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Research Article

Phloretin delays the progression of diabetic cataract by inhibiting lens aldose reductase enzyme and oxidative damage: *In vitro* and *ex vivo* experimental approaches

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Abstract

Aim and objectives: Flavonoids are the most important phyto-biomolecules used in a variety of diseases as an alternative pharmacotherapy, including diabetic cataract. The present study is designed to explore the anticataract activity of phloretin by evaluating aldose reductase inhibitory activity and antioxidant activity against *ex vivo* experimental models in goat lenses. Methodology: DPPH and NADPH-sorbitol assay were used to assessed the antioxidant and aldose reductase inhibitory activity respectively. For the induction of diabetogenic cataract glucose-induced model was used. In this model, goat lenses were incubated in high concentrations of glucose (55 mM) containing physiological salt solution and phloretin (50, 100, and 200 µg/mL), which was assessed against cataract control lenses. Results and Discussion: The results showed that phloretin (100 µg/mL) considerably inhibits the DPPH free radical and lens aldose reductase activity. The results of the *ex vivo* model showed that phloretin retains lens transparency and reduces cataract maturation. Moreover, the phloretin exposure significantly ($P < 0.05$) increased the antioxidant activity (CAT, SOD, and GSH) and reduced the malonaldehyde level. Additionally, phloretin exposure significantly ($P < 0.05$) restored the lens protein content. Conclusion: The results concluded that phloretin showed promising anticataract activity by inhibiting lens aldose reductase and oxidative stress. The detail molecular mechanism of anticataract action of phloretin need to be explored in future study using in vivo model.

Keywords: Aldose reductase activity, Anticataract activity, Antioxidant activity, Diabetic cataract, Glucose-induced cataract**,** Phloretin.

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Introduction

In developed and developing countries, the major cause of blindness is cataract (1). A cataract is characterized by opacity in the clear lens of the eye, which lowers the amount of light entering the lens and impairs vision (2). In 2019, a study was conducted to estimate the global burden of the disease and showed that visual impairment has experienced a massive growth of 58.45% and a daily rate increase of 32.18% over the past 30 years (3). The most common risk factors are aging, diabetes, hypertension, smoking, oxidative stress, sunlight exposure, high body mass index, steroid use, and myopia (4). Among all the above-mentioned risk factors, according to reports, individuals with diabetes mellitus have a fivefold increased risk of developing cataracts, especially when they are young (5). If a patient has diabetes, then his oxidative stress and aldose reductase also increase, which is the reason for cataract development (6). In the Current scenario, only surgical approaches are available for the Management of cataract, but it may result in post-operative complications, including endophthalmitis, uncorrected residual refractive error, and posterior capsular opacification (7). There are many studies demonstrating that non-surgical treatments are as effective as surgical treatments, and they significantly delay or block the onset of cataract and reduce the surgical complications (8).

Cataract alternative therapies are gaining attention as potential non-surgical options for managing this prevalent eye condition. While surgery remains the standard treatment, various alternative approaches are being explored, including stem cell therapy, homeopathic remedies, pharmacological agents, and natural compounds. These alternatives aim to address the underlying cause of cataract and offer potential benefits, particularly in regions with limited access to surgical interventions (9). The literature review (limited to articles, 2016-2025, Source: Dimensions database, https://app.dimensions.ai/, Accessed on 2 May 2025) for the present study indicates that three major

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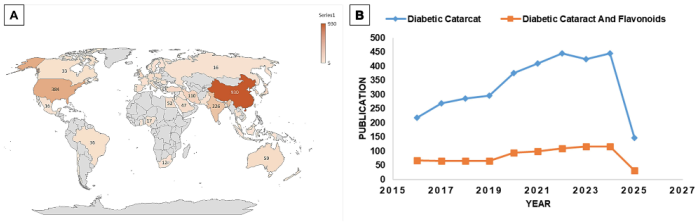
countries, China, India, and the USA, have conducted major documented research on diabetic cataract (Figure 1). Moreover, we concisely a literature survey by using specific keywords, diabetic cataract and flavonoids, and we found that research on flavonoids in diabetic cataract follows the research trends on diabetic cataract. It is well known that flavonoids are the most important biomolecules shown to reduce the progression of cataract formation, like quercetin, catechins, etc (10). In this perspective, we selected a flavonoid, Phloretin, which is a promising biomolecule for cataract management and needs to be explored in detail.

Figure 1: Literature review analysis. (A) Bibliographic matrix and (B) Research trends on diabetic cataract.



Phloretin is a chalcone-class flavonoid, found in the majority of fruits, including apples, pears, and strawberries (11). Phloretin exhibits a variety of pharmacological activities, including antidiabetic, cardioprotective, hepatoprotective, anti-inflammatory, antioxidant, immunosuppressive, and antimicrobial properties (12). Moreover, a study by Sampath et al. (2016) demonstrated that phloretin showed aldose reductase inhibitory activity (13) and therefore, it may be helpful in the management of cataract. In this perspective, we evaluated phloretin's anticataract and aldose reductase inhibitory activity against the glucose-induced cataract model.

Materials and Methods

Drugs and chemicals

Phloretin was purchased from PhytoLab GmbH & Co. KG, Germany. All the other chemicals were of analytical grade and procured from the central chemical store of the department.

In-vitro DPPH assay

2, 2-diphenyl-1-picrylhydrazyl (DPPH) was used to perform antioxidant activity (14). Briefly, we took 1 mL of 100 µg/mL of phloretin and then added 3 mL of 0.1 mM methanolic solution of DPPH, shook it with the help of a vortex shaker and kept it at a dark place for 30 minutes then observed its absorbance at 517 nm in uv-spectrometer ((UV-1780, Shimadzu Scientific instruments, inc., USA)) against blank. The percentage inhibition of DPPH radicals was calculated by using the following formula:

$$Scavenging\ Activity\ (\%\ Inhibition) = \frac{(Ac - At)}{Ac} \times 100$$

Where Ac is the absorbance of the DPPH control, and At is the absorbance of the test sample of phloretin.

In vitro lens aldose reductase activity

In-vitro aldose reductase inhibitory activity was assessed in isolated goat lenses using methods developed by Hayman and Kinoshita (1965). The procedure involved preparing a lens homogenate (10% w/v in phosphate buffer saline, 0.1M, pH 7.4) from normal, transparent lenses. The homogenate was then centrifuged at 10,000 rpm for 30 minutes at 4°C to collect the lens supernatant. Next, the lens supernatant was used to determine the activity of lens aldose reductase. A sample tube was prepared containing 3.5 mL of phosphate buffer saline, 0.5 mL of lens supernatant, 0.5 mL of NADPH (25 x 10^{-5} M), and 0.5 mL of phosphate buffer saline (used as a control) or 0.5 mL of phloretin (100 µg/mL, used as a test). The final reaction mixture was adjusted to a pH of 6.2. The reaction was initiated by adding 0.5 mL of DL-glyceraldehyde (5x10^{-4} M), and the absorbance at 340 nm was monitored for 3 minutes. The unit of aldose reductase activity was calculated for each sample (control and test) based on the change in the absorbance over 3 minutes. A unit of activity was defined as a change in absorbance of 0.001 unit per minute (15, 16). The percentage of aldose reductase inhibitory activity was then calculated using the following formula.

$$Aldose\ reductase\ inhibion\ (\%\ Inhibition) = \frac{(AR\ activity\ in\ control - AR\ activity\ in\ test)}{AR\ activity\ in\ control} \times 100$$

Ex vivo anticataract activity

Phloretin was tested on goat lenses included in a glucose-induced experimental cataract model (17). Fresh goat eyes were collected from a slaughterhouse and isolated using extracapsular extraction. The lenses were kept in freshly prepared Tyrode solution. The anticataract activity of phloretin at 50, 100, and 200 µg/mL was assessed against a high concentration of glucose (55 mM) containing a physiological salt solution, which was used to induce cataract in isolated goat lenses. The experimental groups (each containing 6 lenses) are as follows:

- Group I (Normal Control): Glucose (5.5 mM)
- Group II (Cataract Control): Glucose (55 mM)
- Group III (Phl-50): Glucose (55 mM) + Phloretin (50 µg/mL)
- Group IV (Phl-100): Glucose (55 mM) + Phloretin (100 µg/mL)
- Group IV (Phl-200): Glucose (55 mM) + Phloretin (200 µg/mL)

After 8 hours of incubation, the eye lenses were subjected to evaluation of the pathophysiological parameters of cataract as follows:

Examination of lens opacity

In the *ex vivo* study, after eight hours of incubation in the respective media, the eye lenses were placed on graph paper to monitor the visibility and cloudiness of the lenses. The lines of the graph were visible in normal lenses, while the lines of the graph were unclear in cloudy or cataract lenses. The maturation of cataract was graded as follows: 0 – Clear lens, 1 -Slightly opaque lens, 2- Moderately opaque, 3- Mature opaque.

Examination of oxidative stress markers and protein contents

Oxidative stress markers were assessed in the supernatant of lens homogenates (10% w/v in 0.1M potassium phosphate buffer, pH 7) using spectrometric methods as described in a previous paper (18). The catalase (CAT) enzyme, responsible for converting hydrogen peroxide into water, was measured using the methods of Sinha (1972) (19). The activity of superoxide dismutase (SOD) was estimated using the methods of Kakkar et al.(1984) (20). The reduced glutathione (GSH) was estimated by using Ellman's reagent (21). The lipid peroxidation product malondialdehyde (MDA) was determined using the thiobarbituric acid reaction (22). The soluble and insoluble protein contents in the lens were

quantified using the Lowry method, employing a Folin-phenol reagent (23).

Data Analysis

The GraphPad Prism 8.0 was used for statistical analysis of the results (mean ± SEM) by using one-way analysis of variance (ANOVA). $P < 0.05$ is considered a significant difference between groups.

Results

Effect of phloretin on DPPH assay and aldose reductase assay

Figure 2 depicts the effect of phloretin on the DPPH assay and aldose reductase inhibitory activity. The phloretin at 100 µg/mL scavenged 82.24 % of DPPH free radicals and inhibited 46.42 % of lens aldose reductase activity.

Effect of phloretin on lens opacity

A photographic examination (Figure 3) of the eye lenses suggests that there was increased opacity in the cataract control group compared to the normal group. Further, results showed that Phloretin 50, 100, and 200 µg/mL showed better outcomes when compared to the cataract control group in improving lenticular transparency. Figure 4 depicts the results on cataract maturity. We observed that Phloretin at 50, 100, and 200 µg/mL significantly ($P < 0.05$) mitigated the progression of cataract maturation when compared to the cataract control group. Thus, results indicate that phloretin has a promising anticataract effect against the glucose-induced experimental model.

Effect of phloretin on oxidative stress markers

Figure 5 depicts the effect of phloretin on oxidative stress markers. The cataract control group showed a significant decrease in the level of CAT ($P < 0.05$), GSH ($P < 0.05$), and SOD ($P < 0.05$) as compared to the normal group and an increase in the level of MDA ($P < 0.05$) as compared to the normal group. However, inculcation with phloretin at different concentrations of 50, 100, and 200 µg/mL significantly increased the level of CAT ($P < 0.05$), GSH ($P < 0.05$), and SOD ($P < 0.05$) and decreased the level of MDA ($P < 0.05$). The results also demonstrate that phloretin at 200 µg/mL has the most distinguished effect in restoring the oxidative stress conditions.

Effect of phloretin on soluble and insoluble protein contents

Figure 6 depicts the effect of phloretin on lens protein contents. The cataract control group showed a decrease in the level of soluble protein ($P < 0.05$) and an increase in the level of insoluble protein ($P < 0.05$) as compared to the normal group. However, incubation with phloretin at different concentrations of 50, 100, and 200 µg/mL significantly increased the level of soluble protein ($P < 0.05$) and decreased the level of insoluble protein ($P < 0.05$) as compared to the cataract control group. Results indicate that phloretin mitigated the lens protein modification.

Discussion

The result demonstrated that phloretin has potent anti-cataract activity against the *ex vivo* glucose-induced model which as shown in the results. Phloretin retains the lens transparency and alleviates a variety of pathophysiological parameters involved in cataract formation as compared to the control group, including aldose reductase, oxidative stress, and protein content (24). It is well known that polyol activation within the lens leads to the conversion of glucose into sorbitol by the enzymatic activity of lens aldose reductase. Aldose reductase is highly effective during diabetes because glucose concentration is elevated in the lens. Glucose remains in the lens environment, absorbing it through the glucose transfer system. However, it also exists in the lens when the concentration is high (25). This high glucose concentration activates the aldose reductase enzyme in the lens, which converts glucose into sorbitol, commonly known as polyol. The high sorbitol density renders it imperceptible to the human eye. Subsequently, sorbitol undergoes further metabolic pathways, producing fructose, a toxic substance (26). Fructose-induced oxidative stress leads to the initiation of advanced glycation end products (AGEs) in the protein structure. This process can create a "Schiff base" within the protein, further promoting advanced glycation and potentially causing damage to the cornea and lens transparency (27). The results of the present study demonstrated the inhibitory action of phloretin on lens aldose reductase enzyme, which corroborated a previous report (13). The inhibitory action on lens aldose reductase might be the prime anticataract mechanism of phloretin against diabetic cataracts, which is reflected in the results of lens transparency and cataract maturation. The phloretin, especially at 200 µg/mL, showed significant alleviation in lens transparency.

Concomitant with polyol activation, exacerbation of lenticular oxidative damage, and protein modification enhances the progression of cataract formation (28). In the glucose-induced model, the opacity of the eye lens is observed when it is incubated in a high glucose concentration (50 mM) to induce cataractogenesis by activating the polyol pathway and generating oxidative stress through the excessive production of reactive oxygen species, such as superoxide anion and hydrogen peroxide (29). To combat free radicals, antioxidants are limited in quantity and cannot be eliminated. All free radicals engage in an attack on proteins and lipids, respectively. The accumulation of MDA, a lipid peroxidant within the cornea and lens, can lead to a loss of lens transparency (30). Consequently, we conducted further research on phloretin, including the DPPH free radical scavenging assay, antioxidant activity (CAT, GSH, SOD), and lipid peroxidation (MDA) to evaluate their impact on cataract formation. The finding of the DPPH assay showed the potent antioxidant properties of phloretin, which is also reflected in the *ex vivo* study. The present study's observation revealed that the eye lenses incubated with phloretin exhibited a significant reduction in lenticular oxidative stress as compared to the cataract control lenses, as evidenced by an increase in lens antioxidants (GSH, CAT, and SOD) and a decrease in lipid peroxidant (MAD). The lens antioxidants play a pivotal role in safeguarding the lens from oxidative damage induced by reactive oxygen species. SOD converts superoxide anion I to hydrogen peroxide (31). CAT converts hydrogen peroxide into water and regulates the level of hydrogen peroxide within the cells. GSH maintains the -SH group on the lens protein in its reduced form, thereby attenuating the cross-linking of lens crystalline protein (32). It is widely recognized that elevated reactive oxygen species (oxidants) attack cellular proteins, lipids, and nucleic acids. The elevated MDA level in the cataract group suggests oxidative damage to lenticular lipids. Conversely, the eye lenses exposed to phloretin reduced the MDA level, implying that phloretin may prevent structural modification and cross-links between lens proteins and membranes (33). This observation is further supported by the restoration of protein contents (both soluble and insoluble) by phloretin exposure against glucose. The structural characteristics of proteins play a pivotal role in preserving lens transparency. Notably, the loss of soluble protein content is the defining characteristic of cataract lenses (34), which was observed in the cataract control group. This suggests that phloretin may possess protective effects against protein modification.

Figure 2: Effect of phloretin on DPPH Assay and lens aldose reductase activity. Data were expressed as mean ± SEM (n = 3)

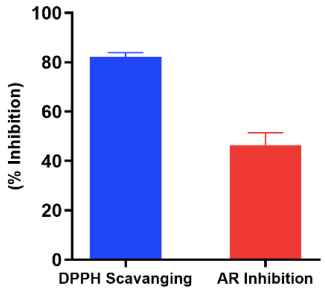


Figure 3: Effect of phloretin on lenticular opacity. (A) Normal control, (B) Cataract control, (C) Phl-50, (D) Phl-100, and (E) Phl-200.

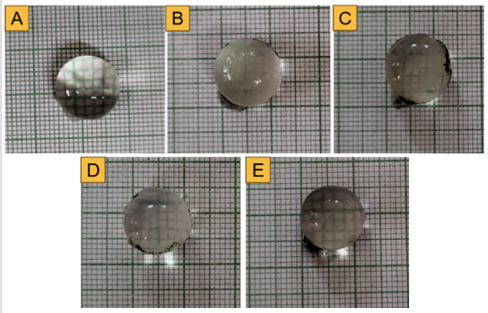


Figure 4: Effect of phloretin on cataract maturation. Data were expressed as mean ± SEM (n = 6), and data were analyzed using one-way ANOVA followed by Tukey's multiple comparison test. *$P < 0.05$ vs normal control group and #$P < 0.05$ vs cataract control group.

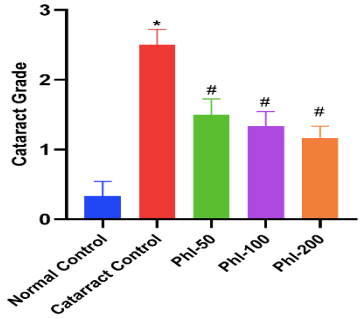


Figure 5: Effect of phloretin on oxidative stress markers. (A) CAT, (B) GSH, (C) SOD, and (D) MDA. Data were expressed as mean ± SEM (n = 6). Data were analyzed using one-way ANOVA followed by Tukey's multiple comparison test. *$P < 0.05$ vs normal control group and #$P < 0.05$ vs cataract control group.

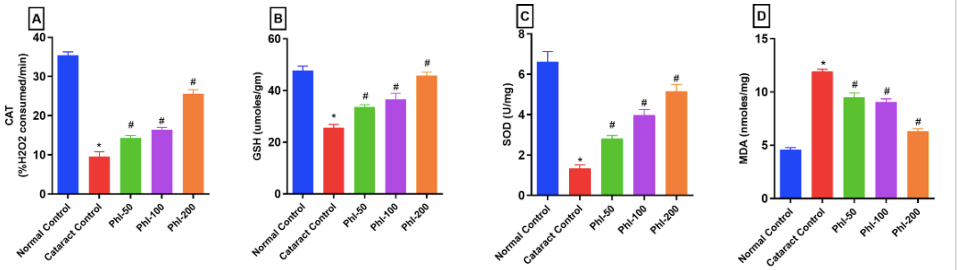
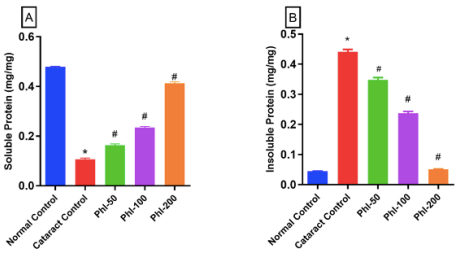


Figure 6: Effect of phloretin on (A) Soluble protein and (B) Insoluble protein contents. Data were expressed as mean ± SEM (n = 6). Data were analyzed using one-way ANOVA followed by Tukey's multiple comparison test. *$P < 0.05$ vs normal control group and #$P < 0.05$ vs cataract control group.



Conclusion

Based on the findings, we concluded that phloretin showed potential anticatarct activity by inhibiting lens aldose reductase enzyme and oxidative stress in glucose-induced models in goat lenses. The current study is limited to the *in vitro* and *ex vivo* models, which do not fully replicate the complex biological system. But the research prepared a path for future research to explore the detailed mechanism of action of phloretin on the biological system (*in vivo* model).

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Conflicting Interests

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

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