Trop J Nat Prod Res, March 2025; 9(3): 1058 - 1066 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Effect of Papaya Peel Nata Oral Administration on the Blood Glucose Level in Male Rats with Streptozotocin-Induced Diabetic Mellitus

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ARTICLE INFO

Article history:
Received 21 November 2024
Revised 20 December 2024
Accepted 06 March 2025
Published online 01 April 2025

ABSTRACT

Papaya peel, an often-discarded by-product of papaya fruit processing, is rich in fiber, making it a potential raw material for producing nata - a gel-like fermented product with potential health benefits. This study aimed to develop nata product from papaya peel and evaluate its effect on blood glucose in diabetic rats. Crude fiber content and antioxidant capacity of papaya peel nata (PPN) were determined. Twenty-five male Wistar rats were divided into five groups of 5 rats each: negative control (administered 2 mL distilled water), positive control (administered 0.6 g cellulose), and the treatment groups - administered PPN at doses of 0.5 g (PPN1), 0.6 g (PPN2), and 0.7 g (PPN3) orally once daily for four weeks. All rats were induced with a single intraperitoneal dose of 40 mg/kg of streptozotocin (STZ). Fasting blood glucose (FBG) was measured before and after STZ induction and post-treatment. Body weight, body length, Lee index, and overall health status of the rats were monitored weekly. The results showed that PPN administration led to a significant reduction in FBG after four weeks of treatment. Body weight recovery and minimal muscle mass loss (as indicated by Lee index) were also observed, particularly in the PPN1 group. PPN exhibited good antioxidant activity, and contained high crude fiber (2.08%), which may have contributed to its blood glucose-lowering effect by increasing food viscosity, thereby reducing appetite and delay the absorption of nutrients, including glucose. These findings support the potential for use of PPN as supportive intervention in diabetes management.

***Keywords*:** Papaya peel, Papaya peel nata, *Acetobacter xylinum*, Dietary fiber, Diabetes mellitus.

Introduction

Carica papaya, the plant species from the *Caricaceae* family, thrives in tropical and subtropical regions, including Indonesia.[1] Its fruits often known as papaya consists of seeds (5.4%), fruit peel (25.3%), and flesh (69.3%).[1] With its high soluble fiber content of 1.7 grams per 100 grams of raw fruit,[2] papaya is widely used in food products such as jams and jellies.[3] However, the papaya peel is often a discarded by-product of these processes.[3] Fruit waste is rich in carbohydrates such as polysaccharides, sucrose, glucose, and fructose, therefore it is suitable for nata production.[4] Nutritional analysis reveals that papaya peel contains carbohydrates (89.9 grams), ash (10.6 grams), protein (15.8 grams), and fat (1.46 grams) per 100 grams of dry weight.[5] A study has shown that mature papaya peel comprises 3.5% protein, 26.2% fiber, 3.05% fat, 15.03% ash, and 52.2% carbohydrates.[6] Nata, a gel-like product, is formed on the surface of fermentation medium by *Acetobacter xylinum*. In Spanish, Nata is a type of cream, such as *nata de coco*, which means coconut water cream.[7] Nata was originally known as *nata de coco*,[7] but it is now known by a variety of names depending on the source of the raw material, one of which is papaya peel.

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Citation: Fitriana N, Yustisia I, Kadir S, Azis I, Hardjo M. Effect of Papaya Peel Nata Oral Administration on the Blood Glucose Level in Male Rats with Streptozotocin-Induced Diabetic Mellitus. Trop J Nat Prod Res. 2025; 9(3): 1058 – 1066 https://doi.org/10.26538/tjnpr/v9i3.21

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

Nata is made up of millions of cellulose fibers, usually in the form of a white or transparent solid. Due to its high carbohydrates content, papaya peel can be used as a biomass source for aerobic fermentation in nata production, with the carbohydrates serving as a primary carbon source.[9]. Nata is a source of insoluble fiber due to its cellulose content. Increased consumption of insoluble fiber can lead to a significant improvement in glucose metabolism, resulting in an increase in insulin sensitivity.[7] Insoluble fiber speeds up the movement of food through the digestive tract, resulting in smoother bowel movements and reduced appetite and food intake. Nata has the ability to regulate blood sugar levels and can be used as a dietary supplement for patients with hyperglycemia.[7]

Diabetes mellitus remains prevalent worldwide and in Indonesia. The International Diabetes Federation reported 536.6 million adults (20–79 years) with diabetes globally in 2021, and was projected to rise to 783.2 million by 2045.[10] In Indonesia, the number of diabetic patients was 19.5 million in 2021, and expected to reach 28.6 million by 2045.[10] Dietary fiber intake has shown potential in the prevention and managing metabolic diseases like diabetes mellitus.[11] However, 95.4% of Indonesians consume insufficient fruits and vegetables weekly.[12]
Dietary fiber in plant-based foods undergoes partial fermentation in the small intestine.[11] Soluble fiber is a non-cellulose polysaccharide comprising indigestible oligosaccharides and polysaccharides, while insoluble fiber includes cellulose, lignin, and certain hemicelluloses. Sources of insoluble fiber include fruits, vegetables, and grains.[11] The World Health Organization recommends 27–40 grams of daily fiber intake to prevent obesity, diabetes, cardiovascular diseases, and various cancers.[13] Another recommendation suggests consuming 35–40 grams of fiber in diabetic diets.[14]
Insoluble fiber has been linked to obesity and diabetes prevention.[15] Soluble fiber can inhibit glucose and fat absorption from the digestive tract, effectively reducing blood sugar and lipid levels.[17] Fiber

fermentation by gut microbiota in the colon produces short-chain fatty acids, impacting glucose and lipid metabolism, further aiding in blood sugar control.[17]

Papaya peel nata is a cellulose-based product produced through the fermentation of papaya peel. The cellulose it contains can be compared to pure cellulose which has been shown to be beneficial in lowering blood sugar levels in diabetic patients. Cellulose increases food viscosity and slows down gastric emptying and digestion.[18-20]

The present study aims to develop an innovative nata product from papaya peel and to evaluate its effects on blood glucose levels in male rats with type 2 diabetes mellitus.

Materials and Methods

Animals

Twenty-five (25) male Wistar rats (6 – 8 weeks old) weighing between 180 – 200 g were obtained from the animal facility of the Faculty of Medicine, Hasanuddin University. The rats were kept in cages and acclimatized to the laboratory conditions for 7 days. The rats were maintained at room temperature (28-32°C). They were fed with standard diet (5-10 grams daily) and allowed access to drinking water *ad libitum*. The cages were kept dry, and cleaned three times a day.

Ethical approval

Ethical approval was obtained from the Health Research Ethics Committee of the State University Hospital, Hasanuddin University (RSPTN UH) – Dr. Wahidin Sudirohusodo Hospital, Makassar, with Approval Number 563/UN4.6.4.5.31/PP36/2024 and protocol number UH24060453.

Induction of diabetes

The rats were fasted overnight, and administered a single intraperitoneal dose of streptozotocin (STZ) at 40 mg/kg BW. STZ was freshly prepared in a 0.1 M citrate buffer pH 4.5 immediately before injection. Sucrose solution (10%) was administrated orally *ad libitum* for 24 hours immediately after diabetes induction to avoid mortality due to hypoglycemic shock that may accompany STZ administration.[21]

Experimental design

The study adopted a Completely Randomized Design (CRD). Wistar rats were divided into 5 groups of 5 rats each. The rats were selected based on inclusion and exclusion criteria. The inclusion criteria were healthy male rats (clear eyes, shiny fur, active movement, well-formed faeces, and no more than 10% body weight loss during acclimatization). The exclusion criteria included rats that became ill or died during the study. The groups include Positive control (PC), negative control (NC), Papaya peel nata groups 1, 2, and 3 (PPN1, PPN2, and PPN3).

The positive control group (PC) consisted of rats given 0.6 grams of cellulose. The negative control group (NC) was given 2 mL of distilled water. The PPN1 group received 0.5 grams of papaya peel nata. The PPN2 group received 0.6 grams of papaya peel nata. The PPN3 group received 0.7 grams of papaya peel nata. Each treatment was administered orally once daily (in the morning) for four weeks.

Determination of treatment doses

The cellulose and papaya peel nata as fiber sources were based on the WHO's recommended fiber intake for humans, which is 27-40 g/day.[13] Another study also suggested a dietary fiber intake of 35-40 g/day for diabetic patients.[14] This was then converted to rat dosage using a conversion factor of 0.018.[22] As a result, the cellulose dose given to the rats was 0.6 grams. The papaya peel nata dose was divided into three: 0.5 grams, 0.6 grams, and 0.7 grams.

Papaya peel nata preparation

The papaya fruits used were sourced from Tidung Market, Rappocini District, Makassar City. They were identified as *Carica papaya L.* at the Pharmacognosy Laboratory of the Faculty of Pharmacy, Hasanuddin University, with the voucher number 036/SKIT/Pharmacognosy/XI/2024. The papaya fruits had clean skin, free of mold, and were not pest-infected. The papaya fruits were peeled, and the skins were collected. A total of 350 grams of papaya peel slices were subjected to blanching. The blanching process involved boiling the papaya peel for about 15 min, then rinsing with cold water. The purpose of blanching was to sterilize the papaya peel from contaminants. After blanching, the papaya peel was blended with 1 liter of water and then filtered to obtain papaya peel extract. To the extract were added 30 grams of sugar and 7 grams of food-grade ammonium sulfate (ZA) and boiled. After boiling, 1 mL of glacial acetic acid was added to achieve an acidic condition (pH 4). The pH of the papaya peel extract mixture was verified using pH paper. When a pH of 4 was reached, the mixture was poured into sterilized media bottles (200 mL each). The bottles were sealed with sterilized HVS paper and secured with rubber bands to prevent air from entering. After cooling, 20 mL of a starter culture containing *Acetobacter xylinum* was added to each papaya peel extract mixture bottle. The bottles were then resealed and kept stable. The mixture was incubated at room temperature for 7 days. After harvesting, the papaya peel nata was washed with sterile water to remove contaminants and then blended to create a solution or slurry ready for testing. It was then weighed according to the required dosage and administered orally using an oro-gastric tube. The flowchart for the papaya peel nata-making process is presented in Figure 1.

Determination of fiber content of papaya peel nata

The fiber content was determined by extracting the sample using acid and base to separate crude fiber from other materials. Papaya peel nata (4 g) was prepared, and then extracted by stirring and settling to separate the fat content. It was poured into an organic solvent three times, dried, and then placed in a 500 mL Erlenmeyer flask. Then, 50 mL of 1.25% H_2SO_4 solution was added and boiled for 30 minutes using a vertical cooler. Thereafter, 50 mL of 3.25% NaOH solution was added, and the sample was boiled for 30 min. The sample was filtered through a Buchner funnel containing ashless filter paper (Whatman 54, 41, or 541) which was dried and weighed. The residue on the filter paper was then washed successively with hot 1.25% H_2SO_4, hot water, and 96% ethanol. The filter paper and its contents were placed in a pre-weighed weighing container, dried at 105°C, then cooled and weighed until a constant weight was obtained.[23]

Determination of antioxidant capacity of papaya peel nata

The antioxidant capacity of papaya peel nata was determined using the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging method with vitamin C as standard. DPPH solution (3.8 mL) was placed in a test tube containing 0.2 mL of distilled water, the solution was vortexed, and the test tube was covered with aluminum foil. It was then incubated at room temperature for 30 min in a dark room. The absorbance was measured using a Genesys 10s UV-VIS spectrophotometer (Thermo Scientific) at a wavelength of 515 nm. In another test tube was placed 0.2 g of papaya peel nata, then 3.8 mL of 70% methanol was added and homogenized using a vortex mixer. A portion (0.2 mL) of the homogenized solution was transferred to a test tube to which 3.8 mL of DPPH solution was added and homogenized again. After homogenization, the test tube was covered with aluminum foil and incubated at room temperature for 30 min in a dark room. The absorbance was measured using a UV-VIS spectrophotometer at a wavelength of 515 nm.[24]

Measurement of fasting blood glucose (FBG)

Fasting blood glucose measurements were done three times in the course of the experiment. The first measurement was taken before STZ induction. The second was three days after STZ induction. The third fasting blood glucose measurement was taken after the final treatment (week 4). The rats were fasted for 16 hours before blood glucose measurement. Blood samples were taken from the tail vein (lateral vein) of the rats, and the blood glucose was measured using a glucoDR Biosensor glucometer.[25] Rats were considered diabetic if their fasting blood glucose was ≥ 150 mg/dL.[21]

Measurement of body weight, body length, and lee index

The body weight and body length of the rats were measured weekly. Body weight was measured using a digital scale.

Figure 1: Flowchart of papaya peels nata-making process

The body length was measured from the nose to the anus using a measuring tape. Obesity status was then assessed using the Lee Index formula as shown below.[26]

Lee Index = The cube root of body weight (g) / naso-anal length (cm)

Monitoring of rats' health status

Health indicators, including the presence of skin lesions, lumps, eye health, faecal consistency, movement, respiration, abdominal swelling, prolapsed rectum, and anorexia were monitored weekly.[27]

Statistical analysis

Statistical analysis was performed using SPSS statistical package. Data were presented as mean ± standard deviation (SD). Homogeneity and normality tests were performed. Fasting blood glucose and body weight data were analyzed using one-way analysis of variance (ANOVA), with pre-and post-treatment body weight and Lee Index was analyzed using paired t-tests. Significance difference was set at $p < 0.05$.

Results and Discussion

Characteristics of papaya peel nata

Nata is relatively new in Indonesia, but this product is already well-known among the populace. Nata is a food product obtained from fermentation process. This food has a thickness similar to agar with a chewy texture. Nata is produced by acetic acid bacteria, namely *Acetobacter xylinum*, which forms a thick layer on the surface of the fermentation medium known as nata.[28] *Acetobacter xylinum* is a cellulose-producing bacterium. During metabolism, these bacteria require nutrients in the form of carbon, hydrogen, nitrogen, and minerals in a controlled process. Due to nutrient deficiencies, the fermentation medium usually contains only part of the necessary nutrients, so supplementation from external sources is required.[9]

This study used ripe papaya peels as the main raw material for making papaya peel nata. Sugar was added as an additional carbon source to be broken down into glucose.[9] This glucose is then converted into cellulose by the nata-producing bacteria, *Acetobacter xylinum*, which is naturally obtained through fermentation. Food-grade ammonium sulfate and glacial acetic acid were added to create an acidic environment and nitrogen source optimal for *Acetobacter xylinum* growth.[9] Sources of organic materials, such as ammonium sulfate and the sugar content are essential factors that determine the water content, hardness, organoleptic properties and other physical properties of nata.[7,9] The macroscopic characteristics including colour, thickness, texture, and aroma of papaya peel nata are presented in Table 1.

Table 1: Macroscopic characteristics of papaya peel nata

Parameter	Macroscopic Results
Colour	White
Thickness	1 cm-1.1 cm
Texture	Gelatinous
Aroma	A little sour

The thickness of the papaya peel nata ranged from 1 - 1.1 cm. According to SNI (Indonesian National Standard), the thickness of nata that meets quality standards ranges from 1 - 1.5 cm.[29] This means that the papaya peel nata obtained from this study met SNI quality standards. This thickness is achieved by the action of *Acetobacter xylinum* which

synthesizes sugar and generates a dense cellulose network. Longer incubation time increases the thickness of nata as more cellulose is produced.[30] However, if incubation lasts too long, the nutrients in the fermentation medium becomes depleted, causing *Acetobacter xylinum* to lose energy and enter the death phase. The incubation process for nata generally lasts 6–21 days.[30]

The sour aroma of papaya peel nata is as a result of the byproduct in the form of acetic acid produced by *Acetobacter xylinum* during fermentation, which lowers the pH and gives nata an acidic property. This aroma usually diminishes after the washing process.[31]

Papaya peel nata has a gelatinous texture, which was similar to previous research results using other raw materials. This texture is influenced by the water and fiber content; the higher the fiber content, the stronger the cellulose bonds, reducing water content and resulting in a gelatinous or firm texture.[32]

Colour is one of the quality indicators of nata. Papaya peel nata is white due to the formation of cellulose from sugar breakdown. Several factors affect the colour of nata, including the proportion of sugar used in the production process. High sugar content in the fermentation medium can increase viscosity, inhibiting microorganism growth.[33] The thickness of nata affects its turbidity, with thicker nata tending to appear cloudier.[30] Additionally, the colour of the original raw material also influences the colour of the resulting nata.[30]

Crude fiber content of papaya peel nata

This study performed a fiber content test on papaya peel nata in duplicate. The fiber content in papaya peel nata per 100 grams was found to be 2.08% (Table 2), which higher than that of papaya peel processed into paste, which contains only 0.94% fiber.[34] However, it is not significantly different when compared to dried papaya peel, which has a fiber content of 2.39%.[35] When compared to nata made from other fruit peels, the fiber content is similar to that of guava peel nata, which contains 2.21% fiber.[36] However, it differs from nata made from dragon fruit peel and pineapple peel. Another study on nata made from dragon fruit peel found a fiber content of 3.83%.[37] Meanwhile, nata made from pineapple peel waste has a fiber content of 5%.[38]

The fiber content in papaya peel nata is lower than that in dragon fruit peel, pineapple peel, and guava peel, which can be due to various factors. The amount of fiber produced is also influenced by the composition of additional ingredients, substrate variations, environmental conditions, and the ability of *Acetobacter xylinum* to produce cellulose.[39] Fiber content in nata production is affected by the nitrogen content in the growth medium; the higher the nitrogen content, the higher the fiber content.[30] Additionally, fermentation duration can influence the fiber content in nata. In the early fermentation phase, *Acetobacter xylinum* produces more cellulose, which is the main fiber component in nata.[39] Another study explains that a fermentation duration of 16 days is optimal.[40] If the fermentation period is too short, such as 8 days, the resulting nata will be thin, reflecting the minimal cellulose produced.[40]

Table 2: Antioxidant capacity and crude fiber content of papaya peel nata

Replicate No.	Parameter	Unit	Result	Method Specification
I	Crude Fiber	%	2.15	Gravimetric
	Total Antioxidant Capacity	µg/g	6.64	Spectrophotometric
II	Crude Fiber	%	2.01	Gravimetric
	Total Antioxidant Capacity	µg/g	6.15	Spectrophotometric

Antioxidant capacity of papaya peel nata

The antioxidant capacity of papaya peel nata was assessed using the DPPH radical scavenging assay with ascorbic acid as the standard. The result was expressed as µg ascorbic acid equivalent per gramme (µg AAE/g). The DPPH radical is stable nitrogen radical commonly used to assess the antioxidant capacity of test substance, including plant extracts, beverages, biological fluids, and other complex substances. The assay is based on the reduction of DPPH radical by a potential antioxidant compound.[41] The results showed an average antioxidant capacity of papaya peel nata of 6.4 µgAAE/g (Table 2). Studies have shown high antioxidant activity of different varieties of *Carica papaya* L. For example, the study evaluated the antioxidant activity of aqueous extracts of three *Carica papaya* varieties cultivated in Senegal using the DPPH assay and Trolox as the standard antioxidant compound, the results showed that the peel extract of *Carica papaya* had high antioxidant capacity with values ranging from 1.96 ± 0.15 to 3.69 ± 0.14 mg TrE/g.[42] In another study, it was found that papaya peel exhibited strong antioxidant properties with IC_{50} value of 55.5 µg/mL in the DPPH assay.[43]

Fasting blood glucose (FBG) of rats

The fasting blood glucose (FBG) in the rats are presented in Figure 2. The results that prior to STZ induction, the average FBG were 110.9 ± 6.2 mg/dL for PPN1, 106.5 ± 4.2 mg/dL for PPN2, 111.4 ± 4.5 mg/dL for PPN3, 105.5 ± 3.7 mg/dL for PC, and 119.8 ± 4.6 mg/dL for NC. These data indicate that the average FBG of rats in all the groups were within the normal range, with no indication of hyperglycemia.

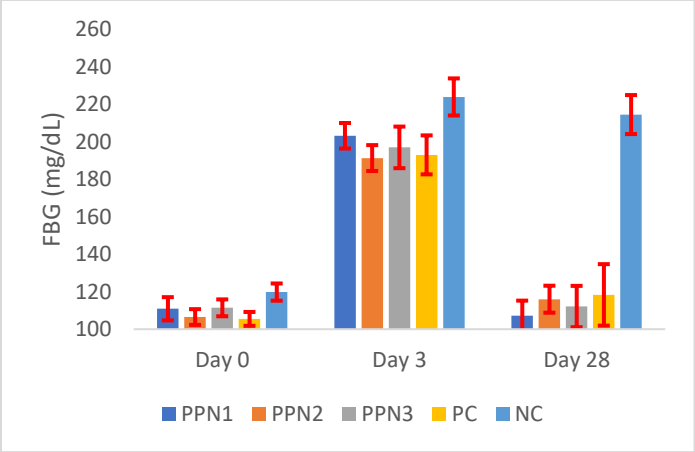

Figure 2: Blood glucose changes for each treatment before STZ-induction, after STZ-induction, and post-treatment. Data represent mean ± standard deviation, n = 5. NC: negative control (distilled water); PC: positive control (cellulose); PPN1: papaya peel nata 0.5 g; PPN2: papaya peel nata 0.6 g; PPN3: papaya peel nata 0.7 g.

After STZ induction, the FBG levels increased to 203.1 ± 6.8 mg/dL for PPN1, 191.3 ± 6.9 mg/dL for PPN2, 197.0 ± 11.1 mg/dL for PPN3, 193.8 ± 10.4 mg/dL for PC, and 223.9 ± 9.9 mg/dL for NC. This FBG results show that all groups of rats reached a hyperglycemic state, confirming successful STZ induction. A moderate STZ injection dose (between 40 and 50 mg/kg BW) causes partial insulin secretion impairment, as seen in the mechanism of Type 2 Diabetes Mellitus.[44]

Streptozotocin inhibits insulin secretion and induces insulin-dependent diabetes mellitus through its alkylating potential.[45] Streptozotocin is a structural analog of N-acetyl glucosamine and is a strong alkylating agent. This compound disrupts glucose transport and glucokinase activity and causes damage to multiple DNA strands.[44] Streptozotocin (STZ) is a nitrosourea compound accumulating in pancreatic beta cells through the GLUT2 transporter. STZ toxicity is mainly due to DNA alkylation activity, resulting in DNA damage and beta cell necrosis. Additionally, STZ reduces NAD+ and ATP levels as cells attempt to repair damaged DNA, thus accelerating beta-cell death. PARP inhibitors like nicotinamide can protect beta cells from STZ's toxic effects. Apart from alkylation, STZ also has the potential to act as a nitric oxide (NO) donor and generate minor ROS; however, these mechanisms are considered to play a lesser role in beta cell damage.[45]
After four weeks of treatment, FBG levels decreased across all groups: PPN1 dropped to an average FBG of 107.2 ± 8.1 mg/dL, PPN2 to 116 ± 7.2 mg/dL, PPN3 to 112.1 ± 11.0 mg/dL, PC to 118.3 ± 16.4 mg/dL, and NC to 214.5 ± 10.4 mg/dL. The reduction in FBG in the papaya peel nata treatment groups at doses of 0.5 grams, 0.6 grams, and 0.7 grams indicated an improvement, with FBG levels returning to normal. In contrast, reduction in the FBG level in the NC group was insignificant, as the FBG level still remained in the hyperglycemic range.
This is consistent with a study that reported that administering STZ at 40 mg/kgBW results in stable long-term effects with blood glucose levels rise in the first one week, and then slowly declined to normal levels after 10 days.[46] Another study observed self-recovery in STZ-induced diabetic rats, defined by initially high blood glucose levels gradually returning to normal naturally.[21] Another mechanism involves endogenous antioxidants in the body interacting with reactive oxygen species (ROS) produced by STZ induction. With low-dose STZ induction, ROS production is also low and can be countered by endogenous antioxidants, thus preventing increased beta cell damage due to ROS.[21]
A statistical analysis was conducted to examine the effect of each treatment group on changes in FBG after STZ induction, comparing FBG before and after treatment. Table 3 shows a significant effect of each treatment on FBG changes, with a p-value of <0.001.

Table 3: Changes in FBG levels in rats following treatment with papaya peel nata

Treatment	Change in FBG Level (Day 28 – Day 3)	P-value
PPN1	95.9 ± 6.1	
PPN2	75.3 ± 8.05	
PPN3	84.9 ± 17.3	< 0.001*
PC	75.5 ± 13.8	
NC	9.4 ± 4.6	

Values are mean ± SD, n = 5, *P < 0.05 indicates significant difference. The change in FBG represents the difference between the FBG on day 3 and day 28. PPN = Papaya peel nata, PC = positive control, NC = Negative control.

A Post Hoc test was then performed to examine differences among treatment groups. Table 4 and Figure 3 showed a significant difference in the FBG levels between the negative control group (NC) and the positive control group (p = 0.002), the 0.5 g papaya peel nata group (p<0.001), the 0.6 g papaya peel nata group (p = 0.003), and the 0.7 g papaya peel nata group (p = 0.001). However, there were no significant differences between the positive control group and the papaya peel nata treatment groups (p > 0.05), and also, no significant difference was observed among the papaya peel nata groups (p > 0.05). This indicates that the observed changes in FBG were not dependent on the dose of papaya peel nata.
Fasting blood glucose has been shown to be influenced by daily fiber intake. A study stated that treatment of rats with ripe and unripe *Carica papaya* methanol fruit extracts resulted in a significant reduction in the blood glucose level.[47] In another study, it was found that low fiber intake was associated with increased FBG in patients with Type 2 DM.[48] Specifically, soluble fiber can decrease blood glucose by increasing food viscosity and slowing stomach emptying and digestion. This results in slower absorption of nutrients, including glucose, and increases feelings of fullness, leading to reduced food intake. Consuming fiber can increase the viscosity in the intestines, which in turn limits the development of insulin resistance.[49] The binding of glucose by fiber makes less glucose available for absorption. The decrease in blood glucose causes the pancreas to reduce insulin secretion as well.[50]

Table 4: Treatment effectiveness analyzed by post hoc test on change in FBG Level in each group

Post Hoc Test	Change in FBG Level (mg/dL)	P-value
NC vs PC	-57.8	0.002*
NC vs PPN 0.5 g	-66.4	< 0.001*
NC vs PPN 0.6 g	-54.7	0.003*
NC vs PPN 0.7 g	-64.5	0.001*
PC vs PPN 0.5 g	-8.6	0.96
PC vs PPN 0.6 g	3.1	0.99
PC vs PPN 0.7 g	-6.7	0.99
PPN 0.5 g vs PPN 0.6 g	11.7	0.88
PPN 0.5 g vs PPN 0.7 g	1.93	1.0
PPN 0.6 g vs PPN 0.7 g	-9.8	0.95

Values are mean ± SD, n = 5, *P < 0.05 indicates significant difference. PPN = Papaya peel nata, NC = Negative Control, PC = Positive Control

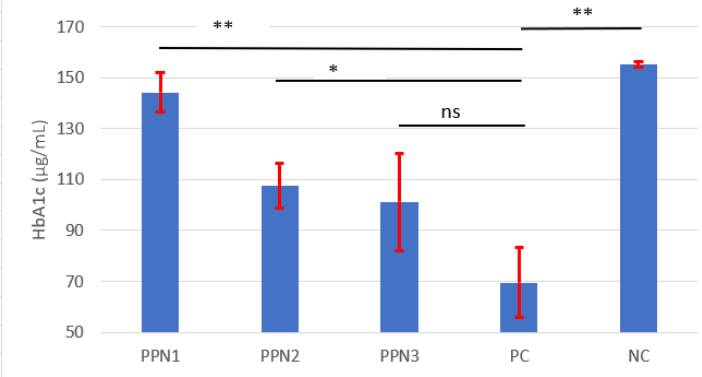

Figure 3: Changes in fasting blood glucose level (Day 28 – Day 3). Data represent mean ± standard deviation, n = 5. NC: negative control (distilled water); PC: positive control (cellulose); PPN1: papaya peel nata 0.5 g; PPN2: papaya peel nata 0.6 g; PPN3: papaya peel nata 0.7 g; ns (p > 0.05); * (p < 0.05); ** (p < 0.01).

Body weight and lee index of rats
During the 4-week study period, changes in rat body weight were observed across all treatment groups (Figure 4). At the beginning of the study, the average body weight of the rats were 202.6 ± 4.3 g for the PPN1 group, 204.2 ± 4.6 g for the PPN2 group, 204.4 ± 7.02 g for PPN3 group, 199.6 ± 4.5 g for the positive control (PC) group, and 204.2 ± 6.7 g for the negative control (NC) group.

Body weight decrease occurred in all groups during the first week post-STZ induction. The average body weight in the first week was 189.6 ± 11.1 g for PPN1, 179.0 ± 22.2 g for PPN2, 173.8 ± 17.4 g for PPN3, 174.4 ± 4.8 g for PC, and 173.0 ± 13.9 g for NC. Weight loss in hyperglycemic rats is closely related to the inability of the body to utilize glucose as the primary energy source.[51] This leads to the breakdown of proteins as an alternative energy source, which results in the loss of muscle mass.[51] Additionally, the effect of hyperglycemia, such as polyuria, is a cause of dehydration in diabetes patients, which also contributes to weight loss.[52]

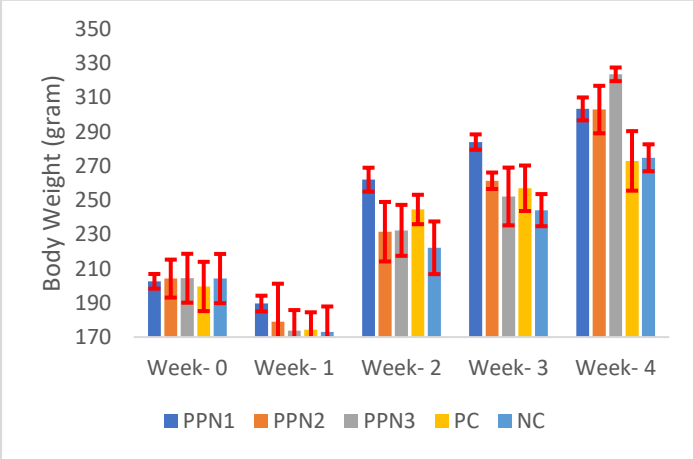

Figure 4: Body weight change for each treatment in week-0, week-1, week-2, week-3, and week-4. Data represent mean ± standard deviation, n = 5. NC: negative control (distilled water); PC: positive control (cellulose); PPN1: papaya peel nata 0.5 g; PPN2: papaya peel nata 0.6 g; PPN3: papaya peel nata 0.7 g.

In the second week post STZ-induction, body weights increased in all groups, with average body weights of 262.0 ± 14.3 g, 231.6 ± 12 g, 232.4 ± 14.9 g, 244.6 ± 16.9 g, and 222.2 ± 4.0 g for the PPN1, PPN2, PPN3, PC, and NC groups, respectively. By week three, the body weight in the PPN2 group significantly increased, with an average body weight of 261.4 ± 10 g. In the fourth week, significant differences in body weights were observed among the various groups, with average body weights of 303.4 ± 14.4 g, 303.0 ± 14.9 g, 323.6 ± 15.4 g, and 274.8 ± 7.9 g in PPN1, PPN2, PPN3, and NC groups, respectively. Table 5 shows the effect of PPN1, PPN2, PPN3, PC, and NC on body weight of rats after four weeks of treatment.

Table 5: Change in body weights of rats in each group over 4 weeks

Treatment	Mean body weight change (g)	P-value
PPN1	100.8 ± 17.3	
PPN2	98.8 ± 12.6	
PPN3	119.4 ± 17.7	< 0.001*
PC	73.4 ± 11.3	
NC	70.6 ± 4.5	

Values are mean ± SD, n = 5, *P < 0.05 indicates significant difference. PPN = Papaya peel nata, NC = Negative Control, PC = Positive Control

The results were recorded as changes in body weight between pre-treatment and post-treatment weights. The result showed significant differences in the body weight change between the papaya peel nata-treated groups and the positive and negative controls groups ($p < 0.001$). High average body weight change was observed in the PPN groups, with values of 100.8 ± 17.3 g, 98.8 ± 12.6 g, and 119.4 ± 17.7 g for PPN1, PPN2, and PPN3, respectively. Whereas, low average body weight change was seen in the PC, and NC groups, with values of 73.4 ± 11.3 g and 70.6 ± 4.5 g for PC and NC, respectively. The higher body weight increase in the papaya peel nata-treated groups compared to the negative and positive control groups could be associated with improved fasting blood glucose levels in the PPN groups. Body weight of diabetic rats induced with alloxan and streptozotocin has been shown to be affected by the rats' self-recovery.[20] In the present study, at fourth week after induction, rats that experienced full recovery had significantly higher body weight than those with stable diabetes. However, there was no significant difference in body weight between rats that experienced temporary recovery and those with stable diabetes. The body weight of diabetic rats is related to hyperglycemia, where rats that experienced full recovery returned to normal body weight more quickly, resulting in less body weight loss.[21] Increased fiber consumption has led to better efficiency in consumed energy utilization.[49] The resulting decrease in blood glucose will lower plasma insulin response, which results in a reduction in fat tissue accumulation caused by decreased lipogenesis or increased β-oxidation of fatty acids.[49]

The weekly changes in the Lee index were statistically analyzed using a parametric test, specifically the Paired Samples T-Test, to identify the effect of each treatment on the obesity status of rats based on the Lee index. The data distribution from week 0 to week 4 followed a normal distribution.

In Figure 5 and Table 6, the average Lee index before treatment was shown to be nearly identical across all groups, with values of 0.33 ± 0.02 for PPN1 and 0.33 ± 0.01 for PPN2, 0.34 ± 0.01 for PPN3, 0.35 ± 0.01 for PC, and 0.36 ± 0.02 for NC. One week after STZ induction and treatment, the average Lee index decreased, reaching 0.30 ± 0.01 in PPN1, 0.30 ± 0.02 PPN2, 0.29 ± 0.01 in PPN3, 0.30 ± 0.01 PC, and 0.30 ± 0.01 in NC groups. However, lee index gradually increased from week 2 until week 4.

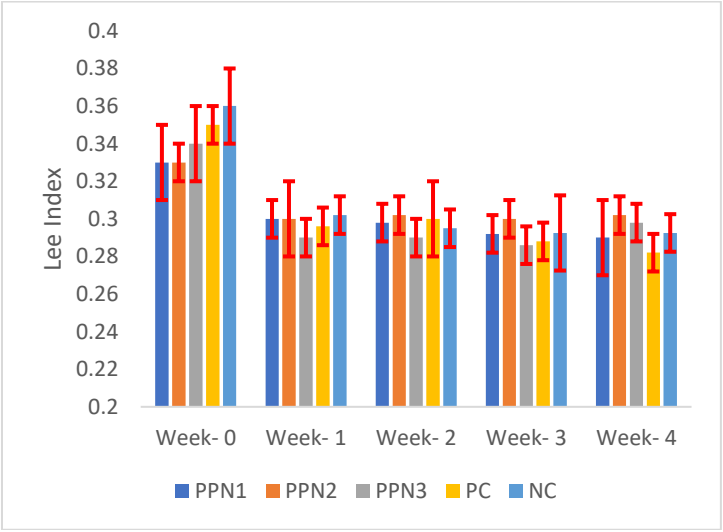

Figure 5: Lee index change for each treatment in week-0, week-1, week-2, week-3, and week-4. Data represent mean ± standard deviation, n = 5. NC: negative control (distilled water); PC: positive control (cellulose); PPN1: papaya peel nata 0.5 g; PPN2: papaya peel nata 0.6 g; PPN3: papaya peel nata 0.7 g.

As shown in Table 6, Paired Samples T-Test was used to compare the differences in the Lee Index change before (week 0) and after treatment (week 4). It was found that there was a significant difference in the Lee Index change in the groups receiving 0.6 grams of papaya peel nata (PPN2), 0.7 grams of papaya peel nata (PPN3), 0.6 grams of cellulose (PC), and 2 mL of distilled water (NC) with average changes of 0.03 ± 0.01, 0.038 ± 0.013, 0.07 ± 0.02, and 0.06 ± 0.03, respectively. Meanwhile, there was no significant difference in the Lee index in the

0.5 grams papaya peel nata (PPN1) group with mean Lee index change of 0.042 ± 0.038. Increased blood glucose in STZ-induced rats leads to weight loss, and a decrease in Lee index.[53] In the PPN1 group, significant blood glucose improvement occurred by the fourth week, with a large reduction in FBG. This helped control muscle mass loss so that Lee index did not decrease significantly compared to the positive control group (0.6 cellulose) and the negative control group given distilled water.

Table 6: Changes in Lee index pre- and post-treatment

Treatment	Mean Lee index		Mean Difference	SD	P-value
	Week- 0	Week- 4			
PPN1	0.332	0.29	-0.042	0.038	0.067
PPN2	0.33	0.30	-0.028	0.0084	0.002*
PPN3	0.336	0.298	-0.038	0.013	0.003*
PC	0.35	0.28	-0.068	0.016	0.001*
NC	0.36	0.30	-0.060	0.026	0.006*

PPN = Papaya peel nata, NC = Negative Control, PC = Positive Control. *P < 0.05 indicate significant difference using Paired Samples T-Test

Table 7: Health status of rats in all the groups over the experimental period

Indicator	Week-1					Week-2					Week-3					Week-4				
	PPN1	PPN2	PPN3	PC	NC	PPN1	PPN2	PPN3	PC	NC	PPN1	PPN2	PPN3	PC	NC	PPN1	PPN2	PPN3	PC	NC
Skin Lesions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lumps	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Eyes	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Movement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Breathing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diarrhea	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Abdominal Swelling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	√ (n= 1)	√ (n= 1)	X
Proalps Rectal	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anorexia	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

PPN = Papaya peel nata, NC = Negative Control, PC = Positive Control. *n = number of rats; x = absent; √ = Present

Effect of papaya peel nata on overall health status of the rats

In this study, several observations were made to assess the overall health status of the rats. From the observations over the four weeks period, two rats in the positive control group and the 0.7-gram papaya peel nata group showed abdominal distension at the end of the treatment period (Figure 7). Upon performing the pitting edema test, there was no indication of fluid accumulation, suggesting that the abdominal enlargement was due to gas buildup or bloating. The abdominal distension or bloating was associated with excessive fiber intake in the rats. Increased dietary fiber can trigger changes in gastrointestinal function, especially during the early phase of dietary change, such as discomfort in the stomach, including bloating or abdominal distension.[54] Dietary fiber also has extra-colonic effects, such as delayed gastric emptying. The delay in gastric emptying is due to the increased viscosity of the stomach contents, which can decrease the pyloric flow, leading to the sensation of bloating or abdominal distension due to slow intragastric redistribution and a higher antrum/fundus ratio.[55] There is the need for further investigation to find ways of minimizing digestive discomfort associated with high-fiber diets consumption, and long-term fiber application.[55]

Conclusion

The findings from this study have shown that papaya peel nata has antioxidant activity, and can lower blood glucose levels in diabetic rats. The Lee index indicates that papaya peel nata administration result in good blood glucose control, helps manage body weight by preventing the loss of muscle mass. The effectiveness of papaya peel nata in lower blood glucose is linked to its high fiber content, suggesting that it could be a useful dietary supplement for managing diabetes mellitus. Further study is needed to determine the optimal dose of papaya peel nata in managing hyperglycemia, and validates its effectiveness in clinical settings.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgments

The authors would like to thank the Graduate School of Hasanuddin University and appreciate the financial support through the BIMA *Kemdikbudristek* Master's Thesis Research Grant (grant number 0459/E5/PG.02.00/2024).

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