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Original Article

Protective Effects of the Phenolic-rich Fraction of Young Corn Silk (*Zea mays L.*) against Pancreatic Islet Destruction in Streptozotocin-induced Diabetic Rats

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ABSTRACT

The phytochemical and bioactive characteristics of plants are influenced by their species and varieties. However, not much is known about the ability of baby corn silk in repairing pancreatic damage. In this study, we investigate the protective effects of the phenolic-rich fraction of vegetable variety baby corn silk (PRFsilk) on the pancreas of streptozotocin (STZ)-induced diabetic rats. Thirty rats were divided into five groups, where Group 1 comprised six nondiabetic control rats; Group 2 was diabetic control; Groups 3 and 4 were diabetic rats treated with 100 and 200 mg/kg/day of PRFsilk, respectively; and Group 5 served as diabetic treatment control with 150 mg/kg/day of metformin. After 28 days of administrating PRFsilk, diabetic rats in Groups 3 and 4 had their blood glucose levels significantly lowered by 67.45% and 66.85%, respectively, compared with the diabetic control group, with more insulin detected in their pancreatic homogenates through ELISA assay. The histological assessment found signs of damage and atrophy in the islet cells of all diabetic rats, with the worst observed in the diabetic control group. However, the islets of PRFsilk-treated rats had little damage caused by STZ induction compared with the pancreas of metformin-treated rats, particularly in Group 3, which was treated with a lower PRFsilk dose. This showed that the PRF of baby corn silk could ameliorate STZ-induced pancreatic damage in rats, most likely through its anti-oxidative and immune-boosting properties.

INTRODUCTION

High blood sugar or hyperglycemia is a characteristic of people with diabetes [1]. Hyperglycemia in diabetes occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces [2]. Insulin is a peptide hormone responsible for maintaining normal blood glucose levels in the body by facilitating cellular glucose uptake, regulating carbohydrate, lipid and protein metabolism and promoting cell division and growth metabolism [3]. Pancreatic β-cells are responsible for insulin production [2]. β-cell dysfunction and declining β-cell numbers are responsible for the loss of endocrine pancreas function in both type 1 and type 2 diabetes. Taking into account the pathology of diabetes, the prevention of beta cells from degenerating and the enhancement of the endogenous regeneration of islets will be a crucial strategy in the management of diabetes.

Multiple interventions have been developed to improve glycemic control and the prevention of diabetes complications [4–6]. In this area, recently, the use of bioactive components has been considered a new approach to preventing and managing diabetes and its complications [7]. The plant-derived phenolic compounds possess a wide range of pharmacological properties and their mechanisms of action have become the subject of considerable interest. In this context, a component known as the phenolic-rich fraction (PRF) has received much attention because of its potent free-radical scavenging and antioxidant action [8]. Plants with high phenolic compounds have been reported to have beneficial properties in managing diabetes [9]. Many studies have shown the effects of plant polyphenolic compounds in lowering postprandial

and fasting hyperglycemia in animal models [10]. Such compounds may affect glucose metabolism in the body by protecting and restoring β-islet cell integrity in the pancreas, improving cellular glucose absorption and enhancing insulin-releasing activity [8,11].

The use of corn silk (CS) in traditional medicine may be traced back to Ayurvedic healers in India, who have been utilizing it mostly to treat diabetic symptoms and complications [12]. In-vivo studies on some of its polysaccharides and different extracts have shown considerable anti-diabetic effects in mice and rat models [13–21]. Baby CS is known to have a high content of phenolic compounds, which may reduce insulin resistance. However, not much systematic information is available about the potential of PRF extracted from baby CS in repairing pancreatic damage that causes diabetes. Hence, the present study aims to investigate the beneficial effects of PRF from baby corn silk of the vegetable variety on the pancreas morphology of streptozotocin-induced diabetic rats.

MATERIALS AND METHODS

Preparation of PRF from Baby Corn Silk

Fresh baby corns aged around 40 to 45 days were obtained from a farm in Pasir Mas district in the state of Kelantan, Peninsular Malaysia. The corns were immediately taken to a lab at the Health Campus of Universiti Sains Malaysia (USM) near the state capital of Kota Bharu. The PRF of baby CS (PRFsilk) was extracted as described in our previous study [22]. A specimen of the source plant with voucher number 11801 was deposited at the Herbarium Unit, School of Biological Science, at the USM main campus in the state of Penang.

Experimental Setup and Diabetes Induction

The research was carried out as previously described by Hamzah *et al.* [23] with ethical approval by the institution's Animal Ethics Committee [USM/IACUC/2017/(832)]. Briefly, 30 male Sprague-Dawley rats were divided into five groups comprising six rats each, namely the negative control group (NCG), diabetic control group (DCG), three diabetic groups treated with PRFsilk at 100 and 200 mg/kg/day (100PRFsilk and 200PRFsilk) and metformin at 150 mg/kg/day (150met). Metformin was used as a positive treatment control as it was widely prescribed for the management of diabetes in human.

Diabetes was induced in rats through peritoneal administration of streptozotocin (STZ) (Merck, Darmstadt, Germany) as described by Hamzah *et al.* [23]. STZ powder was dissolved in 0.1 M sodium citrate buffer (pH 4.5) and injected once directly into the rats' abdomen at a dose of 55 mg/kg/day. Food and water intake were closely monitored and diabetes was validated by checking the fasting blood glucose (FBG) of the rats using a glucose strip on the third and seventh-day post-STZ injection. Rats with consecutive FBG levels of ≥13 mmol/L on the screening days were considered diabetic [24]. The diabetic rats were treated with PRFsilk and metformin once a day for up to four weeks (D28) through gavage. The dosages of PRFsilk rats used in this experiment were based on a study by Patel *et al.* [25] that used a fractional extract of the plant for their anti-hyperglycemic study in STZ-induced diabetic rats.

Determination of Fasting Blood Glucose and Pancreatic Insulin

The rats were fasted overnight prior to the FBG test. On dosing days and every subsequent week, blood samples were collected by nicking the tip of the tail vein and dripping one to two drops onto the glucose test strip, which was then read using the Roche Accu-Chek glucometer (Roche Diagnostics, Mannheim, Germany). After treatment for 28 days, the rats were sacrificed under anesthesia. The pancreas was excised, washed with saline and divided into two portions for histological study and insulin quantification.

The latter portion was homogenized in cold PBS (1:9 w/v) on ice. The pancreatic homogenates were then centrifuged for five minutes at 5000 g, and the supernatant was collected for analysis on a Rat INS (Insulin) ELISA Kit (Elabscience, Houston, Tx, USA) according to the manufacturer's instructions.

Histopathological Studies

The remaining pancreatic portions of all rat groups were fixed in 10% buffered formalin (Sigma, St Louis, Mo, USA) and processed into paraffin blocks on a tissue embedding machine. The blocks were sectioned using a microtome (5 μm) and tissues were placed on silane-coated slides. The sectioned tissues were stained with hematoxylin and eosin for histological evaluation according to our previous publication [23].

Data Analysis

Statistical tests were performed using IBM SPSS Version 24 (IBM Corp, Armonk, NY, USA). The results were presented as mean ± standard error (SEM). Statistical differences in mean FBG and insulin levels between treatment groups were determined using a one-way analysis of variance (ANOVA), followed by the Duncan post-hoc test ($p<0.05$).

RESULTS AND DISCUSSION

Effect of PRFsilk on FBG Levels

Fig. 1 illustrates the effect of PRFsilk on FBG. STZ-induced diabetic rats showed a significant increase ($p<0.05$) in blood glucose when compared to NCG. After treatment for four weeks, a significant decrease ($p<0.05$) in FBG levels was seen in diabetic rats treated with the PRFsilk (100 and 200 mg/kg) and metformin (67.45%, 66.85% and 66.76%, respectively) compared to the DCG. The increased levels of FBG in STZ-induced diabetic rats were significantly lowered by the administration of PRFsilk.

In the present study, on treating diabetic rats with PRFsilk, the FBG levels were significantly lowered compared to metformin. This anti-hyperglycemic activity of PRFsilk was possibly attributed to the additive effect of activation of a number of molecular pathways by the various enriched bioactive components. These phytoconstituents present in PRFsilk may enhance glucose uptake, increase insulin-sensitizing and secreting properties [26]. PRFsilk has been reported to contain different sub-classes of flavonoids [22]. Some of these sub-classes have been reported to have anti-diabetic activity such as flavones, flavonols and flavanols [27]. Therefore, these flavonoids might contribute to the anti-diabetic potential of PRFsilk.

Effect of PRFsilk of Baby Corn Silk on Pancreatic Insulin Concentration

The mean insulin concentration in pancreatic homogenates of each rat group is displayed in Fig. 2. The pancreatic insulin concentrations were significantly reduced ($p<0.05$) in diabetic mice compared with NCG. However, 100PRFsilk, 200PRFsilk and 150met groups exhibited higher concentrations (68.33, 115.83 and 59.17 ng/mL, respectively) than the DCG (5.5 ng/mL).

The development of diabetes was the effect of significant pancreatic injury, which decreased the total surface area of the islets due to the destruction of β-islet cells [28]. The death of β-islet cells was believed to be brought on by oxidative stress caused by excessive production of reactive oxygen species (ROS), leading to a decrease in insulin production. Insulin is the only hormone known to reduce the level of glucose in the blood by stimulating its uptake in tissues and organs [29]. In the present study, insulin levels in DCG rats were significantly lower compared with NCG, indicating β-islet dysfunction since prolonged exposure to high glucose concentrations would impair the responsiveness of insulin release from cells [30]. However, the insulin concentrations in the pancreatic homogenates of PRFsilk-treated groups were higher than DCG. This result might be attributed to the effects of flavonoids, a major phenolic compound found in PRFsilk, as reported in our previous study [22]. The flavonoids detected in PRFsilk comprised flavones, flavonols, flavone *C*-glycoside, flavonol *O*-glycosides, flavonols and isoflavonoids [22]. A growing number of evidence has supported the efficacy of flavonoids in protecting β-islet cells in the pancreas [31]. Flavonoids such as EGCG [32], eupatilin [33] and proanthocyanidins [34] have been shown to increase pancreatic insulin production in animal models of diabetes.

Morphological Condition of the Pancreas in PRFsilk-treated Rats

The morphological grading of the pancreas in all rat groups is shown in Table 1. In NCG, normal pancreatic structures were seen in the islets of Langerhans and acini tissues (Fig. 3A). Many round-to-elongated islets were evenly distributed all around the pancreatic acini. The borders of the islets were well-defined and homogenous in appearance. The pancreatic sections of the DCG demonstrated severe pathological alteration, which indicated degeneration of islets and acini (Fig. 3B). The DCG rats showed a decrease in the number of islets, which were mostly atrophied and damaged with irregular borders. The pancreatic sections of 100PRFsilk rats exhibited mild pathological alterations (Fig. 3C). The islet's borders could be clearly differentiated in the slide samples. Additionally, this group exhibited near-normal pancreatic acinar morphology. The 200PRFsilk rats had moderate pathological alterations, including islet degeneration with irregular borders.

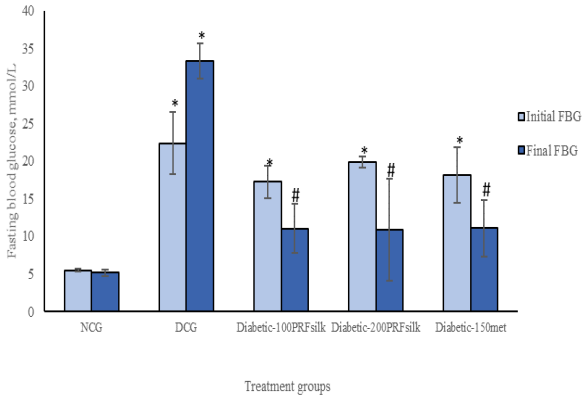

Fig. 1 Comparison of initial and final fasting blood glucose (FBG) concentrations in the different experimental groups. Values are means ± SEM of 6 rats from each group. A mean value was revealed by the Duncan comparisons test (p<0.05). *Significant difference compared to NCG (p<0.05). #Significant difference compared to DCG (p<0.05).

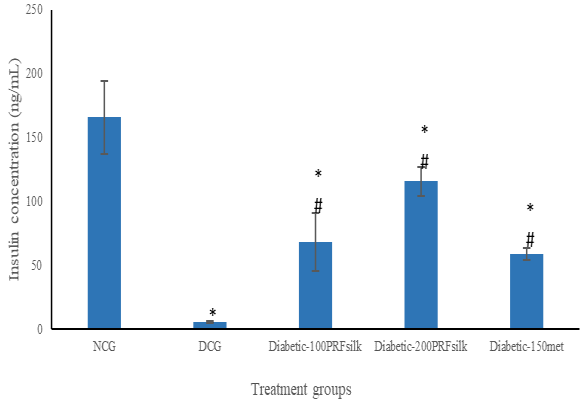

Fig. 2 Effects of PRFsilk administration on level of Insulin production. Values are in mean ± SEM of all six rats from each group. A mean value was revealed by the Duncan comparisons test (P < 0.05). *Significant difference compared to NCG (p<0.05). #Significant difference compared to DCG (p<0.05).

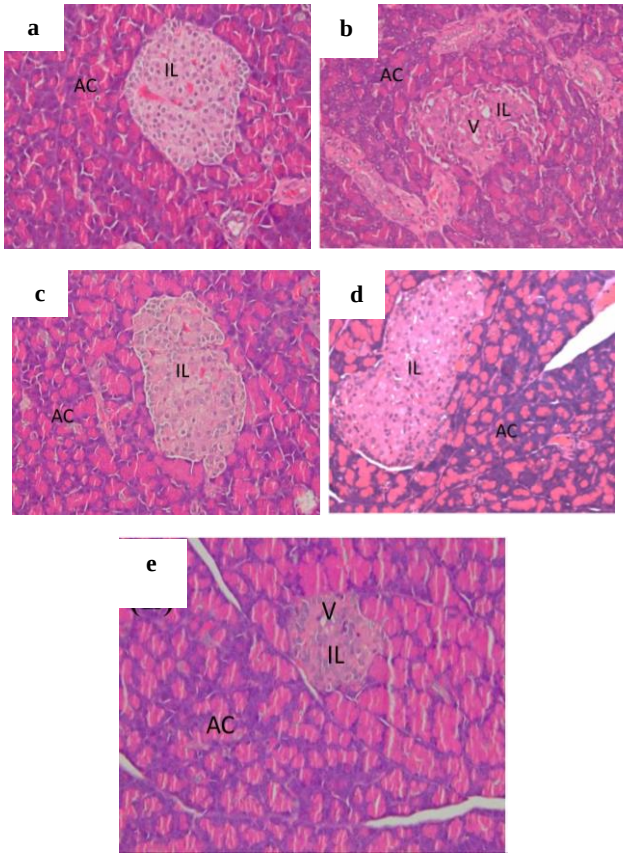

Fig. 3 H&E staining of rat pancreas captured under 40× magnification. a: Pancreas of the NCG; b: Pancreas of the DCG; c: Pancreas of diabetic rats treated with 100 mg/kg of PRFsilk; d: Pancreas of diabetic rats treated with 200 mg/kg of PRFsilk; E: Pancreas of diabetic rats treated with 150 mg/kg of metformin. Islet of Langerhans (IL); acini (AC); vacuolations (V).

However, compared with DCG, this group exhibited less severity of the condition (Fig. 3D). In comparison with the PRFsilk-treated groups, the 150met group revealed moderate pathological alterations with improved morphology, which was more similar to those of the 200PRFsilk group (Fig. 3E).

Table 1 Grading of the morphological changes in the pancreas of rats

Morphological Changes / Treatment groups (n=6)	Degeneration of islet and acini	Decrease in islet number and size	Damaged cells in islets
NCG	-	-	-
DCG	+++	+++	+++
Diabetic-100PRFsilk	+	+	+
Diabetic-200PRFsilk	++	++	++
Diabetic-150met	++	++	++

Note: (–) none, (+) mild, (++) moderate, (+++) severe.

Additionally, this group exhibited near normal pancreatic acinar morphology. However, a moderate, irregular border of the islets could be observed.

In the current study, histological examination of the pancreas found various degrees of damage to the islet of Langerhans in rats administered with STZ, including the loss of cellular boundaries and acini degeneration. However, oral treatment of PRFsilk and metformin could ameliorate these damages, thereby preserving tissue integrity and allowing the cells to produce insulin to maintain glucose homeostasis. The pancreatic islets could have been protected through the neutralizing of free radicals and hyperglycemic-induced oxidative stress generated by STZ, and other researchers had proposed a similar series of action to improve the body's antioxidant defense mechanism [28,35]. Reduction and inhibition of the toxic effects of STZ on the rats' pancreas by PRFsilk could be attributed to its phenolic content, which was mainly responsible for the antioxidant activity. The antioxidants in PRFsilk could boost the quenching of free radicals generated inside the cells, as well as having the capability to protect organ tissues from oxidative stress damage.

It was interesting to note that the 100PRFsilk group had demonstrated less histological damage compared with the 200PRFsilk and 150met groups. These findings suggested that a low dose of PRFsilk might confer better protection on the pancreas against pathological alterations associated with diabetes development. A similar result using a different extract had been observed by Xiangyang *et al*. [30], which reported that treatment of alloxan-induced diabetic mice with a low dose of monk fruit extract (*Siraitia grosvenori*) could significantly reduce the severity of islet cell injury compared with a high dose, presumably due to the presence of mogrosides. Just like phenolic compounds, mogrosides had also been shown to exhibit antioxidant activities [36], and the diabetic mice given a low dose of the extract were observed to have improved immune cell function and CD4/CD8 T-cell balance in the pancreas. The expression of pro-inflammatory TH1 cytokines that leads to tissue damage was also altered towards a TH2 pattern, which promoted a humoral response [30]. Hence, a lower dose of PRFsilk could hypothetically elicit a similar mode of action as the monk fruit extract in terms of alleviating oxidative stress caused by STZ. However, in our case, this needs to be proven in future studies to observe T-cell response and cytokine expression patterns in STZ-induced diabetic rats treated with PFRsilk.

CONCLUSION

In summary, the treatment with PRFsilk exerted an anti-hyperglycaemic effect that could maintain pancreatic tissue integrity and increase insulin production in STZ-induced diabetic rats, thus exerting its beneficial anti-diabetic effects. Therefore, the PRFsilk of baby CS from the vegetable variety could potentially be developed into an effective supplement and formulation of a dosing regimen in the management of diabetes.

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Conflicts of Interest

The authors declare they have no conflict of interest.

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