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Antidiabetic Activity of Microcapsules of *Protium javanicum* Leaf Extract in Streptozotocin-induced Diabetic Rats

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Abstract

Protium javanicum leaves contain phenolic compounds that can be developed as antidiabetic agents. Extraction and microencapsulation are two ways to utilize phenolic compounds in *P. javanicum* leaves to be applied as antidiabetic agents. The study aimed to assess the antidiabetic potential of *P. javanicum* leaf extract microcapsules in streptozotocin-induced diabetic rats. The parameters observed in this research included the chemical composition of microcapsules, rats' weight, insulin levels, blood glucose concentration, and pancreatic histopathology of streptozotocin-induced diabetic rats. One-way variance analysis was performed to identify the significant difference among the samples at p-value < 0.05. The findings indicated that administration of microcapsules at 100 mg/kg bw effectively reduces blood glucose levels by 66.25%, increases insulin levels by 36.45% and reduces the number of β-cells undergoing necrosis. The antidiabetic properties of microcapsules of ethanol extract of *P. javanicum* leaves are thought to be through the mechanism of inhibition of α-glucosidase enzyme activity and pancreatic β-cell repair. Improvement of pancreatic conditions will increase insulin secretion, resulting in decreased blood glucose.

Keywords: Antidiabetic; Extract; *Protium javanicum*; Microcapsules; Streptozotocin

Introduction

Diabetes mellitus is a metabolic disorder distinguished by elevated blood sugar levels and irregularities in carbohydrate, lipid and protein metabolism resulting from compromised insulin sensitivity, secretion, or both (American Diabetes Association 2011). The criteria for diagnosing diabetes mellitus are fasting glucose concentrations over 126 mg/dL, postprandial glucose levels exceeding 200 mg/dL, and HbA1c levels exceeding 6.5%.

The growing number of diabetics in Indonesia has encouraged efforts to develop natural antidiabetic drugs. This is because the use of oral antidiabetic drugs has side effects, is tedious for patients, and fails to inhibit the complications of diabetes mellitus. Therefore, studies and research on antidiabetic agents derived from plant/animal extracts continue to be developed to find antidiabetic agents that are safe, cost-effective, and have minimal side effects.

Several studies have revealed that phenolic compounds (flavonoids, phenolic acids, tannins, stilbenes) in plants can act as antihyperglycemic, antidiabetic agents, and antioxidant (Bansal *et al*. 2012; Alkhalidy *et al*. 2018; Laddha and Kulkarni 2019). The function of bioactive compounds in diabetic mellitus medication has been confirmed. Mendes *et al*. (2015) stated that most bioactive components in plant extracts exhibit hypoglycemic activity due to their role as antioxidants. These antioxidants can increase the pancreatic beta cell number and stimulate insulin release.

Protium javanicum is a native Indonesian plant of the Burceraceae family used in traditional medicine. *P. javanicum* leaf extract contains bioactive substances, including phenolics, flavonoids, tannins (Yolanda *et al*. 2021), steroids and terpenoids (Suirta *et al*. 2016), α, β amyrin, and β sitosterol (Puspawati *et al.* 2019). These bioactive compounds have the potential for the management of diabetes mellitus. It has also been proven that the bioactive components of *P. javanicum* leaf extract can act as immunostimulants (Jayawardhana and Puspitasari, 2017), anti-inflammatory (Ahujaa *et al*. 2019), and potentially

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anticancer (Puspawati *et al*. 2021), able to raise SOD enzyme activity and lower MDA levels in mice exposed to cigarette smoke (Puspawati *et al*. 2024).

The phenolic compounds in *P. javanicum* leaf extract have the potential to be developed as an agent to both prevent and treat illnesses. Phenolic compounds are highly vulnerable to deterioration due to temperature, oxygen content, and light exposure during storage. According to Boonchu and Utama-Ang (2015) and Kalušević *et al*. (2017), when taken orally, phenolic chemicals are restricted in permeability and absorption, and they are unstable in the digestive tract, which results in decreased bioavailability.

Yusasrini *et al*. (2024) successfully microencapsulated ethanol extract of *P. javanicum* leaves using maltodextrin and gelatin to maintain its stability, bioavailability, and biological activity. Microencapsulation is the technology of covering liquids, solids, and gases with capsules in a micro form where the capsule can release its contents under certain conditions (Khasanah *et al*. 2015). As stated by Pérez *et al*. (2020), microencapsulation of Xoconostle extract can maintain its bioactive compounds, antioxidant, and antidiabetic activities up to 60-80%. Pérez *et al*. (2020) also reported that microcapsules of phenolic compounds from tamarind cactus (Xoconostle) fruit extract showed higher antidiabetic activity (α-amylase and α-glucosidase enzyme inhibition) than extracts without microencapsulation. Similarly, Tran *et al*. (2020) reported that microcapsules of *Euphorbia hirta* extract successfully lowered the blood sugar levels in diabetic rats by 23.32%, slightly less than the activity of acarbose (30.87%). Research investigating the potential of *P. javanicum* leaf extract microcapsules as an antidiabetic agent has never been reported. This study aimed to assess the antidiabetic properties of *P. javanicum* leaf extract microcapsules in streptozotocin-induced diabetic rats.

Materials and Methods

Material

P. javanicum leaves were obtained from Negara, Jembrana regency, and the criteria were mature and light green leaves. Other materials used were maltodextrin, gelatin, maize starch, casein (Sigma), sugar, soybean oil, carboxymethylcellulose (CMC), L-cystine, choline bitartrate, vitamin mixture and mineral mixture (ICN Biomedical), and white Wistar rats. Chemical reagents used for analysis were ethanol, streptozotocin (Sigma), α-glucosidase enzyme (Sigma), 4-nitrophenyl-α-D-glucopyranoside (Sigma), acarbose, aquabidestilata, NaOH, H_2SO_4, boric acid, HgO, Na_2SO_4, concentrated HCl, hexanes, Rat Super Oxidase Dimutase ELISA Kit, Elabscience Malondialdehyde (MDA) Assay Kit (100T/96S), Rat INS (Insulin) ELISA Kit FineTest ER1113.

Instrumentations

The principal instruments used in this study are a rotary vacuum evaporator (IKA RV 10 Basic), an SEM (JSM-IT200), a freeze dryer (DW-10N Freeze Dryer), an analytical balance (Shimadzu ATY224), an oven, a mixer (Cosmos), a centrifuge (DLAB), a vortex (Maxi), aluminum foil (Klin Pack), a spectrophotometer (Genesys 10S UV-Vis), a micropipette (Socorex), and glassware.

Extraction and microencapsulation

Extraction and microencapsulation of *P. javanicum* leaf extracts were carried out in reference to Yusasrini *et al*. (2024). The extraction was performed using 90% ethanol solvent with the maceration method for 24 h at an ambient temperature. The solution was passed through a Whatman No. 1 filter paper to separate the components. A rotary vacuum evaporator was then used to concentrate the filtrate at 40ºC, 200 mBar, a speed of 60 rpm. Maltodextrin and gelatin were prepared in a 1:1 ratio for the coating material. The total coating material used was 10% of the solution volume. Gelatin was dissolved in warm water and stirred at 300 rpm, while maltodextrin was dissolved in distilled water and stirred until homogeneous. Five percent extract was mixed with the maltodextrin solution and stirred until dissolved. The gelatin solution was gradually added to the core material solution, stirred at 750 rpm for 30 min and homogenized at 18000 rpm for six min. The mixture was lyophilized at -54.8ºC, 4.4 Pa, for 72 h.

Standard diet preparation

The standard diet is prepared using AIN 1993 as a guide (Reeves *et al*. 1993). Table 1 lists the ingredients of the standard diet. The ingredients were combined and worked into a uniform dough. The mixture was shaped into an elongated cylinder and dried for 4 h at 50°C. The dehydrated standard diet was kept in a refrigerator and sealed tightly.

Bioassay procedures

Animal Ethics Committee, Faculty of Veterinary Medicine, Udayana University, approved utilizing laboratory animals in this work, as stated in the Animal Ethics Approval Certificate No. B/113/UN14.2.9/PT.01.04/2024. A total of 28 male Wistar rats, 3 months old and 100 ± 5 g in weight, were used in the bioassay. Rats were acclimated for 1 week and maintained a standard diet. Upon completion of the acclimation phase, the mice were weighed, and an initial blood glucose analysis was performed. Rats were fasting overnight with *ad libitium* drinking water. A total of 4 rats were randomly selected and induced with aquabidestilata, while 24 other rats were induced with streptozotocin (STZ) intraperitoneally at a 40 mg/kg body weight dosage (Saputra *et al*. 2018). The rats were grouped as follows:

Table 1: Standard feed composition

Ingredients*	Quantity (g/kg)
Corn starch	620.69
Casein	140
Sucrose	100
Soybean oil	40
CMC	50
Mineral mix	35
Vitamin mix	10
L-cysteine	1.8
Choline bitartrate salt	2.5
Total	999.99

*Reeves *et al*. (1993)

PS = Control/placebo rats
DPS = Diabetic rats
DPSa = Diabetic rats + microcapsules (100 mg/kg bw)
DPSb = Diabetic rats + microcapsules (250 mg/kg bw)
DPSc = Diabetic rats + microcapsules (500 mg/kg bw)
DPSd = Diabetic rats + acarbose (100 mg/kg bw)
DPSe = Diabetic rats + extract (100 mg/kg bw).

Total phenolic content

The total phenolic content of microcapsules was evaluated using the Folin-Ciocalteu technique, as described by Baba and Malik (2015), with certain modifications. One milliliter of ethanol: acetic acid: water mixture (50:8:42) was used to dissolve 100 mg of microcapsules, and the mixture was vortexed for 1 min. The solution passed through filtration using Whatman No. 1 filter paper. A total of 50 µL of the filtrate was added to 150 mL of methanol, 3 mL of distilled water, and 0.5 mL of Folin-Ciocalteu reagent. The mixture was stirred for 3 min, and 2 mL of 20% (w/v) sodium carbonate was added. After 60 min of standing in the dark, the mixture's absorbance at 650 nm was determined.

Total flavonoids

Total flavonoid analysis was based on Cilek *et al*. (2012) and Baba and Malik, (2015) with modifications. Samples (100 mg) were dissolved in 10 mL ethanol: acetic acid: water (50: 8: 42) solution, vortexed for 1 min, and filtered with Whatman No.1 filter paper. After pipetting the filtrate to a volume of 50 µL, 450 µL of methanol, 2.5 mL of distilled water, and 150 µL of 5% $NaNO_2$ solution were added. After incubating for 5 min, 300 µL of 10% AIC13 was added to the mixture. The mixture was incubated for another 6 min before adding 1 mL of 1 N NaOH and 1 mL of distilled water. The mixture was incubated for 15 min, and the absorbance was measured at 510 nm with a spectrophotometer. The total flavonoid concentration was matched to a quercetin standard curve.

Antioxidant activity

The antioxidant activity of microcapsules was measured using the 1,1-diphenyl-2-picryl-hydrazyl (DPPH) assay, which refers to Villano *et al*. (2007). Briefly, 100 mg of microcapsules were dissolved in 1 mL of ethanol: acetic acid: water mixture (50: 8: 42) and vortexed for 1 min. The solution underwent filtration using Whatman No. 1 filter paper. A variation of the sample concentration was made, ethanol was added to a volume of 500 µL, and 500 µL of DPPH solution was added. After 30 min of incubation at 25^0C, UV-Vis spectrophotometry determined the mixture's absorbance at a wavelength of 517 nm. To assess the sample's capacity to scavenge DPPH radicals, the following formula was employed:

$$DPPH\ Scavenging\ (\%) = \frac{OD\ Control - OD\ Sampel}{OD\ Control}\ x\ 100\%$$

Analysis of inhibition of α-glucosidase enzyme activity

The inhibition assay of α-glucosidase enzyme activity was performed following Indrianingsih *et al*. (2015). Samples (10 µL) were dissolved in various doses of dimethyl sulfoxide, and p-NPG (250 µL, 3 mM), phosphate buffer solution (490 µL, 100 mM, pH 7) were added. For five minutes, the solution was preincubated at 37°C. After adding 250 µL of α-glucosidase enzyme (0.065 U/mL), the reaction proceeded for 15 min. The addition of 1 mL of 0.2 M Na_2CO_3 terminated the reaction. The mixture was measured at a wavelength of 400 nm using a spectrophotometer. Acarbose was used as a positive control.

Blood glucose level

Gluko-Dr® is a blood glucose meter that utilizes enzymes to react precisely with glucose in the blood. The enzyme glucose oxidase (GOD) facilitates the oxidation of glucose molecules, resulting in the generation of electrons. These electrons are then caught by electrodes, allowing for a direct correlation between the glucose level and the electronic signal received. Blood was collected from the lateral vein of the rat's tail. 2.5–4.0 µL of blood is required to measure blood glucose. Blood is dropped on the right side of the test strip, and the Gluko-Dr® meter detects the measurement findings after eleven seconds. The unit of measurement for blood glucose is mg/dL.

Serum insulin levels

Serum insulin concentrations were assessed using the RAT INS (Insulin) ELISA Kit FineTest ER1113 and a microplate reader. The collected blood samples underwent a 30 min centrifugation at 3000 rpm and 4ºC. The blood serum is reacted with monoclonal anti-mouse insulin (antibody) coated on the bottom of the microplate wells and reagents provided in the rat insulin ELISA kit. After several reactions, the sample is read with a microplate reader at a wavelength of 450 nm.

Histopathology of the pancreas

Analysis of pancreatic histopathology using the Hematoxylin-Eosin (HE) staining method refers to Swarayana *et al*. (2012). Pancreatic organs were washed with 0.9% physiological NaCl and fixed with 10% buffered neutral formalin (BNF), followed by histopathological preparation. The stages of pancreas histopathology preparation include necropsy, sample isolation, fixation, dehydration, clearing, embedding, tissue sectioning, staining, and microscopic observation.

Statistical analysis

A completely randomized experimental design was performed in this research. Every experiment was carried out three times. The results were presented as mean ± standard error. To determine the significant difference among the samples at p-value < 0.05, a one-way variance analysis was performed (Harsojuwono *et al.* 2011).

Results

Chemical composition of *P. javanicum* leaf extract and microcapsules

Table 2 presents statistical data indicating that microcapsules and *P. javanicum* leaf extract contain phenolic compounds, especially from the flavonoid group, that can function as an antioxidant source. The microcapsules *of P. javanicum* leaf extract exhibited 47.18% inhibitory efficacy against the α-glucosidase enzyme, higher than the extract's α-glucosidase enzyme's inhibitory effect. Compared to the inhibition of acarbose, the microcapsules and *P. javanicum* leaf extract had lower α-glucosidase enzyme inhibitory activity.

Blood glucose levels

The diabetes criteria used in this study were moderate diabetes, with values of blood glucose ranging from 200 mg/dL to 400 mg/dL. Repeated observations of blood glucose concentrations were made at the beginning of grouping/day 0 and day 30. Observations on day 0 showed that the STZ-injected rat groups (DPS, DPSa, DPSb, DPSc, DPSd, and DPSe) were in a moderate diabetic condition with mean blood glucose levels ranging from 295 mg/dL to 364 mg/dL. The rats in the placebo group (PS) had normal blood glucose levels of 73.33 ± 5.68 mg/dL. The blood sugar concentrations of the DPS, DPSa, DPSb, DPSc, DPSd, and DPSe groups did not significantly differ, according to the findings.

At the end of the bioassay, the blood glucose concentrations of the rats ranged from 77.00 mg/dL to 414.33 mg/dL. The lowest blood glucose level was found in DPSd group rats at 77.00 mg/dL, which was not significantly different from PS, DPSb, DPSc and DPSe groups but significantly different from DPSa and DPS group rats. The highest blood glucose concentrations were found in DPS group rats, significantly different from all other groups. Dietary intervention for 30 days was effective in lowering blood sugar concentrations in the DPSa, DPSb, DPSc, DPSd and DPSe groups by 66.25%, 75.23%, 73.22%, 79.55% and 77.31%, respectively. There was no apparent distinction in the blood glucose concentrations between the DPSe group and the DPSb, DPSc and DPSd groups.

Table 2: Chemical properties of *P. javanicum* leaf extract and microcapsules

Parameter	Extract	Microcapsules
Total phenolics (mg GAE/g)	243.81±0.70*	119.77 ± 0.78
Total flavonoids (mgQE/g)	33.02 ± 0.716	9.19 ± 0.06
Antioxidant activity (IC_{50}) (ppm)	20.60 ± 0.46*	163.28 ± 0.01
α-glucosidase enzyme inhibitory activity (%)	40.88 ± 0.003	47.18 ± 0.01

*Yusasrini *et al.* (2024)

Rat weight

The weight of the rats at the beginning of the treatment was not significantly affected (P>0.05) by the feeding treatment. The weight of rats on day 0 ranged from 115.33 g to 151.67 g. The average weight of rats is presented in Table 2. Rats in the PS group gained 23.15% more weight after a 30-day dietary intervention, whereas the body weights of the DPSa, DPSb, DPSc and DPSe groups increased by 37.09%, 6.57%, 4.02% and 6.53%, respectively. The body weight of the mice in the DPS group decreased by 1.15%.

Insulin levels

The variance analysis indicated that the rats' blood insulin levels were significantly affected (P<0.05) by the dietary treatment. The blood insulin levels ranged from 1.92 mIU/L to 3.54 mIU/L. The DPS group had the lowest blood insulin concentration (1.92 mIU/L), while the DPSc group had the highest insulin concentration. The DPS group had significantly different insulin levels from the PS, DPSb, DPSc, and DPSe groups. Meanwhile, the PS, DPSa, DPSb, DPSc, DPSd, and DPSe groups showed insulin levels that were not significantly different. The administration of *P. javanicum* leaf extract and microcapsules at different doses increased blood insulin levels. Administration of microcapsules at the lowest dose (100 mg/kg bb) increased insulin levels by 36.45% compared to the DPS group. The higher the dose of microcapsules, the higher the blood insulin levels.

Histopathology of the pancreas

Based on qualitative observations, the diagnosis of pancreatic cells for the control group (PS) shows that the pancreatic cell structure is typical, has an ovoid-round islet shape, has clear islet boundaries with an arrangement of endocrine cells that appear to be regularly distributed in the islets of Langerhans, and found few cells experiencing

necrosis. In the diabetic rat group (DPS, DPSa, DPSb, DPSc, DPSd and DPSe), many cells experienced necrosis characterized by pycnotic conditions (characterized by small dark purple dense nuclei) in cells and experienced karyolysis.

Discussion

Considering the information in Table 2, the total phenolic content of microcapsules and *P. javanicum* leaf extract is related to their antioxidant and antidiabetic activities. Adfa *et al*. (2013) documented that *P. javanicum* extract contained the bioactive compounds quercetin and scopoletin, which have antioxidant and antidiabetic potential. Procházková *et al*. (2011) reported, in general, the mechanism of flavonoids acting as antioxidants in several ways, namely radical scavenging, metal binding, inhibition of the enzymatic activity responsible for generating free radicals, and stimulation of the activity of internal antioxidant enzymes.

It has been found that quercetin exhibits antioxidant activities through metal-chelating and radical-scavenging mechanisms (Islam *et al*. 2013). Several researchers have also documented that flavonoid compounds had antidiabetic properties via lowering glucose absorption in the small intestine through the inhibition of α-amylase and α-glucosidase enzyme activity (Bule *et al*. 2019; Kahksha *et al*. 2023; Ghorbani 2017). Xu (2010) reported that the mechanism of flavonoids in inhibiting the α-glucosidase enzyme is through the interaction of the 3', 4'-hydroxy group on the B-ring that binds to the active side of the enzyme, while the 3-OH group on the flavonoid carbon ring functions to maintain binding to the flavonoid molecule.

At the stage of the bioassay, STZ-induced rats have elevated blood glucose levels and are classified as moderately diabetic. Elevated blood glucose concentrations in rats are caused by the disruption of pancreatic β-cells by the agent streptozotocin. Greenspan (1998) reported that streptozotocin binds to GLUT-2, which facilitates the entry of STZ into the cytoplasm of pancreatic β-cells, increasing depolarization in the mitochondria as a result of Ca^{2+} ion entry followed by excess energy consumption, resulting in an energy deficit in the cell. This mechanism disrupts insulin production, resulting in insulin deficiency, which causes all glucose consumed by the body not to be processed entirely, resulting in elevated glucose levels in the body.

The results in Table 3 reveal that, in streptozotocin-induced diabetic rats, microcapsules and *P. javanicum* leaf extract tend to decrease blood glucose concentrations. The lowest dose of microcapsules (100 mg/kg bw) effectively reduced blood sugar concentrations within range of normal levels. This shows that the administration of microcapsules or *P. javanicum* leaf extract can provide the same effect as the marketed antidiabetic drugs in lowering blood glucose concentration. The research findings related to the results published by Mutmainah *et al.* (2021) that administering stevia leaf extract microcapsules at 100 mg/kg bw effectively reduced blood glucose concentration in diabetic rats.

Table 3: Changes in blood glucose levels of rats during treatment

Treatments	Blood glucose concentration (mg/dL)	
	At day 0 (initial)	At day 30 (final)
PS	73.33 ± 5.68^{a}	81.67 ± 11.01^{ab}
DPS	356.00 ± 66.20^{b}	414.33 ± 7.57^{c}
DPSa	314.33 ± 49.65^{b}	106.07 ± 17.00^{b}
DPSb	323.00 ± 89.11^{b}	80.00 ± 20.50^{ab}
DPSc	295.00 ± 64.28^{b}	79.00 ± 7.21^{ab}
DPSd	376.67 ± 116.80^{b}	77.00 ± 11.93^{a}
DPSe	364.33 ± 92.41^{b}	82.67 ± 7.33^{ab}

Notes: Superscripts in the same column denote significant differences ($P < 0.05$)

Table 4: Weight of rats during treatment

Treatments	Rat weight (g)	
	At day 0 (initial)	At day 30 (final)
PS	126.67 ± 17.24^{a}	156.00 ± 6.00^{bc}
DPS	115.33 ± 9.01^{a}	114.00 ± 17.52^{a}
DPSa	133.00 ± 21.65^{a}	182.33 ± 36.55^{c}
DPSb	142.00 ± 33.18^{a}	151.33 ± 29.90^{abc}
DPSc	116.00 ± 7.00^{a}	120.67 ± 5.68^{ab}
DPSd	151.67 ± 19.13^{a}	151.00 ± 16.52^{abc}
DPSe	122.33 ± 15.14^{a}	130.33 ± 13.27^{ab}

Notes: Superscripts in the same column denote significant differences ($P < 0.05$)

Table 5: Insulin levels

Treatments	Insulin Level (mIU/L)
PS	2.94 ± 0.08^{b}
DPS	1.92 ± 0.07^{a}
DPSa	2.62 ± 0.47^{ab}
DPSb	3.45 ± 1.16^{b}
DPSc	3.54 ± 0.28^{b}
DPSd	2.76 ± 0.08^{ab}
DPSe	3.35 ± 0.35^{b}

Notes: Superscripts in the same column denote significant differences ($P < 0.05$)

P. javanicum extract and microcapsules contain phenolic compounds, especially the flavonoid group, which are believed to contribute to controlling blood sugar concentrations. As antidiabetic agents, phenolic compounds generally work by modulating the activity of enzymes involved in glucose metabolism, enhancing the function of pancreatic beta-cells (insulin synthesis and secretion), lowering the amount of glucose produced in the liver, and adjusting the effectiveness of insulin receptors and glucose transporters (Bahadoran *et al*. 2013) (Table 4).

The administration of extracts or microcapsules of *P. javanicum* leaves also affects the level of feed consumption and increases the body weight of rats. In diabetic conditions, the unavailability of glucose will lead to excessive gluconeogenesis, so liver cells will increase glucose production from other substrates by breaking down proteins. Amino acids from the breakdown are transaminated to produce substrates for glucose production. This event occurs continuously because there is little or no insulin to limit gluconeogenesis. The glucose produced is excreted in the urine. As a result, there is a significant reduction in the amount of muscle tissue and fat tissue. The outcome is a reduction in body weight (Granner 2003) (Table 5).

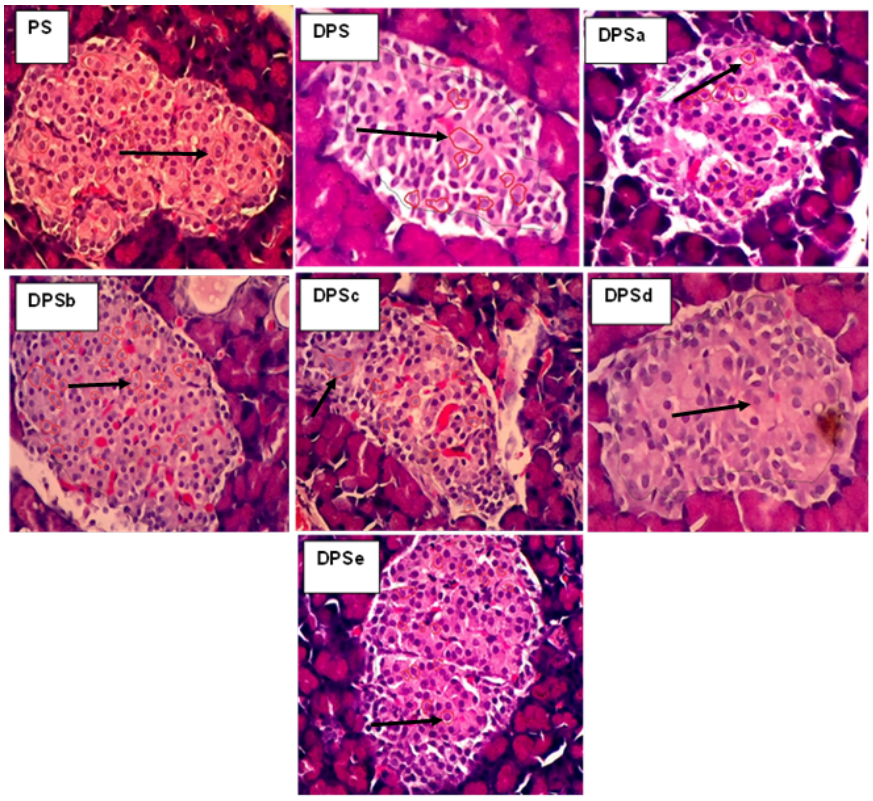

Fig. 1: Histopathology of rat pancreas of PS, DPS, DPSa, DPSb, DPSc, DPSd and DPSe groups, (Arrows indicate necrotizing cells)

A strong and significant correlation was observed between the decrease in blood glucose concentrations in experimental animals and the increase in insulin levels. Relating to the information provided in Table 2 and Table 3, it can be seen that higher insulin levels were found in the rats with diabetes mellitus administered either microcapsules or leaf extract from *Protium javancum*. Phenolic compounds can increase insulin synthesis and secretion by improving pancreatic beta cell function through the activation mechanism of sirtuin 1 (Sirt 1) and glucose transporter 2 (Glut 2), modulating insulin-dependent pathways involving changes in cellular redox status and cell signaling activity (Kang *et al*. 2020). Phenolic compounds may also improve peripheral insulin sensitivity by activating phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT), Glut 4, and peroxisome proliferator-activated receptor gamma (PPAR-γ) in muscle, adipose, and other tissues. In addition, phenolic compounds activate AMP-activated protein kinase (AMPK) in the liver, muscle, and adipose tissue through insulin-dependent pathways (Kang *et al*. 2020).

The effects of phenolic compounds on insulin-dependent pathways correlate with improved beta-cell function and insulin sensitivity, reduced inflammation and lipotoxicity, and improved hepatic glucose output and glucose uptake. These conditions maintain glucose homeostasis in a normal state.

In this study, the improvement of hyperglycemic conditions in the DPSa, DPSb, DPSc, DPSd and DPSe groups was supported by better pancreatic conditions. Chronic hyperglycemic conditions cause β-cell degeneration characterized by cytoplasmic vacuolization, nuclear pyknosis, and cell necrosis (Feeney 2012). Based on the histopathological image of the pancreas, Fig. 1 shows that dealing with *P. javanicum* leaf extract or its use in the form of microcapsules can reduce the level of cell damage in diabetic animals by providing an opportunity for cells to regenerate.

Conclusion

It can be inferred from the study's findings that microcapsules of ethanol extract from *P. javanicum* leaves have antidiabetic properties. It is thought that the phenolic compounds present in the microcapsules contribute to their antidiabetic properties by inhibiting the activity of the α-glucosidase enzyme *in vitro* and ameliorating the conditions of the β-pancreatic cells, which are marked by a reduction in the degree of cell damage in rats with diabetes. Repairing β-pancreatic cells will induce insulin secretion and lowering blood glucose levels.

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Author Contributions

Each author has made an equal role in this work and has permitted it to be published.

Conflicts of Interest

All authors declare no conflicts of interest.

Data Availability

The data stated in this work will be made accessible upon a reasonable request to the corresponding author.

Ethics Approval

Not applicable in this paper

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