Article

Antiglycation Effect of Jabuticaba (*Plinia cauliflora*) and Its Potential Role in Delaying Cataract Formation in Streptozotocin-Induced Diabetic Rats

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Abstract: Jabuticaba fruit (*Plinia cauliflora*) is widely consumed in various forms such as juice, jam, wine, and liquors; however, its potential therapeutic effects on diabetic complications remain inadequately explored. We aimed to investigate the potential antiglycation activity of Jabuticaba, identify the active compounds through bioassay-guided fractionation, and assess its effects on cataract formation in a Streptozotocin-induced diabetic type 1 rat model. Through bioassay-guided fractionation, we identified gallic acid (IC_{50}: 24.7 µg/mL), protocatechuic acid (IC_{50}: 1.22 µg/mL), and an ellagitannin, Repandinin B (IC_{50}: 0.55 µg/mL), as active compounds contributing to antiglycation effects. In the animal study, the addition of Jabuticaba juice extract to the drinking water at a concentration of 0.5% (*w/v*) for 12 weeks demonstrated an amelioration in cataract progression. These results suggest that Jabuticaba has high antiglycation effects leading to the delaying of cataract formation in type 1 diabetes.

Keywords: Jabuticaba; glycation; ellagitannins; cataract

1. Introduction

The progressive opacification of the lens, cataract, is the primary cause of vision impairment and blindness, contributing to about 51% of global cases [1]. Cataracts can be caused by various factors, including aging, diabetes, smoking, alcohol consumption, overexposure to UV radiation, and nutritional deficiencies. Clinical studies have shown that the diabetic population is 3–5 times more likely to develop cataracts compared to the non-diabetic population. With the increasing global prevalence of both diabetes type 1 and 2 worldwide over decades, the risk of diabetic cataract incidence has also risen [2–4]. Unfortunately, cataracts can only be treated surgically by replacing the affected lens with artificial ones [5]. Therefore, investigating non-invasive approaches for the prevention and treatment of diabetic cataract is critical.

Recent evidence revealed that protein glycation plays a causative role in lens opacification [6]. Glycation is a complex chemical process that involves the reaction of reducing sugars with free amino groups of protein or lipids. This glycation process consists of a series of events, including oxidation, dehydration, and cyclization, as well as producing irreversible molecules known as advanced glycation end-products (AGEs). Previous studies demonstrated that cataract progression is associated with lens proteins glycation, the accumulation of AGEs, and cross-linking proteins [7–9].

Given the rising concerns over decades about cataracts in elderly and diabetic patients, targeting protein glycation can be used for intervention. Aminoguanidine, a synthetic compound, is one of the superior glycation inhibitors, which had been developed for renal disease. However, considering its adverse effect on humans, such as anemia, liver damage, and vitamin B_6 deficiency, aminoguanidine is not applied clinically [10–12]. Therefore, we have been interested in nutraceutical approaches to circumvent the problem.

In this study, we focused on the exploration of Jabuticaba juice and its cataract suppressing effect in diabetic rats. Jabuticaba (*Plinia cauliflora*) is a fruit native to Brazil, belonging to the myrtaceae family, characterized by its unique growth directly on trunks, and the diameter of the fruit is approximately 2–3 cm. In Brazil, it is consumed fresh and is used to make a variety of products such as juice, jams, wines, and liquors. Traditional beliefs suggest that Jabuticaba can treat or prevent diarrhea and asthma and has anti-inflammatory properties [13,14]. The statement is also supported by another study that showed that drinking Jabuticaba juice before meals enhanced antioxidant status and plasma glucagon-like peptide 1 (GLP-1) concentrations in healthy subjects [15]. Here, we report the antiglycative effect of Jabuticaba, bioassay-guided fractionation, and in vivo cataract delaying effect of Jabuticaba extract.

2. Materials and Methods

2.1. Chemicals

All the chemicals used for this study were of analytical grade. Acetonitrile (AcCN), ethanol (EtOH), methanol (MeOH), as well as standard gallic acid and protocatechuic acid, were purchased from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan).

2.2. In Vitro Antiglycation Assay

The method was adapted from the previous report with some modifications [16–18]. Briefly, the protein–glucose glycation model was used by mixing the protein and glucose in buffer (reaction solutions). Two reaction solutions (A and B) were prepared, a solution (A) was made by mixing human serum albumin (3 mg/mL), 2 M glucose, 0.1 M phosphate buffer (pH 7.4), and distilled water in a volume ratio of 5:2:2:1. As a background, solution B was prepared similarly but without the addition of glucose. In order to clarify the antiglycation effect of Jabuticaba juice extracts, samples were mixed and added to the reaction solution in the presence and absence of glucose. Thus, 20 μL of the sample (125, 250, 500, 1000 μg/mL) or H_2O as a control was added into 180 μL solution A and solution B in a black microplate. The microplate containing the glycation reaction mixtures was incubated for 48 h at 60 °C. Aminoguanidine was used as a positive control. Glycation was measured by using spectrofluorometry (excitation wavelength 355 nm/fluorescence wavelength 460 nm). Glycation (%) was calculated as follows: $\{(FI_{sample+glu} - FI_{sample-glu})/(FI_{control+glu} - FI_{control-glu})\} \times 100$, where $FI_{sample+glu}$ is fluorecent intensity (FI) of sample with glucose, $FI_{sample-glu}$ is that of sample without glucose, $FI_{control+glu}$ is that of control with glucose, and $FI_{control-glu}$ is that of control without glucose.

2.3. Extraction and Bioassay-Guided Fractionation of Jabuticaba Juice Powder

In this study, we used Jabuticaba juice powder made from whole Jabuticaba fruits and provided by Nature's Power Nutraceutical Co., Ltd., Gardena, CA, USA. The Jabuticaba juice powder (500 g) was initially extracted with 5 L of 60% EtOH at 40 °C for 4 h. The extract was evaporated under vacuum and lyophilized to yield 60% EtOH extract (Jabuticaba juice extract). Further, Jabuticaba juice extract was subjected into DIAION HP20 (Mitsubishi Chemical Corporation, Tokyo, Japan) to give water, 40% MeOH, 100% MeOH fractions. The active fraction (40% MeOH fraction) was fractionated using an open column with Toyopearl HW-40C gel to obtain water (T-W), 40% MeOH (T-40M), 100% MeOH (T-100M), and 70% acetone (T-70Ac) fractions. The active fraction (T-40M) was further purified using an ODS gel open column to afford 5%, 15%, 30%, 50%, and 100% AcCN fractions. Finally, we obtained the 5% AcCN fraction as the active fraction. The fraction was separated by preparative HPLC using a Cosmosil C18 PAQ column (10 mm I.D. × 250 mm, 5 μm, Nacalai Tesque, Kyoto, Japan) with a flow rate of 4.5 mL/min. Mobile phase A was ultrapure water with 0.01% TFA, and mobile phase B was AcCN with 0.01% TFA. The liquid-phase program was as follows: 0−5 min 0% B, 5−40 min 50% B, 40−50 min 100% B, and 50–60 min 0% B. As a result, six fractions (F1 to F6) were obtained.

2.4. Identification of Active Compounds

The active compounds were identified using HPLC and LC-MS. HPLC analysis was performed using a Shimadzu HPLC system equipped with photodiode array. The samples were injected into a YMC hydrosphere column, YMC Co., Ltd., Kyoto, Japan (4.6 mm I.D. × 250 mm) at 40 °C with a flow rate 1 mL/min. The mobile phase consisted of mobile phase A (ultrapure water with 0.1% TFA) and mobile phase B (AcCN with 0.1% TFA). The gradient was started from 0 to 5 min 0% B, 5 to 40 min 50% B, 40 to 50 min 100% B, 50 to 55 min 100% B, 55 to 70 min 0% B. The LC-MS equipment was Shimadzu LC-MS-8045, Shimadzu, Kyoto, Japan. The chromatography was carried out in reverse phase by automatically injecting a 10 μL sample into a YMC Triart C-18 column, YMC Co., Ltd., Kyoto, Japan (2.1 mm I.D. × 100 mm, 1.9 μm) with a flow rate 0.3 mL/min at 40 °C. The mobile phase A was ultrapure water with 0.1% formic acid, and the mobile phase B was AcCN with 0.1% formic acid. The gradient system was used, 0–5 min, 50% B, 5–7 min, 100% B, following the reconditioning to the initial conditions from 7 to 10 min. The mass parameters were set as follows: ionization type, electrospray ionization (ESI), gas temperature set at 250 °C, and a drying gas flow of 10 L/min.

2.5. Animal Study

All experimental procedures in this study were approved by the Committee on Animal Research and Ethics of Pharma Foods International Co., Ltd. (Approval Number: 21KRD-002) and conducted in accordance with the "Basic guidelines for the conduct of animal experiments in implementing agencies under the jurisdiction of the Ministry of Health, Labor, and Welfare".

Five-week-old, male Sprague Dawley (SD) rats were purchased from Shimizu Laboratory Supplies, Co. Ltd., Kyoto, Japan. All rats were housed in a climate-controlled room at 24 °C, 55% humidity and maintained on a 12:12-h light–dark cycle with free access to water and a standard rodent diet (MF laboratory chow, Oriental Yeast Co., Tokyo, Japan). The rats were allowed to acclimatize for the 7 days prior to the experiment. After acclimatization, diabetes was induced by a single intraperitoneal injection of Streptozotocin (60 mg/kg). The rats with blood glucose levels of 300 mg/dL or higher were used for the experiment. The rats were randomly divided into a diabetic control group ($n = 7$) and a Jabuticaba Juice Extract (JJE) group ($n = 8$), which received drinking water and drinking water containing 0.5% (w/v) Jabuticaba juice extract, respectively. Both groups were fed with the same diet with free access during the 12-week experiment period. Bodyweight was measured weekly, while blood glucose, HbA1c, and glycoalbumin were measured at weeks 4, 8, and 12. On the last day, the animals were euthanized, and the lenses were extirpated.

2.6. Grading the Opacity of Lens

Rat lenses were placed on the grid sheet and photographed. The cataract severity was examined and graded on a scale 1 to 4 as described in the previous method, as follows: grade 1—clear lens (grid lines were clearly visible); grade 2—lens with a slight cloudy appearance (grid lines were visible); grade 3—lens with cloudy appearance (part of grid could be confirmed); grade 4—lenses were completely opaque, grid lines could not be seen [19,20].

2.7. Statistical Analysis

Sample groups were compared, and statistical significance was determined by one-way ANOVA with Tukey post-hoc multiple comparison and Wilcoxon sum-rank analysis. All data are reported as mean ± SD. Significant level (p-Value < 0.05 and <0.01) was performed to determine significant differences between samples.

3. Results

3.1. In Vitro Antiglycation Effect of Jabuticaba

For studying the antiglycation effect of Jabuticaba, samples were administered into glycation reaction solutions. After a two-day glycation period at 60 °C, the fluorescence was measured, and glycation activity was represented as percent change against percent of control. As indicated by the fluorescence measurements, Jabuticaba juice was found to lower the glycation in a concentration-dependent manner, as shown in Figure 1. The activity of Jabuticaba was comparable to that of the positive control, aminoguanidine.
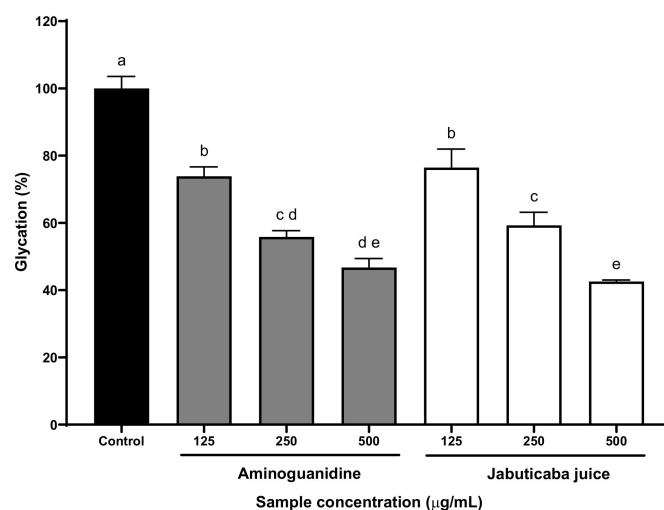

Figure 1. Antiglycation effect of Jabuticaba juice on human serum albumin–glucose glycation model (mean ± SD, *n* = 3; the letters represent the results of a one-way ANOVA with Tukey post-hoc multiple comparisons).

3.2. Screening of Optimal Extraction Solvent through Antiglycation Activity

Prior to identifying the active compound in Jabuticaba, at first, we determined the optimal extraction solvent for obtaining a Jabuticaba juice extract with strong antiglycation activity; the juice was extracted using EtOH at solvent fractions from 40 to 60% EtOH. As indicated in Table 1, the strongest antiglycation activity was observed in 60% EtOH extract (IC_{50} = 230 μg/mL). Our result suggested that 60% EtOH is the most appropriate extraction solvent for further fractionation for finding the active components.

Table 1. Percentage yield and IC_{50} value for antiglycation of different extraction solvents of Jabuticaba juice.

Extraction Solvent	IC_{50} Value (μg/mL) for Antiglycation	Yield (%) [1]
60% EtOH	230	47.0
50% EtOH	394	63.3
40% EtOH	436	80.5

[1] Yield percentage *w/w* of dry weight extract/initial weight of Jabuticaba juice.

3.3. Identification of Active Substance in Jabuticaba

Jabuticaba juice powder was further extracted and subjected to repeated chromatography with the guidance of the antiglycation assay in each fractionation step (Figure 2). Bioassay-guided fractionation led to the isolation of the 5% AcCN fraction as the active fraction. This fraction was further fractionated by preparative HPLC, resulting in three active substances, F-2, F-4, and F-5, with IC_{50} values shown in Table 2. Based on a comparison of the spectroscopic data with the standards, F-2 and F-4 were identified as gallic acid and protocathecuic acid, respectively. The MS/MS spectra of F-5 yielded deprotonated

ions at *m/z* 771, with product ions at *m/z* 726 indicating the loss of a carboxylic acid group ([M-H-COOH]$^-$). Fragment ions at *m/z* 632 suggested cleavage of the oxygenated brevifolin carboxylic acid moiety, while fragment ions at *m/z* 613 indicated dehydration at the sugar moiety. Fragment ions at *m/z* 301 and 275 were characteristic of the hexahydroxydiphenic acid (HHDP) and galloyl moieties, respectively. To validate our identification, we compared the fragmentation data to those of the standard Corilagin and the ellagitannin Repandinin B, which chemical structure had previously been assigned by NMR in the literature (Figure 3) [21]. All the data allowed us to tentatively identify F-5 as Repandinin B.
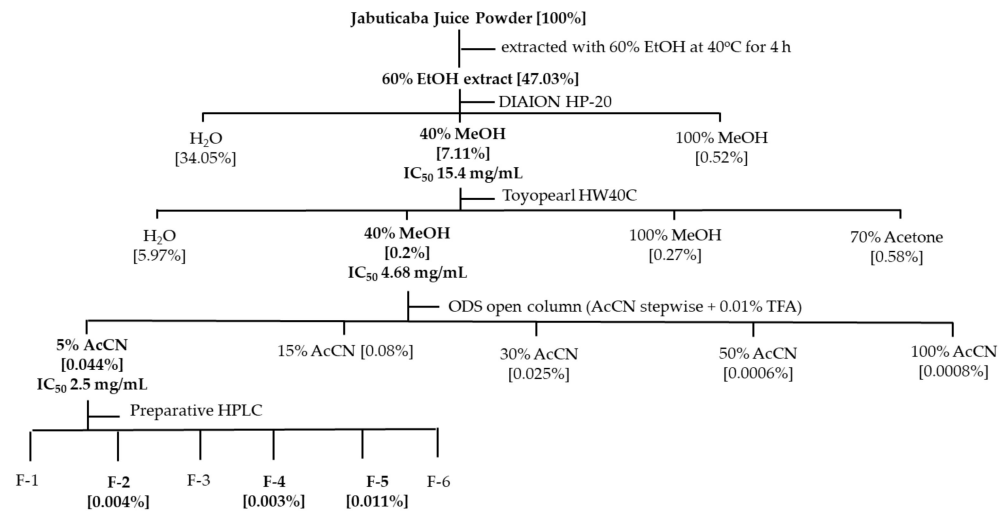

Figure 2. Flow chart of the extraction, fractionation, and purification of antiglycation active compounds from Jabuticaba juice. The active fractions are shown as bold. The percentages in parentheses denote the yields.

Table 2. MS/MS identification and their inhibitory activity against fluorescent AGE formation.

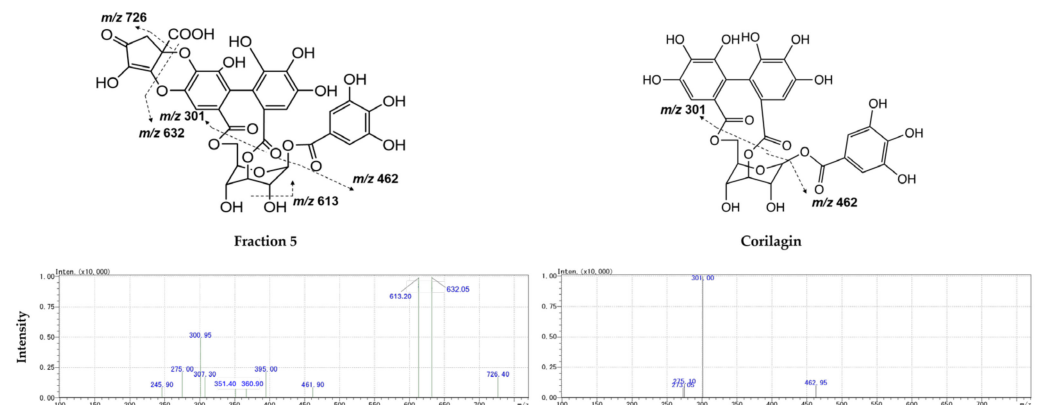| Fraction	Precursor Ions (*m/z* [M-H]$^-$)	Product Ions *m/z*	Compound Identification	Antiglycation (IC$_{50}$ µg/mL)
Fraction-2	169	125, 79	Gallic acid	24.7
Fraction-4	153	108, 91, 65, 53	Protocatechuic acid	1.22
Fraction-5	771	726, 632, 613, 301, 275	Repandinin B	0.55

Figure 3. Chemical structure and MS/MS fragmentation of Fraction 5 and Corilagin.

3.4. Effect of Jabuticaba Juice Extract on Diabetic Cataractogenesis

Prior to treatment with JJE, no significant differences in bodyweight and blood glucose levels were found in the control and Jabuticaba juice extract (JJE) groups. Within the experimental period, the JJE group received Jabuticaba juice extract at concentration 0.5% (*w*/*v*) in their drinking water (JJE group), and plain drinking water was provided for the control group. During our study, there was no significant change in bodyweight, blood glucose, glycoalbumin, and HbA1c levels between the groups. Despite both groups showing high levels of these biomarkers, the JJE group exhibited a suppression of cataract formation at 12 weeks compared to the control group. Later on, lenses were enucleated and classified into four grades. As shown in Figure 4, administration of Jabuticaba juice extract showed a higher number of clear lenses and lower number of grade 4 lenses compared to the diabetic control, and cataract prevalence was significantly different compared to the control group.
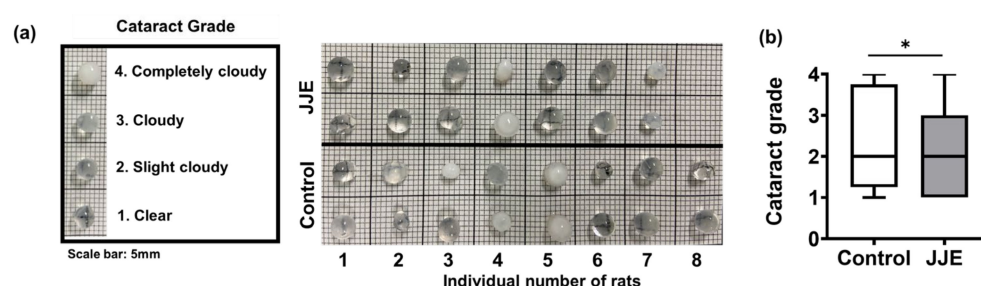

Figure 4. Evaluation of cataract grade between diabetic control and Jabuticaba juice extract (JJE) groups. (**a**) Rat lenses were removed from the eyes, and the degree of light backscattering was assessed by placing the lenses on a grid sheet. (**b**) The cataract prevalence based on grade was compared in each group (* $p < 0.05$, Wilcoxon sum-rank analysis).

4. Discussion

Jabuticaba fruit has gained attention due to its high polyphenol content, including anthocyanins, tannins, flavonoids, and phenolic acids. Although the antiglycation properties of Jabuticaba peel extract have been reported, little research has been done on the impact of Jabuticaba on AGE-induced clinical onset [22]. To our knowledge, this is the first study to examine the effect of Jabuticaba juice on cataractogenesis in a diabetic rat model and also the first report to evaluate an active fraction that contains Repandinin B as an antiglycation substance.

Our bioassay-guided fractionation resulted in the phenolic compounds, gallic acid and protocatechuic acid, and an ellagitannin type compound, Repandinin B, as the main contributing compounds to the antiglycation activity. Gallic acid and protocatechuic acid have been well researched for their antioxidation and antiglycation activities in in vitro and in vivo experiments [23–26]. To the best of our knowledge, Repandinin B has not yet been reported in Jabuticaba, and this is the first report to find antiglycation activity of Repandinin B. In another study, Repandinin B was isolated from a whole plant of *Phyllanthus urinaria* L. and leaves of *Mallotus furetianus* with antioxidant properties [21,27]. In our study, fraction 5, which contains Repandinin B, demonstrated the strongest antiglycation activity. Given the antioxidant property of Repandinin B, we suggest that Repandinin B has a high potential for antiglycation activity.

The structure of phenolic acids that contain hydroxyl groups plays a crucial role in their ability to inhibit glycation. This is because they can bind to the glycation site of albumin through a metal-catalyzed oxidative mechanism [28,29]. In vitro glycation assay has shown that the ellagitannin-type compound (F-5) exhibits higher antiglycation activity than other compounds, which may be attributed to its unique structure containing multiple hydroxyl groups and a hexahydroxydiphenic acid unit that enables it to form stable complexes with metal ions. Therefore, foods that are rich in phenolic acids may have excellent antiglycative properties.

The administration of Jabuticaba juice extract (0.5% *w/v*) in water for 12 weeks suppressed the onset of diabetes cataract. However, Jabuticaba juice extract administration had no impact on blood glucose, HbA1c, or glycoalbumin levels in our animal experiment. Our finding was in good agreement with other studies where curcumin and water chestnut (*Trapa bispinosa*) suppressed the progression of streptozotocin-induced cataract. Interestingly, even though curcumin and water chestnut were reported as antihyperglycemic, antioxidant, and antiglycation, none of them improved blood glucose and insulin level in animal studies [30–32]. On the basis of our study and other evidence, we believe that simply reducing glycemic markers such as blood glucose alone is insufficient to prevent cataract formation. Hence, it is crucial to address the manifestations of hyperglycemia, particularly glycation events, in order to effectively suppress the onset of diabetic cataract. Several studies have identified the accumulation of various advanced glycation end products (AGEs) in cataract lenses, including *N*-(carboxymethyl)-L-lysine, pentosidine, fluorophore LM-1, pyrraline, and *N*-carboxyethyl-lysine [33–38]. However, during the experiment, we did not investigate glycation and AGEs levels in both the diabetic control and diabetic treatment. In this study, we focused on cataract, because surgery is currently the only way to improve it. To address this, we established streptozotocin-model rats (high expression of aldose reductase) that were suitable for the cataract experiment. The results show that Jabuticaba juice extract is able to improve it effectively. As Jabuticaba juice extract was also revealed to have high antiglycation activity, we would like to create a model animal suitable for research on improving diabetes symptoms such as hyperglycemia, insulin resistance, etc.

The causes of diabetic cataract are thought to be complex and involve polyol accumulation mediated by aldose reductase, oxidative stress, inflammation, and accumulation of advanced glycation end-products (AGEs). It has been long believed that under persistent hyperglycemia, glucose is reduced to sugar alcohol by aldose reductase. Since sugar alcohols are not easily metabolized, they accumulate in lens fibers and increase intracellular osmotic pressure. The high osmotic pressure causes the lens fibers to swell, which is the essence of lens opacification [39]. Clinically, it has been reported that increased aldose reductase levels in red blood cells may lead to a greater tendency for posterior subcapsular cataract [40]. In addition to the aforementioned mechanisms, in a larger framework of diabetes pathophysiology, we also considered other factors that exacerbate diabetic pathogenesis, such as the alteration of the gut microbiome. Even though concrete evidence directly linking gut microbiome to diabetic cataract remains unknown, recent findings showed a supporting link among gut microbiome, glycation, and inflammation. In the animal studies, a high-AGEs diet promotes the microbial dysbiosis, leading to elevated levels of inflammatory markers compared to a normal diet [41,42]. We hypothesize that in a hyperglycemic state, elevated glycation levels trigger alterations in gut flora, which in turn increase circulating inflammatory and oxidative stress biomarkers. Consequently, this exacerbates the pathogenesis of diabetes, including the development of diabetic cataract. Accordingly, dietary intervention aimed to suppress glycation levels could be crucial to mitigate diabetic complications. Our research revealed that Jabuticaba, with its demonstrated in vitro anti-glycation activity, significantly suppressed cataract formation in the diabetic rat model. Moreover, Jabuticaba has been reported to possess antioxidant and anti-inflammatory properties, along with its prebiotic role of modulating gut microbiota composition and its metabolites [15,22,43]. Considering that, Jabuticaba may be a promising candidate as a food material with a diabetic cataract preventing function.

Although Jabuticaba fruit has been extensively studied for its biological activities such as antiglycation properties in vitro, its effect on in vivo studies remained unexplored; therefore, in this study, we employed a high-dose concentration (0.5% *w/v*) or 3000 mg/kg/day to observe its effect clearly. This dosage would be approximately 500 mg/kg/day in a human dose [44], which is a high concentration to achieve. In the future, further research is needed to determine the most effective dose of Jabuticaba.

5. Conclusions

Our study provides evidence of the in vitro antiglycation effect of Jabuticaba, which may have potential implications in managing cataract formation and increasing our expectations for Jabuticaba to be used for treatment of diabetic complications. The ease of formulation, oral administration, and the fruit source makes Jabuticaba juice extract an interesting potential nutraceutical for prophylaxis towards cataractogenesis. Further studies are under consideration for human clinical trials so as to understand Jabuticaba's potential in delaying cataract severity and thereby avoiding surgical intervention.

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