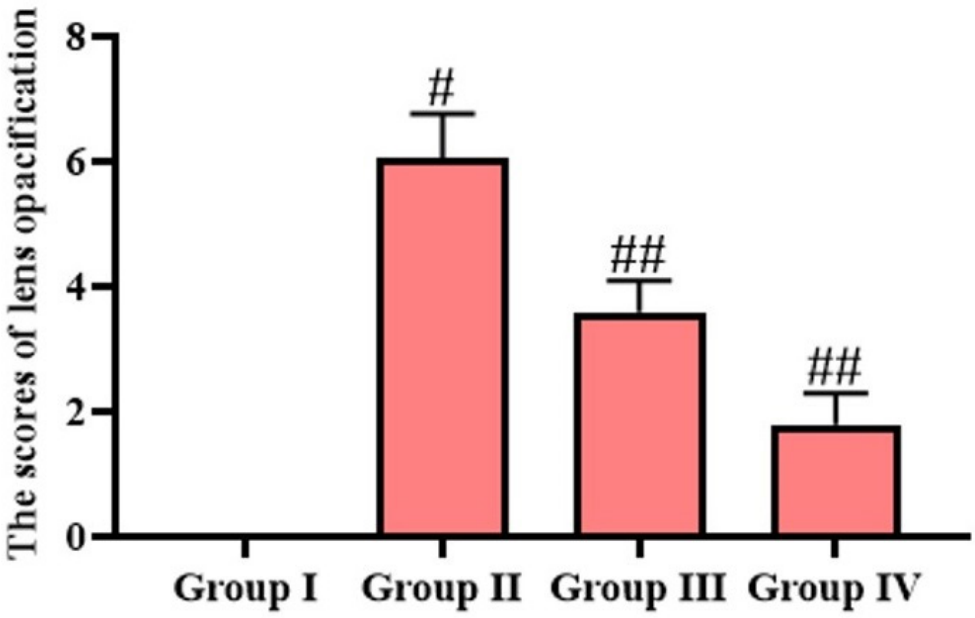

Figure 1: Effect of hederagenin on the lens opacification levels in the experimental rat pups. The data were expressed as the Mean±SD of triplicates. A one-way ANOVA and DMRT were used to assess the differences in values between treatment groups utilizing GraphPad Prism software. The symbol '#' indicates that data vary significantly at $p<0.01$ from the control group; '##' indicates that data vary significantly at $p<0.05$ from the cataract-induced group.

rats. Fascinatingly, the hederagenin treatment considerably reduced the MDA and NO levels, subsequently elevated the sulfhydryl iNOS concentrations in the lens tissues of sodium selenite-induced rats.

The lens, a highly specialized avascular tissue, maintains its transparency through a precise balance of ion concentrations, protein organization, and redox state, making it particularly vulnerable to age-related changes and environmental insults. ASA, a potent antioxidant, is found in high concentrations in the aqueous humor and lens, where it plays a crucial role in protecting against oxidative damage induced by UV radiation, pollution, and metabolic byproducts. The lens epithelium actively transports ASA against a concentration gradient, highlighting its importance in maintaining lens health.[30] ASA's antioxidant properties are crucial for neutralizing ROS that can damage lens proteins, lipids, and DNA, resulting in protein aggregation and light scattering. The interruption of redox balance in the lens, with a shift towards oxidative stress, is a hallmark of cataractogenesis. Furthermore, ASA is involved in the synthesis of collagen, a key component of the lens capsule and zonules, which contribute to maintaining lens shape and structural integrity. A compromised antioxidant defense system, resulting from decreased ASA levels or impaired antioxidant enzyme activity, can accelerate lens opacification.[31] Ca homeostasis is equally vital for maintaining lens transparency and proper function. Ca ions regulate various cellular processes within the lens, including cell signaling, enzyme activity, and membrane permeability. The lens upholds a low Ca level through the action of ATP-dependent Ca pumps and other transport mechanisms.[32] Disruptions in Ca regulation have been implicated in cataract development, as elevated intracellular Ca levels can induce a series of events resulting in lens protein aggregation and cellular damage. The influx of Ca into lens fiber cells can activate calpains, a family of Ca-dependent proteases that degrade lens proteins, disrupting their ordered arrangement and contributing to opacity. Moreover, increased Ca concentrations can promote the development of insoluble Ca-protein complexes, further contributing to lens opacification.[33] Here, the rats with sodium selenite-induced cataract demonstrated a considerable increase in Ca level and decrease in ASA levels in their lens. Interestingly, the hederagenin treatment successfully decreased the Ca levels and elevated the ASA levels in the lens of cataract-induced rats.

The lens, being an avascular tissue, depends on a sophisticated antioxidant mechanism to maintain its transparency and integrity. SOD catalyzes the dismutation of superoxide radicals into hydrogen peroxide and molecular oxygen, serving as the first line of defense against superoxide-mediated damage. Consequently, CAT decomposes hydrogen peroxide into water and oxygen, preventing its accumulation and subsequent conversion into more reactive hydroxyl radicals. Glutathione, a primary non-enzymatic antioxidant functions by scavenging free radicals and as a substrate for GPx and GST. GPx utilizes GSH to reduce hydrogen peroxide and lipid peroxides, detoxifying

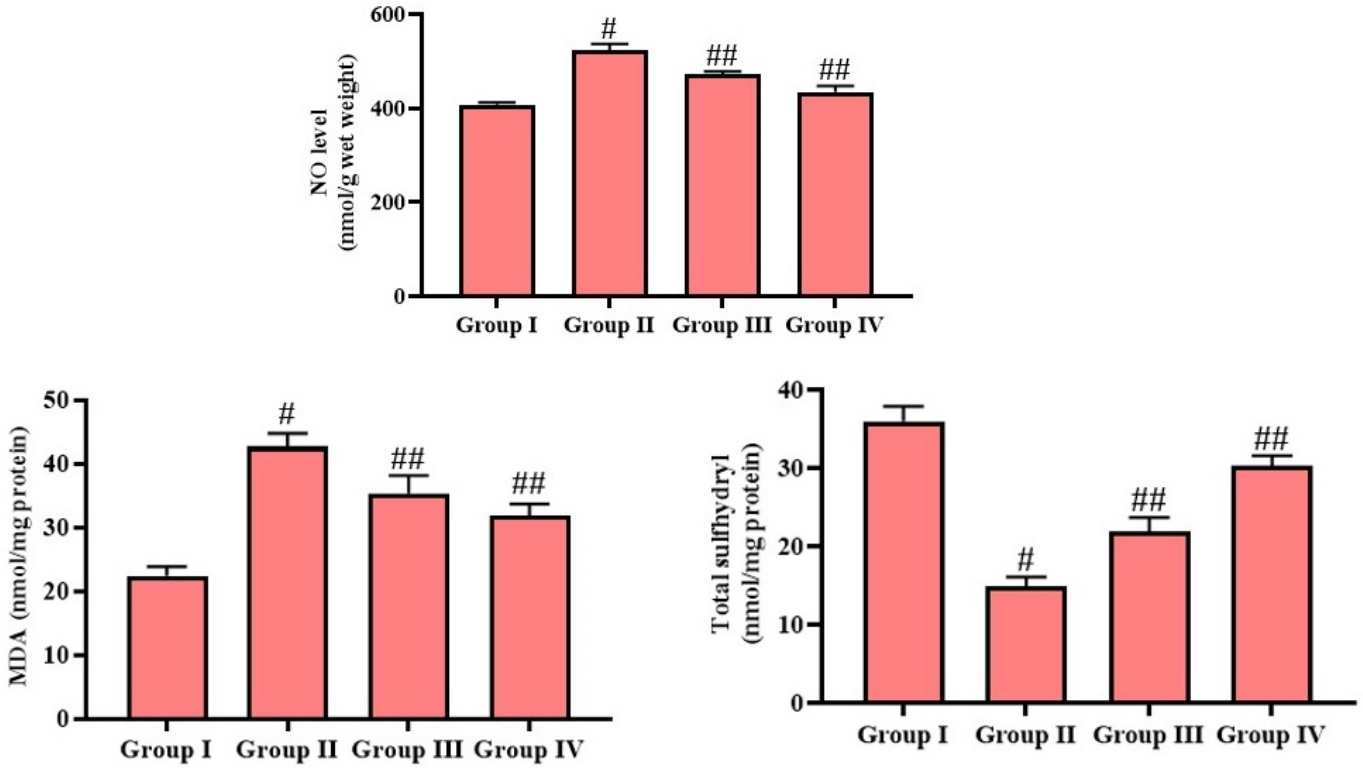

Figure 2: Effect of hederagenin on the MDA, NO, and sulfhydryl levels in the experimental rat pups. The data were expressed as the Mean±SD of triplicates. A one-way ANOVA and DMRT were used to assess the differences in values between treatment groups utilizing GraphPad Prism software. The symbol '#' indicates that data vary significantly at $p<0.01$ from the control group; '##' indicates that data vary significantly at $p<0.05$ from the cataract-induced group.

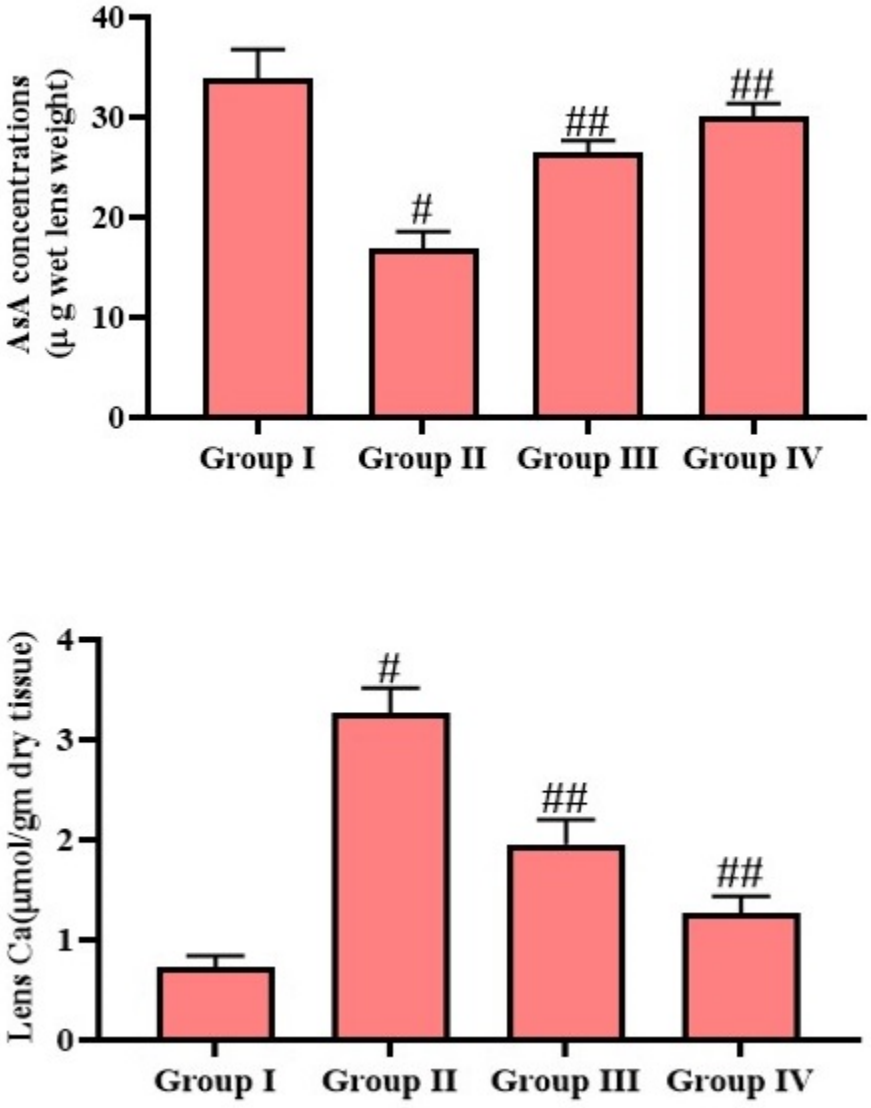

Figure 3: Effect of hederagenin on the lens ASA and Ca levels in the experimental rat pups. The data were expressed as the Mean±SD of triplicates. A one-way ANOVA and DMRT were used to assess the differences in values between treatment groups utilizing Graphpad Prism software. The symbol '#' indicates that data vary significantly at $p<0.01$ from the control group; '##' indicates that data vary significantly at $p<0.05$ from the cataract-induced group.

these reactive species and preventing lipid peroxidation.[34] GST coverts the GSH to several electrophilic compounds, facilitating their detoxification and excretion. GR maintains the pool of reduced GSH by catalyzing the NADPH-dependent reduction of glutathione disulfide, ensuring the availability of GSH for antioxidant defense. The disruption of redox homeostasis can trigger inflammatory responses, which further worsen oxidative stress and participate in the pathophysiology of various diseases.[35] Here, the present findings showed the decreased CAT, SOD, GSH, GPx, GST, and GR concentrations in the lens of sodium selenite-induced rats. However, the hederagenin treatment showed a marked elevation in the concentrations of antioxidants in the lens of sodium selenite-induced rats, which proves its antioxidant activity.

The intricate mechanisms governing cellular defense against oxidative stress are pivotal in sustaining the transparency and functionality of the lens, and among these mechanisms, the Nrf-2 pathway stands out as a critical regulator. Nrf2, a transcription factor, orchestrates the expression of an antioxidant and cytoprotective genes, effectively mitigating the damaging effects of ROS and other electrophiles.[36] Nrf2's activity is finely tuned through multiple layers of regulation, encompassing protein stability, transcriptional control, and post-transcriptional modifications, ensuring a balanced and responsive defense against oxidative insults. Upon exposure to oxidative stress, Nrf2 detaches from its inhibitor Keap-1 and translocates into the nucleus, initiating the transcription of cell defense genes. The activation of Nrf2 leads to the upregulation of numerous downstream targets, including HO-1 and NQO-1, both of

which play essential roles in cellular protection. The induction of these enzymes helps to restore redox balance and prevent cellular damage.[37] HO-1 catalyzes the breakdown of heme into biliverdin, carbon monoxide, and free iron, each exhibiting unique biological functions. Biliverdin is later transformed into bilirubin by biliverdin reductase, and both compounds demonstrate significant antioxidant capabilities, neutralizing free radicals and safeguarding against lipid peroxidation.[38] HO-1's expression is activated by several stimuli, including oxidative stress, inflammation, and heavy metals, reflecting its role as a broad-spectrum cytoprotective agent. HO-1 emerges as a crucial anti-inflammatory and cytoprotective enzyme, residing among the genes governed by Nrf2 activation. Nrf2 mediated HO-1 activation curtails the generation of pro-inflammatory mediators and cytokines, impacting various biological processes, including the reduction of neuroinflammation related neurodegenerative ailments.[39]

NQO-1, a flavoprotein, catalyzes the two-electron reduction of quinones, protecting the development of semiquinone radicals and decreasing oxidative stress. NQO1 also implicates in the detoxification of xenobiotics and protects against the damaging effects of electrophiles, further contributing to cellular defense. NQO1 safeguards cells from the damaging effects of ROS and electrophiles by catalyzing the reduction of quinones, thereby preventing the formation of semiquinone radicals.[40] NQO1 also exhibits a multifaceted role in cellular defense, participating in antioxidant defense, detoxification of xenobiotics, and stabilization of tumor suppressor proteins, contributing to its protective effects against various diseases. The disruption of NQO1 leads to increased oxidative stress, heightened inflammation, and impaired detoxification, collectively contributing to cellular dysfunction and disease pathogenesis.[41] The disruption of redox balance within the lens, driven by elevated ROS production and diminished antioxidant capacity, initiates a cascade of events that lead to cataract formation. The impairment of Nrf2 signaling and dysregulated HO-1/NQO1 expressions have been involved in the onset of age-related cataracts, diabetic cataracts, and other forms of lens opacification.[42] Here, the rats with cataract displayed increased NQO-1 and subsequently reduced HO-1 and Nrf-2 levels in their lens. Though, the treatment with hederagenin evidently reduced the NQO-1 levels and elevated the HO-1 and Nrf-2 concentrations in the lens of cataract-induced rats.

NF-κB, a pivotal regulator of inflammatory and immune responses, modulates the expression of a plethora of genes involved in cellular stress, apoptosis, and cytokine production. COX-2, an inducible enzyme responsible for the synthesis of prostaglandins, mediates inflammatory processes and oxidative stress, both of which influence significantly to lens damage.[43] Dysregulation of NF-κB and COX-2 signaling has been observed in cataracts, suggesting their involvement in the initiation and progression of lens opacification. Understanding the precise mechanisms by which NF-κB and COX-2 contribute to cataract development is essential for identifying potential therapeutic targets and developing novel pharmacological interventions aimed at preventing or delaying cataract formation.[44] In this work, we have found that the rats with sodium selenite-induced cataract illustrated increased COX-2 and NF-κB concentrations in their lens. Interestingly, the hederagenin treatment successfully decreased the COX-2 and NF-κB levels in the lens of sodium selenite-induced rats.

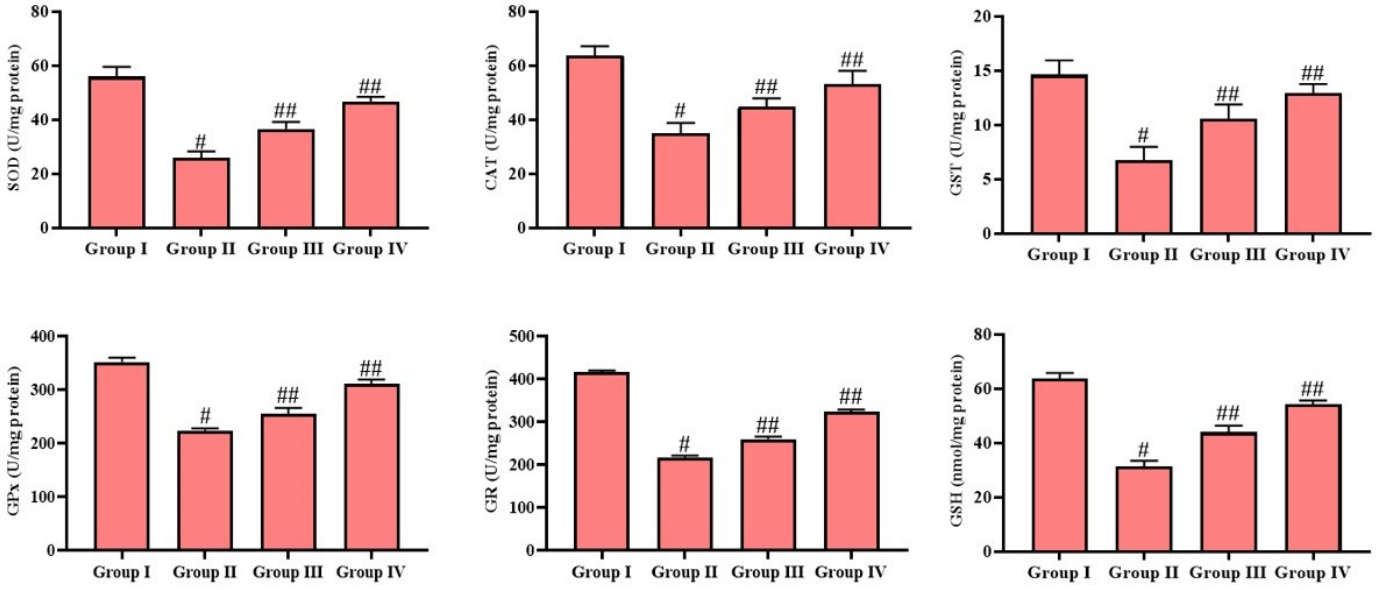

Figure 4: Effect of hederagenin on the antioxidant levels in the experimental rat pups. The data were expressed as the Mean±SD of triplicates. A one-way ANOVA and DMRT were used to assess the differences in values between treatment groups utilizing Graphpad Prism software. The symbol '#' indicates that data vary significantly at $p<0.01$ from the control group; '##' indicates that data vary significantly at $p<0.05$ from the cataract-induced group.

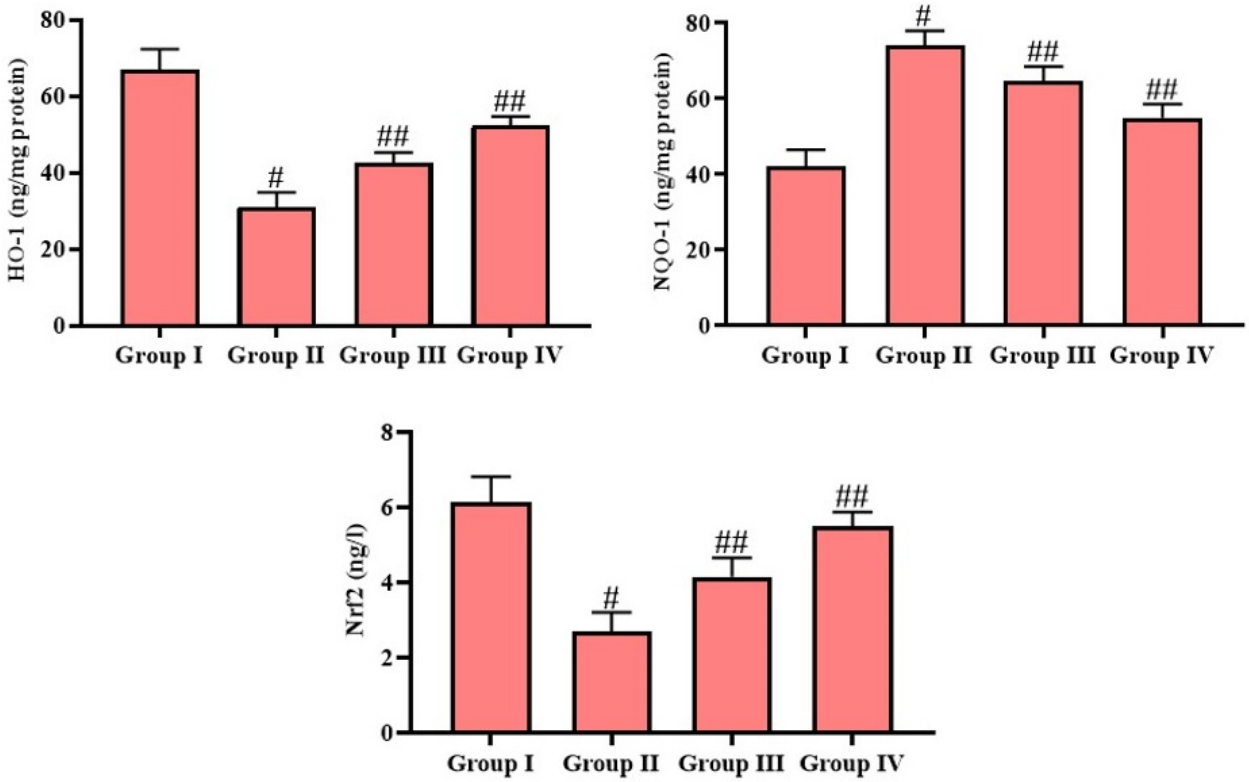

Figure 5: Effect of hederagenin on the Nrf-2, HO-1, and NQO-1 levels in the experimental rat pups. The data were expressed as the Mean±SD of triplicates. A one-way ANOVA and DMRT were used to assess the differences in values between treatment groups utilizing Graphpad Prism software. The symbol '#' indicates that data vary significantly at $p<0.01$ from the control group; '##' indicates that data vary significantly at $p<0.05$ from the cataract-induced group.

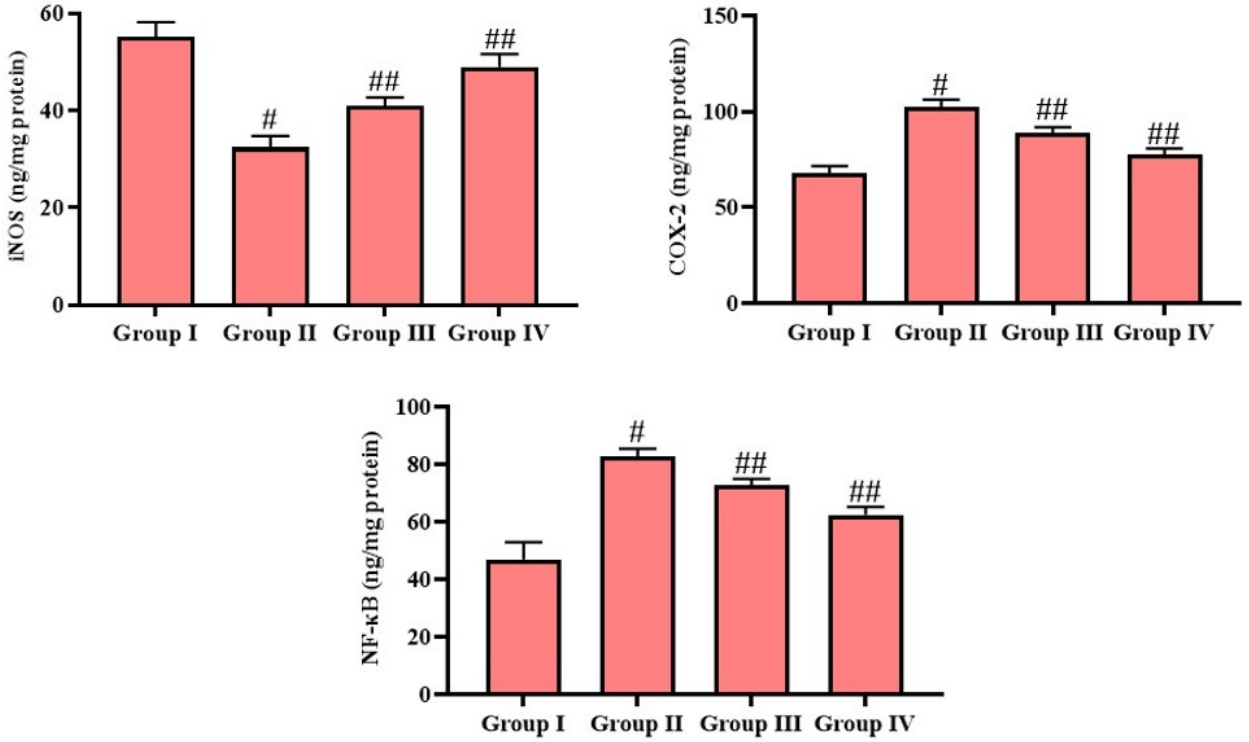

Figure 6: Effect of hederagenin on the inflammatory biomarker levels in the experimental rat pups. The data were expressed as the Mean±SD of triplicates. A one-way ANOVA and DMRT were used to assess the differences in values between treatment groups utilizing GraphPad Prism software. The symbol '#' indicates that data vary significantly at $p<0.01$ from the control group; '##' indicates that data vary significantly at $p<0.05$ from the cataract-induced group.

CONCLUSION

This study indicated that hederagenin effectively protected the progression of selenite-induced cataract formation in rat pups, evidenced by reduced lens opacification, lens Ca, and increased lens ASA levels. Furthermore, the hederagenin treatment also increased the antioxidant concentrations, decreased the NF-κB and COX-2 levels, and activated the Nrf-2/HO-1 signaling in the lens of the cataract-induced rat pups. The findings of this work indicate that hederagenin may serve as a viable treatment option for cataract and warrants further investigation in clinical trials.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

Ca: Calcium; **ASA:** Ascorbic acid; **PD:** Postpartum day; **NO:** Nitric oxide; **MDA:** Malondialdehyde; **SOD:** Superoxide dismutase; **GSH:** Glutathione; **GPx:** Glutathione peroxidase; **Nrf2:** Nuclear factor erythroid 2-related factor 2; **HO-1:** Heme oxygenase-1; **NQO1:** NAD(P)H:quinone oxidoreductase 1; **iNOS:** Inducible nitric oxide synthase; **COX-2:** Cyclooxygenase-2; **NF-κB:** Nuclear factor-κB.

ETHICAL APPROVAL

This work has approved by the institutional animal ethical committee by Xi'an Aier Ancient City Eye Hospital, Xi'an 710014, Shaanxi Province, China.

SUMMARY

Cataracts, a common eye disease, are characterized by the gradual opacification of the lens, resulting in a reduction in visual clarity and even blindness. The opacification of the lens impedes light transmission to the retina, leading to hazy or distorted vision. Notwithstanding the effectiveness of cataract surgery, encompassing methods such as phacoemulsification and tiny incision cataract surgery, numerous challenges remain. This study demonstrated that hederagenin treatment significantly inhibited the progression of selenite-induced cataract formation in rat pups, as seen by decreased lens opacification, reduced lens Ca levels, and elevated lens ASA levels. Moreover, the hederagenin treatment elevated antioxidant concentrations, reduced NF-κB and COX-2 levels, and activated the Nrf-2/HO-1 signaling pathway in the lenses of cataract-induced rat pups.

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