

Antidiabetic Power of *Belalai gajah* Plant (*Clinacanthus nutans*)

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Abstract: This study aims to determine the decrease in rat blood glucose levels, MDA levels, and the histopathological description of pancreas after giving ethanol extract of *belalai gajah* plant. This study used 25 rats, grouped into 5, namely normal control, negative control (CMC-Na 0.5% dose 2 mL/200 g b.w), positive control (glibenclamide dose 0.09 mg /200 g b.w), *belalai gajah* plant ethanol extract (dose 30 mg/200 g b.w., and 60 mg/200 g b.w). Prior to treatment, the rats were induced into diabetes with streptozotocin-nicotinamide. The content of *belalai gajah* plant was tested phytochemically and antidiabetic. Potential of *belalai gajah* plant was tested by induction for 14 days. The results showed that ethanol extract of *belalai gajah* plant contained alkaloids, flavonoids, steroids, terpenoids, and phenolics. The decrease in blood glucose and MDA levels in the group given the ethanol extract of *belalai gajah* plant at dose of 60 mg/200 g b.w. was the same as the dose of glibenclamide 0.09 mg/200 g b.w. The results of histopathological of pancreas showed that the ethanol extract of *belalai gajah* plant at dose of 60 mg/200 g b.w. could improve the structure of Langerhans islets in the pancreas of diabetic rats.

Keywords: *Belalai gajah* (*Clinacanthus nutans*); Blood glucose; Diabetes mellitus; MDA levels; Pancreatic Histopathology

Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia that occurs due to defects in insulin secretion, insulin action or both (Bahagia et al., 2018). Diabetes mellitus is a non-communicable disease but has a serious impact on the individual sufferer. This disease occurs due to the inability of the pancreas to produce insulin (Safitri & Nurhayati, 2019). Insulin is a hormone that controls blood glucose levels. High blood glucose levels are influenced by the hormone insulin that does not work properly (Fatimah, 2015) Uncontrolled diabetes mellitus can lead to acute metabolic complications and chronic vascular complications, which can be in the form of microangiopathy or macroangiopathy (Bahagia et al., 2018). Treatment of diabetes mellitus is currently still limited to the use of oral hypoglycemic drugs (OHO) such as biguanides, sulfonylureas, glinides,

thiazolidinediones, acarbose, and insulin injections. These diabetes drugs can cause various side effects such as diarrhea, dizziness, headache, nausea and vomiting, weight gain, hypoglycemia, and if not treated immediately, coma and even death can occur (Puspitasari & Choerunisa, 2021).

The use of traditional medicines in Indonesia is part of the Indonesian culture and has also been used by the Indonesian people since ancient times. Although there are conventional antidiabetic drugs, people in Indonesia prefer traditional treatment using medicinal plants because it is considered cheaper and easily available (Kooti et al., 2016). In addition, traditional medicine is still used by the community because the side effects are considered safer. Compounds contained in traditional medicine are biologically active and can affect the cells of living organisms (Surbekti et al., 2022).

One type of plant that is widely used as traditional medicine is *belalai gajah* plant (*Clinacanthus nutans*).

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Belalai gajah is a herbaceous plant that grows in Southeast Asia and lives in lowland areas. This plant by community is often used as an antidiabetic drug, antidote, anti-inflammatory, pain reliever, and antioxidant (Arullappan et al., 2014). The part of *belalai gajah* plant that is usually used in medicine is the leaves (Viena et al., 2018). The content of natural ingredients found in *belalai gajah* plants include flavonoids, alkaloids, and saponins (Abdullah & Kasim, 2017). The results of other plant studies show that flavonoid compounds can modulate blood glucose by increasing insulin secretion, increasing pancreatic β -cell proliferation, reducing apoptosis, reducing insulin resistance, reducing inflammation and oxidative stress in muscles, and increasing Glucose Transporter Type 4 (GLUT4) translocation (Vinayagam & Xu, 2015). The hypoglycemic powers are saponins through insulin rejuvenation, insulin signal renewal, insulin release from β cells, inhibition of disaccharide activity, activation of glycogen synthesis, inhibition of gluconeogenesis, inhibition of α -glucosidase activity, inhibition of mRNA expression of glycogen phosphorylase and glucose 6-phosphatase (G-6P) as well as increasing GLUT4 expression (Barky et al., 2017), while tannins play a role by increasing glucose uptake through the activation of mediators of insulin signaling pathways such as phosphoinositide 3-kinase (PI3K), and Mitogen Activated Protein Kinase (p38 MAPK), as well as GLUT-4 translocation (Kumari & Jain, 2012).

Previous research on *belalai gajah* leaves stated that *belalai gajah* leaves at a dose of 75 mg/kg body weight could significantly reduce blood glucose levels in diabetic rats at week 4 (Nizar et al., 2020). Another research on *belalai gajah* leaves was conducted by (Arullappan et al., 2014) showed that *belalai gajah* leaves has potential as an antidote, antioxidant, and antibacterial. Other researches have shown that *belalai gajah* leaves have potential as anti-inflammatory (Mai et al., 2016). Based on the above research, the researchers are interested in conducting further research on the antidiabetic activity of *belalai gajah* plant extracts on male white rats (*Rattus norvegicus*) Wistar strain induced with a combination of streptozotocin and nicotinamide (STZ-NA).

This study has differences from previous studies regarding the *belalai gajah* anti-diabetic test. The difference between this study and previous studies such as that conducted by Anggraeny et al. (2021; Dewinta et al. (2020); Retnaningsih et al. (2019) lies in the differences in the plant organs used, the solvent used in the extraction process, the length of maceration, the form of the extract, the ingredients used to keep the rats in a state of diabetes, and the dose of the extract to be used.

Method

Materials

The materials used in this research were *belalai gajah* plant, white rat Wistar strain, 96% ethanol, aquades, 0.5% CMC-Na, glibenclamide, streptozotocin and nicotinamide (STZ-NA), and feed. The tools used in this research are gastric probe, surgical instrument, rat cage, UV-Vis spectrophotometer, and microscope.

Extraction and Phytochemical Test

The process of extracting *belalai gajah* plant samples is carried out based on Panjaitan et al. (2013). *Belalai gajah* plant samples were cut, dried, and powdered, then macerated with 96% ethanol at room temperature. The maceration process was repeated 3 times by changing the solvent. Furthermore, the filtrate from the maceration was concentrated using a rotary evaporator and the yield was calculated.

Qualitative Phytochemical Testing

Qualitative phytochemical tests were carried out according to the (Harborne, 1987) procedure. Phytochemical test reagents were made, namely alkaloid reagents which included Mayer, Wagner, and Dragendorff reagents, and the manufacture of steroid and terpenoid test reagents, namely Lieberman-Burchard reagents. In addition to the manufacture of phytochemical test reagents, activities to purify 96% technical ethanol and manufacture 10% ethanol were also carried out. Furthermore, the identification of secondary metabolite compounds was carried out. The secondary metabolite compounds identified were alkaloids, flavonoids, saponins, terpenoids, steroids, and phenolics. Phytochemical testing is done by looking at the color test reaction using a color reagent.

Test Animal Treatment

The test animals used in this study were male white rats of the Wistar strain. The 25 rats used were 2 months old and weighed 200-250 g. Before the experiment started, all test animals were adapted to the treatment environment for 7 days. During acclimatization, all test animals were given standard feed and drinking ad libitum. Health conditions were also observed by weighing the body weight. This test has obtained a statement of eligibility from the Health Research Ethics Commission, Faculty of Health Sciences, Universitas Respati Yogyakarta No. 039.3/FIKES/PL/VI/2022.

Antidiabetic power of *belalai gajah* plant extract

The research design used was a completely randomized design (CRD). After all the test animals were adapted for 7 days, then the test animals were randomly divided into 5 groups with each group

consisting of 5 rats. The antidiabetic power test procedure refers to Panjaitan & Novitasari (2021). All rats were fasted for \pm 8-12 hours. After that, 0.5 mL of blood was drawn through the orbital sinus to measure the initial blood glucose level (day 0). Measurement of blood glucose levels using glucose reagent (Glucose GOD FS DiaSys) and homogenized with a vortex. After homogenization, the blood samples were measured using a UV-Vis spectrophotometer. On the same day, all mice were induced with a combination of streptozotocin and nicotinamide (STZ-NA) at a dose of 45 mg/kg body weight and 110 mg/kg body weight, respectively. STZ-NA induction was performed intraperitoneally.

Nicotinamide induction was performed 15 minutes earlier than streptozotocin. After 72 hours (day 3), the blood glucose levels of rats that had been induced by STZ-NA were examined. Rats were diagnosed with type 2 diabetes mellitus if the blood glucose level was >200 mg/dL (Ghasemi et al., 2014). All mice used in this experimental study had blood glucose levels >200 mg/dL after administration of STZ-NA. After that, it was continued by giving the test preparation once a day for 14 consecutive days. Administration of test preparations orally. The first group as a normal control or without treatment, the second group as a negative control (NC) was given 0.5% CMC-Na solution at a dose of 2 mL/200 g body weight, the third group as a positive control (PC) was given glibenclamide at a dose of 0,09 mg/200 g body weight, the fourth group was given *belalai gajah* plant ethanol extract at a dose of 30 mg/200 g body weight (E1), and the fifth group was given *belalai gajah* plant ethanol extract at a dose of 60 mg/200 g body weight (E2). *Belalai gajah* plant test dose refers to Dewinta et al. (2020). The administration of the test preparation was started from the 4th day to the 17th day, and on the 18th day, blood was drawn to determine the antidiabetic power.

Measurement of MDA Level

MDA levels were measured using the Thiobarbituric Acid Reactive Substances (TBARS) method. On day 18, white rats were fasted for 10-12 hours while still being given water, then the serum MDA levels were measured. Blood taken from the orbital sinus was then centrifuged to obtain blood serum which was then read the results of the rat blood glucose levels using a UV-Vis spectrophotometer (Febrina et al., 2016).

Preparation of Pancreatic Organ Histopathology

Preparation of histopathological preparations of pancreatic organs refers to Panjaitan et al. (2013). Animals were anesthetized using chloroform, then euthanized, dissected, and pancreas organs were taken. Pancreatic organ samples were washed with physiological NaCl solution, then fixed with 10%

formalin buffer. Furthermore, the preparation of paraffin-preserved preparations was carried out on the pancreas organ with a series of stages starting from fixation, dehydration, purification, infiltration, planting, slicing, staining with hematoxylin-eosin dye, and mounting.

Data Collection Technique

Blood samples of the test animals were collected on the 0, 3, and 18 days, then blood glucose and MDA levels were measured using serum. Pancreatic organs were taken on the 18th day, and the histopathological picture of pancreas of the test animals was observed by viewing the pancreatic tissue in several fields of view under a microscope.

Result and Discussion

Belalai gajah Plant Phytochemical Results

Phytochemical test is a way to identify bioactives that have not been seen through a test or examination that can quickly separate natural materials that contain certain phytochemicals from natural materials that do not contain certain phytochemicals. Phytochemical screening is a preliminary stage in a phytochemical research that aims to provide an overview of the class of compounds contained in the plant being studied (Saragih & Arsita, 2019).

The phytochemical test results from the *belalai gajah* plant extract can be seen in Table 1. The identification of alkaloids showed negative results in the *belalai gajah* plant extract added with Mayer and Dragendorff reagents. While the identification of alkaloids in the extract of *belalai gajah* plant which was added with Wagner's reagent showed positive results where in Table 1 the alkaloid content was low. The identification of saponins showed negative results, which means that the *belalai gajah* plant extract did not contain saponins. The identification of terpenoids and steroids showed positive results where in Table 1 the *belalai gajah* plant extract had sufficient levels of terpenoids and steroids. While the phenolic identification showed positive results where in Table 1 the *belalai gajah* plant extract had high phenolic levels. Therefore, the *belalai gajah* plant contains phytochemical compounds in the form of alkaloids, flavonoids, terpenoids, steroids, and phenolics.

Results should be clear and concise. The discussion should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Table 1. Phytochemical results of *belalai gajah* plant

| Test Parameters | Sample |
|-------------------------|--------|
| Alkaloids (Mayer) | - |
| Alkaloids (Wagner) | + |
| Alkaloids (Dragendroff) | - |
| Flavonoids | ++ |
| Saponins | - |
| Terpenoids | ++ |
| Steroids | ++ |
| Phenolic | +++ |

Note:
 (-) no contain
 (+) low rate
 (++) moderate
 (+++) high rate

Blood Glucose Levels and MDA Levels in White Rats

Measurement of blood glucose levels was carried out three times; i.e. initial blood glucose levels or before STZ-NA induction (day 0), blood glucose levels 72 hours

after STZ-NA induction (day 3), and overall blood glucose levels after 14 days of treatment (day 3rd). 18). In the initial measurement of blood glucose levels, all mice had normal blood glucose levels; after STZ-NA induction, all blood glucose levels in rats increased; and after giving treatment for 14 days, the positive control group and the extract treatment experienced a decrease in blood glucose levels. After that, the MDA levels were measured using the TBARS method, namely, on day 18 the white rats were fasted for 10-12 hours while still being given water, then the serum MDA levels were measured. Blood taken from the orbital sinus was then centrifuged to obtain blood serum which was then read the results of rat blood glucose levels using a UV-Vis spectrophotometer (Febrina et al., 2016). The results of measuring blood sugar levels in white rats on day 0, 3, and 18 and MDA levels in white rats on day 18 can be seen in Table 2.

Table 2. The average blood glucose levels of rats in each treatment group on day 0, 3, 18 and the average level (MDA) of malondialdehyde in each treatment group on day 18

| Treatment Group | Blood Glucose Levels (mg/dL) | | | MDA Levels (nmol/mL) |
|-----------------|------------------------------|-----------------------------|----------------------------|--------------------------|
| | Day 0 | Day 3 | Day 18 | |
| N | 66.22 ^a ± 2.13 | 67.34 ^a ± 2.05 | 68.82 ^a ± 1.44 | 1.56 ^a ± 0.15 |
| K (-) | 66.61 ^a ± 1.09 | 268.49 ^{bc} ± 3.75 | 270.30 ^d ± 3.83 | 9.39 ^d ± 0.31 |
| K (+) | 66.30 ^a ± 1.07 | 273.90 ^c ± 5.40 | 113.85 ^b ± 3.72 | 3.24 ^b ± 0.31 |
| P1 | 65.20 ^a ± 2.13 | 264.17 ^b ± 2.49 | 151.48 ^c ± 6.54 | 6.14 ^c ± 0.36 |
| P2 | 65.83 ^a ± 1.13 | 270.81 ^{bc} ± 7.26 | 120.29 ^b ± 3.72 | 3.68 ^b ± 0.33 |

Data displayed in the form of Mean ± Standard Deviation (SD)
 Groups given the same letter are not significantly different (p>0,05)
 Explanation:

- N = Normal Control
- K (-) = Negative Control (CMC-Na 0.5% dose 2 mL/200 g body weight)
- K (+) = Positive Control (Glibenclamide dose 0.09 mg/200 g body weight)
- P1 = *Belalai gajah* plant ethanol extract dose 30 mg/200 g body weight
- P2 = *Belalai gajah* plant ethanol extract dose 60 mg/200 g body weight

Histopathological Overview of White Rat Pancreatic Organs

The histopathological preparations for the pancreas of white rats were made by anesthetizing the animals using chloroform, then euthanized, dissected, and the pancreas organs were taken. Pancreatic organ samples were washed with physiological NaCl solution, then fixed with 10% formalin buffer.

Furthermore, the preparation of paraffin-preserved preparations was carried out on the pancreas organ with a series of stages starting from fixation, dehydration, purification, infiltration, planting, slicing, staining with hematoxylin-eosin dye, and mounting. The results of the histopathological picture of the pancreas of white mice can be seen in Figure 1.

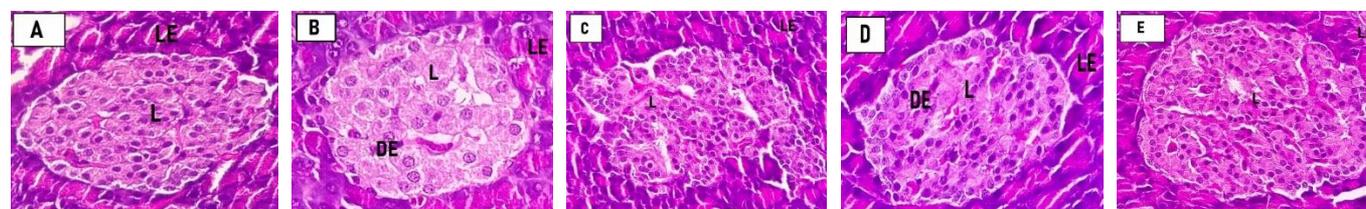


Figure 1. A: normal control; B: negative control; C: positive control; D: *belalai gajah* plant ethanol extract treatment dose 30 mg/200 g body weight; E: *belalai gajah* plant ethanol extract treatment dose 60 mg/200 g body weight; L: islets of Langerhans; LE: exocrine lobe; DE: Degeneration (magnification 40X).

Discussion

Diabetes mellitus is a metabolic disorder with high glucose levels in the blood, as a result of pancreatic disorders due to not actively producing insulin at optimal levels or our bodies cannot use insulin effectively. The decreased function of the pancreas in producing insulin causes disturbances in carbohydrate, lipid, and protein metabolism which can lead to hyperglycemia conditions (Panjaitan & Novitasari, 2021). Therefore, one way that can be done to diagnose diabetes mellitus is to measure blood glucose levels.

Based on Table 2, on day 0 (before being induced with STZ-NA), the blood glucose levels of white rats showed normal levels, namely 65.20-66.61 mg/dL. According to Samsuri et al. (2020), normal blood glucose levels in white rats ranged from 50-135 mg/dL. On the 3rd day, the blood glucose levels of white rats increased, namely 264.17-273.90 mg/dL. According (Ghasemi et al., 2014), blood glucose levels in white rats increased after 72 hours induced with STZ-NA.

Streptozotocin is a chemical that works by forming highly reactive free radicals that can cause damage to cell membranes, proteins, and Deoxyribonucleic Acid (DNA), causing disruption of insulin production by pancreatic β -cells. Streptozotocin enters pancreatic β -cells via Glucose Transporter 2 (GLUT 2) and causes alkylation. This is preceded by restriction of the formation of adenosine triphosphate in the mitochondria due to the formation of free radicals, an increase in the enzyme xanthine oxidase, and inhibition of the Krebs cycle. There are two types of streptozotocin-induced diabetes mellitus (STZ), namely type 1 diabetes mellitus and type 2 diabetes mellitus (Saputra et al., 2018). Nicotinamide is a material that is safe for human consumption so that it meets the requirements of a substance that can be used as a cofactor. Based on its chemical structure, nicotinamide has a great opportunity to form co-crystals with various pharmaceutical active ingredients (Hairunnisa. et al., 2019). The combination of streptozotocin and nicotinamide can prevent excessive hyperglycemia and mortality in rats. Nicotinamide can stimulate pancreatic cell regeneration, Langerhans cell growth, and can block apoptotic reactions. In addition, nicotinamide induction before streptozotocin induction can act as a methyl group acceptor so that it can reduce the DNA methylation process in pancreatic cells (Ghasemi et al., 2014).

After giving treatment for 14 days, it was found a decrease in blood glucose levels in the positive control group, namely glibenclamide at a dose of 0.09 mg/200 g body weight, *belalai gajah* plant ethanol extract treatment group at a dose of 30 mg/200 g body weight and

treatment of *belalai gajah* plant ethanol extract with a dose of 60 mg/200 g body weight.

In the positive control group, there was a decrease in blood glucose levels of 113.85 mg/dL, while in the treatment group the ethanol extract of *belalai gajah* plant at a dose of 30 mg/200 g body weight obtained blood glucose levels of 151.48 mg/dL, and the treatment group ethanol extract of *belalai gajah* plant with a dose of 60 mg/200 g body weight obtained blood glucose levels of 120.29 mg/dL. On the other hand, the negative control group, namely CMC-Na 0.5% with a dose of 2 mL/200 g body weight did not show a decrease in blood glucose levels, this was because CMC-Na 0.5% did not have antidiabetic activity which was marked with a decrease in blood glucose levels (Panjaitan & Novitasari, 2021). *Carboxymethyl Cellulose Sodium* (CMC-Na) is a cellulose derivative compound that is soluble in water. CMC-Na is often used as an additive in industries such as the food, pharmaceutical, detergent, textile and cosmetic products industry as a thickener, stabilizer of emulsions or suspensions, and binders (Salimi et al., 2021).

Overall it can be seen that glibenclamide is more effective in reducing blood glucose levels in white rats compared to the ethanol extract of the *belalai gajah* plant at a dose of 30 mg/200 g body weight and a dose of 60 mg/200 g body weight, although the results of the analysis of blood glucose levels of glibenclamide and ethanol extract of *belalai gajah* plant with a dose of 60 mg/200 g body weight was not significantly different ($p > 0.05$). Glibenclamide is an oral antidiabetic sulfonylurea generation II where the mechanism of action of glibenclamide in lowering blood glucose levels is to stimulate insulin secretion from granules of pancreatic β -cells, stimulate through its interaction with ATP sensitive K channels on the membrane and this condition will open Ca^{2+} ion channels by opening Ca^{2+} ion channels then Ca^{2+} ions will enter the β -pancreatic cells thereby stimulating insulin cells (Widyastuti et al., 2022).

Table 2 presents the mean MDA levels of all treatment groups ranging from 1.56-9.39 nmol/mL, which means that MDA levels in normal control rats are in the normal range. MDA (Malondialdehyde) is a highly reactive three-carbon dialdehyde which can also be obtained from the hydrolysis of pentoses, deoxyribose, hexoses, some amino acids and DNA. The MDA test can be used to measure peroxidation that occurs in lipid membranes. The MDA profile in serum serves as a marker of cellular damage caused by free radicals. The higher the levels of free radicals, the higher the levels of MDA formed (Zaetun et al., 2017). According to Sutaryono. et al. (2018), the normal range for MDA levels is 1.09-1.64 nmol/mL. In the normal control treatment, the average MDA level was 1.56 nmol/mL, because the normal control group was not

given STZ-NA induction before. In the negative control treatment (CMC-Na 0.5%) the highest average MDA level was 9.39 nmol/mL. This is because CMC-Na does not have the ability to lower blood glucose levels and MDA levels. In addition, streptozotocin will increase lipid peroxidation and MDA levels (Panjaitan & Astuti, 2021). In the positive control treatment given glibenclamide, the average MDA level was 3.24 nmol/mL. This is because glibenclamide can stimulate insulin secretion from pancreatic β -cell granules so that it can reduce blood glucose levels (Widyastuti et al., 2022). In the treatment group of *belalai gajah* plant ethanol extract at a dose of 30 mg/200 g body weight, the average MDA level was 6.14 nmol/mL. The treatment group of *belalai gajah* plant ethanol extract with a dose of 60 mg/200 g body weight obtained an average MDA level of 3.68. The MDA levels of rats treated with glibenclamide and *belalai gajah* plant ethanol extract at a dose of 60 mg/200 g body weight were closest to the normal range and the results of the analysis were not significantly different ($p > 0.05$). *Belalai gajah* plant has the potential to protect the body from free radical attacks caused by streptozotocin. This is because *belalai gajah* plant has secondary metabolites, namely alkaloids, flavonoids, terpenoids, steroids, and phenolics.

Alkaloids have antioxidant properties by inhibiting oxidation reactions so that the formation of free radical chains is inhibited by proton donors to stabilize free radicals (Anggi et al., 2022) and can lower blood sugar in an extra pancreatic mechanism, namely by increasing glucose transport in the blood, inhibiting glucose absorption in the intestine, stimulating synthesis. glycogen, and inhibits glucose synthesis, and increases glucose oxidation (Larantukan et al., 2014). Flavonoids are scientifically proven to lower blood glucose levels. Flavonoid compounds are able to lower blood glucose with their ability as antioxidants. Flavonoid compounds are protective against damage to cells as insulin producers and can increase insulin sensitivity (Hidayat & Setyaningsih, 2021).

Terpenoids have the ability to inhibit the action of alpha glucosidase enzymes on the walls of the small intestine (Sinulingga et al., 2020). Steroids play an important role for the body in maintaining salt balance, controlling metabolism and improving the function of sexual organs as well as differences in other biological functions between the sexes. Steroids in plants show cholesterol-lowering and anticarcinogenic effects (Maryam et al., 2020). Phenolic compounds are the largest group of compounds that act as natural antioxidants in plants. Phenolic compounds have one (phenol) or more (polyphenol) phenol rings, namely hydroxy groups attached to aromatic rings so that they are easily oxidized by donating hydrogen atoms to free

radicals. Its ability to form stable phenoxy radicals in oxidation reactions causes phenolic compounds to be very potential as antioxidants (Dhurhania & Novianto, 2018). Therefore, the results of this study prove the antidiabetic power of ethanol extract of *belalai gajah* plant assessed based on blood glucose levels and MDA levels. In addition, the potential properties are confirmed by the antioxidant content found in the ethanolic extract of *belalai gajah* plant so that it can repair damage caused by free radical attacks.

Based on the results of histopathological analysis of the pancreas of white rats in Figure 1, it can be seen that the normal control treatment showed a normal structure of the islets of Langerhans which was characterized by β -pancreatic cells with round nuclei with a good picture, and no degenerating and necrotic cells were found. cells are very dense, and there are no cells that experience edema (swelling). According to Prameswari & Widjanarko (2014), histopathological characteristics of the pancreas of normal white rats did not show necrosis, the cell nucleus looked very dense, and there were no swollen cells. In the negative control treatment (CMC-Na 0.5%) there was structural damage to the islets of Langerhans which was characterized by degeneration and atrophy (shrink in size of the islets of Langerhans), and pancreatic β -cells with enlarged nuclei and visible nucleoli. This shows that the administration of streptozotocin can form free radicals that cause oxidative stress (Saputra et al., 2018). The positive control treatment (glibenclamide) showed an improvement in the structure of the islets of Langerhans which was characterized by the monomorphous shape of β -pancreatic cells, no degenerated cells were found, and β -pancreatic cells with enlarged nuclei and visible nucleoli. This is because the main mechanism of action of glibenclamide is to increase insulin secretion and repair of pancreatic β -cells (Widyastuti et al., 2022). In the treatment of ethanol extract of *belalai gajah* plant at a dose of 30 mg/200 g body weight, there was damage to the structure of the islets of Langerhans which was characterized by degeneration, while the ethanol extract of *belalai gajah* plant at a dose of 60 mg/200 g body weight showed an improvement in the structure of the islets. Langerhans characterized by monomorphic β -pancreatic cells, no degenerating cells were found, and β -pancreatic cells with enlarged nuclei and visible nucleoli. This shows that the ethanol extract of *belalai gajah* plant at a dose of 60 mg/200 g body weight is more effective in reducing blood glucose levels and has potential as an antioxidant compared to the ethanol extract of *belalai gajah* plant at a dose of 30 mg/200 g body weight. Overall, it can be seen that ethanol extract of *belalai gajah* plant has a mechanism as antidiabetic. Based on the results of study conducted by Arullappan et al. (2014) leaves of *belalai gajah* plant have antioxidant

activity and so did (Nizar et al., 2020), leaves of *belalai gajah* plant have antioxidant activity. According to Prawitasari (2019), antioxidants can increase the ability of defense enzymes against free radicals to prevent the emergence of oxidative stress.

This study differs from previous studies that have been conducted regarding the antidiabetic test of *belalai gajah*. In a study conducted by Dewinta et al. (2020) regarding the antidiabetic test of *belalai gajah*, the plant organs used were the leaves, the solvent used for the extraction process was 70% ethanol, the maceration was carried out for 24 hours, the material used to make rats in a diabetic state was streptozotocin, the dose of ethanol extract *belalai gajah* leaves used were 75 mg/kg body weight, 150 mg/kg body weight, and 300 mg/kg body weight. In a study conducted by Anggraeny et al. (2021) regarding the hypoglycemia test of *belalai gajah* microcapsules, the plant organs used were the leaves, maceration was carried out for 5 days. The ingredients used to make rats in a diabetic state were fructose and HFF high-fat feed (combination of lard and duck egg yolk with the ratio of (3:1)), and the doses of *belalai gajah* microcapsules used were 15.89 mg/kg body weight, 31.78 mg/kg body weight, 47.67 mg/kg body weight, 63.56 mg/kg body weight, and 79.45 mg/kg body weight. In a study conducted by Retnaningsih et al. (2019) regarding the hypoglycemia test of the *belalai gajah* water fraction, the plant organs used were the leaves, the solvent used for the extraction process was 96% ethanol, the maceration was carried out for 5 days. The material used for rats in a state of diabetes is fructose and HFF high-fat feed (combination of lard and duck egg yolk with the ratio of (3:1)). The doses of the water fraction of *belalai gajah* leaves used were 15.89 mg/kg body weight, 31.78 mg/kg body weight and 47.67 mg/kg body weight.

The advantage of this research is that in the extraction process, the solvent used is 96% ethanol which is a volatile polar compound so it is good to use as an extract solvent. The maceration carried out in this study was carried out for 3x24 hours so as to maximize the process of taking chemical compounds contained in the test material. The induction agent used to induce diabetes in rats uses streptozotocin-nicotinamide. Nicotinamide induction before streptozotocin induction can act as a methyl group acceptor so that it can reduce the DNA methylation process in pancreatic cells (Ghasemi et al., 2014).

Conclusion

Ethanol extract of *belalai gajah* plant (*Clinacanthus nutans*) at a dose of 60 mg/200 g body weight has antidiabetic activity which can reduce blood glucose levels, MDA levels, and can improve the structure of the

islets of Langerhans in the pancreas of diabetic white rats induced by streptozotocin-nicotinamide.

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Author Contributions

Nur Annisa conducted proposal preparation, research preparation, histopathology preparation, and preparation of activity and financial logbooks; Ananda Dwi Putri carried out the preparation of proposals, preparation of extracts and phytochemical tests, preparation of research, and preparation of progress reports; Ariesta Albriyanti did the research preparation, final report preparation, and article manuscript preparation; Panjaitan & Astuti (2021) conducted thorough research starting from the preparation of proposals, designing research, research preparation, preparation of activity and financial logbooks, preparation of progress reports, preparation of final reports, and preparation of article manuscripts.

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Conflicts of Interest

The authors declare no conflict of interest.

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