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Mentawai Taro Corm Flour's Benefits on Hyperglycemia and Pancreas Histopathology in Diabetic Mice

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Abstract: Diabetes mellitus (DM) is among the most severe health issues globally. This study aimed to determine the beneficial effects of Mentawai taro (Colocasia esculenta var. Mentawai) in managing hyperglycemia and attenuating inflammation in pancreatic ß-cells in alloxan-induced diabetic mice. Twenty-one adult male mice were divided into three groups: healthy (non-DM), alloxan-induced DM, and DM mice fed with a diet containing 25% Mentawai taro flour. The treatments were administered for four consecutive weeks. Various parameters, including blood glucose levels, glucose tolerance, and insulin tolerance, were assessed, alongside microscopic examination of pancreatic histology. The results demonstrated that supplementation with 25% Mentawai taro corm significantly lowered fasting blood glucose levels (**P<0.01) and improved glucose tolerance (*P<0.05) and insulin tolerance (*P<0.05) compared to untreated diabetic mice. Mentawai taro corm also ameliorated pancreatic degeneration, as indicated by a larger islet of Langerhans area, a higher total cell number per islet, and a significantly lower number of degenerated cells in pancreatic tissue (**P<0.01). In conclusion, supplementing Mentawai taro corm at 25% in the diet could effectively help manage diabetic issues, including hyperglycemia and pancreatic degeneration.

Keywords: Alloxan-induced, *Colocasia esculenta* var., fasting blood glucose, mentawai corm.

Introduction

Diabetes mellitus has garnered international attention as a prevalent health issue worldwide. According to data from the International Diabetes Federation (IDF), approximately 6.8% of people aged 20-79 years worldwide had diabetes mellitus in 2021. This percentage is projected to rise to 9.9% by 2045. The increasing prevalence of diabetes mellitus can be attributed to factors such as unhealthy dietary habits, obesity, and a sedentary lifestyle (Mujumdar and Vaidehi, 2019; Kumar *et al*., 2018).

Diabetes mellitus (DM) is characterized by persistent high levels of blood glucose resulting from disruptions in insulin secretion, action, or both (Anaya-Isaza and Zequera-Diaz, 2022). The underlying cause of insulin dysfunction is impaired or deficient insulin production by pancreatic Langerhans β-cells (Chen *et al*., 2017). Insulin insufficiency occurs when these β-cells in the pancreas become impaired, rendering them unable to release the necessary hormone to regulate hyperglycemia (Bhattacharya *et al*., 2019).

Diabetes mellitus can be managed through exogenous insulin administration (Chaudhury *et al*., 2017). However, long-term use of exogenous insulin may lead to compromised hematologic conditions, characterized by reduced mean corpuscular hemoglobin and elevated monocyte count (Kusuma *et al*., 2022), injection site lipodystrophy, nerve damage, thermal instability, and microbial contamination (Kassab, 2023).

One alternative to preventing the development of diabetes mellitus without side effects is consuming functional foods

(Alkhatib *et al*., 2017). Mentawai taro (*C. esculenta*) is a primary food crop in Mentawai Island (Santoso, 2022), belonging to the genus Colocasia and exhibiting relatively high genetic diversity that sets it apart from other taro varieties popular in Indonesia (Maideliza *et al*., 2018). Its corm contains various compounds such as resistant starch, fiber, and flavonoids (Santoso, 2022). Previous studies have found that polysaccharides from *Colocasia esculenta* had hypoglycemic effects on streptozotocin-induced rats (Zhang *et al*., 2022). Li *et al*. (2021) examined the potential of flavonoids from various taro plants in reducing blood sugar levels, while research by Kumar *et al*. (2020) focused on the antioxidant activity of taro leaf extracts.

There has been a lot of research on *Colocasia esculenta* in general, but most have focused on using extracts of its active components such as flavonoids, polysaccharides, or antioxidants. However, this study focuses on the whole flour of Mentawai taro (*Colocasia esculenta*) corm as an alternative for diabetes mellitus treatment. This flour is not simply a single-component extract, but includes all the active components in their natural form, potentially working synergistically. This differs from previous extraction approaches, as this study uses whole flour without complex chemical processes, making it more affordable and easier to apply as a natural treatment alternative. This study aims to investigate the effects of consuming Mentawai taro corm on blood glucose levels and pancreatic histopathology in diabetic mice. The benefits of this study as a potential alternative treatment for diabetes mellitus.

Materials and Methods

Ethical approval

Animal care, use, and experimental procedures follow the standard guidelines set by the Research Ethics and Regulation Committee of Andalas University, Indonesia (Approval No. 528/UN.16.2/KEP-FK/21).

Isolation of Mentawai taro corm

Mentawai taro (*C. esculenta*) corm samples were collected in Bosua village, South Sipora District, Mentawai Island, West Sumatra. The corms were washed and peeled before being grated using a manual grater and a stationary blender (Philips HR2116/30, Bogor, Indonesia). Subsequently, the grated corms were filtered and steamed for 15-30 minutes at 100°C. The resulting flour was dried in a dehydrator for 16 hours at 70°C and then ground into powder using a blender (Santoso *et al*., 2024).

Research design

This study used an experimental method using a Complete Random Design (CRD) with three treatments and seven replicates. The research design is as follows:
P0 = Healthy mice (non-DM)
P1 = Alloxan-induced diabetes mellitus (DM) mice
P2 = DM + 25% Mentawai taro flour (MT) in diet (feed)
The dosage of Mentawai taro flour 25% in feed refers to the dose used in previous studies (Santoso *et al.*, 2024).

Experimental animals

Healthy adult male Bagg and Albino (BALB)/c mice (*Mus musculus*; 20-25 g: two months old) were used as experimental animals in this study. The animals were purchased from Lubuk Begalung, Padang, West Sumatra, and housed at the Animal House of Andalas University. The animal protocols used in this study were approved by the Committee of Research Ethics and Regulation of Andalas University, Indonesia.

The mice were acclimatized and kept under standard laboratory conditions, including a 12:12 h light-dark cycle, room temperature maintained at 22-24°C, and relative humidity of 50-60%, in the animal house at the Faculty of Mathematics and Science, Andalas University. They were fed a standard diet and had access to drinking water ad libitum. During the acclimatization period, the animals were habituated to daily handling to minimize stress responses during the experiment. After the acclimatization period, mice were conditioned with diabetes mellitus with induction of alloxan at a dose of 200 mg/kgBB. The test animals were fasted (12-14 hours), then the weight and fasting blood glucose levels of the test animals were measured using a glucometer (AGM-4000 Allmedicus, Anyang, Gyeonggi-do, South Korea). After that, the test animal is

injected with an alloxan solution intraperitoneally. Blood glucose levels are measured seven days after the alloxan injection. Animals with blood glucose levels ≥ 250 mg/dL are categorized as diabetes mellitus (DM) positive (Santoso *et al.*, 2023). After being categorized as DM, the mice were treated with Mentawai taro tuber flour for four weeks.

Observation Parameters

Fasting blood glucose measurement

Fasting blood glucose levels of mice were measured at the end of the treatment period. The mice underwent an 18-hour fasting period from 6:00 a.m. to 9:00 a.m. using a standardized automated blood glucose meter (AGM-4000 Allmedicus, Anyang, Gyeonggi-do, South Korea). Measurements are carried out by following the recommended protocol (Santoso *et al*., 2021).

Glucose tolerance dan insulin tolerance test

Glucose tolerance test (GTT) and *insulin tolerance test* (ITT) are performed at the end of the treatment period. In the GTT test, mice were fasted for 6 hours (from 8:00 a.m. to 2:00 p.m.), then injected with a glucose solution (Sigma-Aldrich, Merck Darmstadt, Germany) with a concentration of 2g/kgBB intraperitoneally (i.p.) (Maejima *et al*., 2015; Santoso *et al*., 2021; Santoso *et al*., 2023). Furthermore, the ITT test, carried out three days after GTT, insulin solution (Actrapid®HM) was injected intraperitoneally with a concentration of 0.5 IU/kgBB (Vinué and Navarro, 2015). Blood glucose levels were measured at minutes 0, 15, 30, 60, 90, and 120 after solution injection using a glucometer (Santoso *et al*., 2023). *The area under curve* (AUC) data was then calculated using Microsoft Excel Office 2019 from blood glucose levels obtained during GTT and ITT.

Histopathology of the pancreas of mice

Pancreatic tissue samples of mice were collected at the end of the treatment. The preparation of histological preparations was carried out using conventional techniques, which included the process of fixation, dehydration, *embedding*, and *sectioning* with a thickness of 5 µm. The preparation is then stained with hematoxylin-eosin (HE) staining (Imtiaz *et al*., 2023). What was observed was in the form of measuring the area of each Langerhans islet, the total cells of each Langerhans islet, and the percentage of cells that underwent degeneration. Observations were made using a light microscope (Olympus CX43).

Data dnalysis

The data is presented in the form of averages ± standard errors (SE). Quantitative data were analyzed using Analysis of Variance (ANOVA). If significance is found, it will be continued with the *Duncan New Multiple Range Test* (DNMRT) with statistical significance set at P <0.05 and P <0.01. All analyses were performed using SPSS version 29.

Results and Discussion

Effects of Mentawai taro corms on fasting blood sugar levels in mice

The measurement of fasting blood glucose levels at the end of treatment showed a significant increase in the diabetes mellitus (DM) mice group compared to the healthy mice (non-DM group) (**P<0.01; Fig. 1). However, after four weeks of treatment, the DM mice group that received Mentawai taro corm flour at a dose of 25% exhibited a significant reduction in fasting blood glucose levels, which were comparable to those of the non-DM group (**P<0.01; Fig. 1).

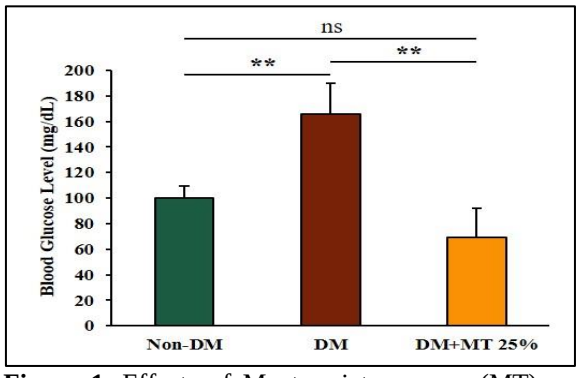

Figure 1. Effects of Mentawai taro corm (MT) on fasting blood glucose levels. Non-DM (healthy mice); DM (diabetes mellitus mice); MT 25% (25% of Mentawai taro flour in the diet); ** indicates statistically significant differences between groups by ANOVA and subsequent post-hoc test at P<0.01; ns (not significant).

Effects of Mentawai taro corms on glucose tolerance test (GTT)

The GTT test conducted at the end of treatment, following intraperitoneal injection of

glucose at 2 g/kg body weight, revealed glucose intolerance characterized by a significant increase in blood glucose levels in the DM mice group, particularly at 15th and 30th minutes (*P<0.05; Fig. 2, A) and at 60th minutes (**P<0.01; Fig. 2, A). This glucose intolerance was further evidenced by increased area under the curve (AUC) values. The DM mice group exhibited significantly higher AUC values compared to the non-DM mice group (**P<0.01; Fig. 2, B). The group of mice treated with 25% Mentawai taro corm showed a tendency towards lower AUC values compared to the DM mice group not treated with Mentawai taro corm (*P<0.05; Fig. 2, B).

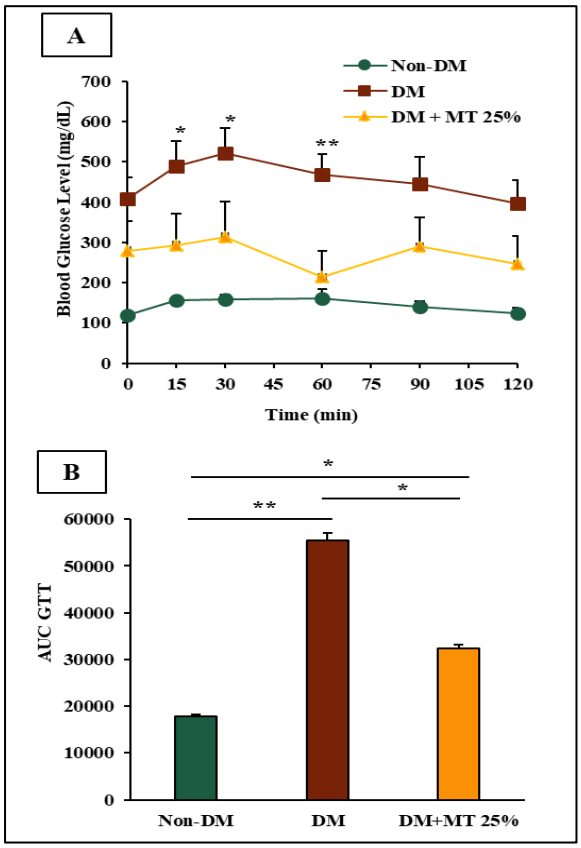

Figure 2. Effects of MT on glucose tolerance. (A) blood glucose levels during GTT, (B) AUC values of GTT. Non-DM (healthy mice); DM (diabetes mellitus mice); MT 25% (25% of Mentawai taro flour in the diet); * and ** indicate statistically significant differences between groups by ANOVA and subsequent post-hoc test at P<0.05 and P<0.01, respectively.

Effects of Mentawai taro corms on insulin tolerance test (ITT)

The insulin tolerance test (ITT) was performed to assess insulin function and sensitivity in each group. Both the non-DM and DM mice groups exhibited a decline in blood glucose levels at the 15th and 30th minutes (Fig. 3, A), indicating absence of insulin resistance in the mice. From the 90th to the 120th minute, blood glucose levels began to increase in the non-DM mice group, returning to pre-insulin injection levels, followed by the DM mice group treated with 25% Mentawai taro corm at the 120th minute (Fig. 3, A). In contrast, the DM mice group showed a significant decrease in blood glucose levels at the 90th and 120th minutes (*P<0.05; Fig. 3, A).

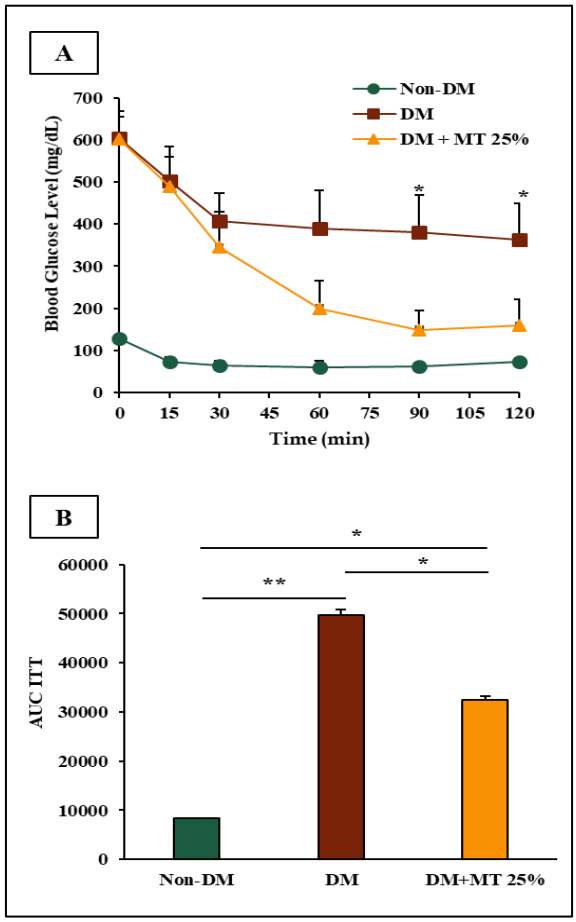

Figure 3. Effects of MT insulin tolerance. (A) Blood glucose levels during ITT, (B) AUC values of ITT. Non-DM (healthy mice); DM (diabetes mellitus mice); MT 25% (25% of Mentawai taro flour in the diet); * and ** indicate statistically significant differences between groups by ANOVA and subsequent post-hoc test at P<0.05 and P<0.01, respectively.

Insulin intolerance was characterized by increased area under the curve (AUC) values, with the DM mice group displaying significantly higher AUC values compared to the non-DM

mice group (**P<0.01, Fig. 3, B). The DM mice group treated with 25% Mentawai taro corm showed significantly lower AUC values compared to the DM mice group not treated with Mentawai taro corm (*P<0.05, Fig. 3, B).

Effects of Mentawai taro corms on pancreatic histological structure

As shown in Fig. 4, the DM mice group exhibited smaller islet cells compared to the other groups. However, DM mice treated with 25% Mentawai taro (MT) corm showed potential regeneration of cells damaged by alloxan induction, resulting in improved size of the Islet of Langerhans and increased numbers of cells suspected to be pancreatic beta cells that produce insulin.

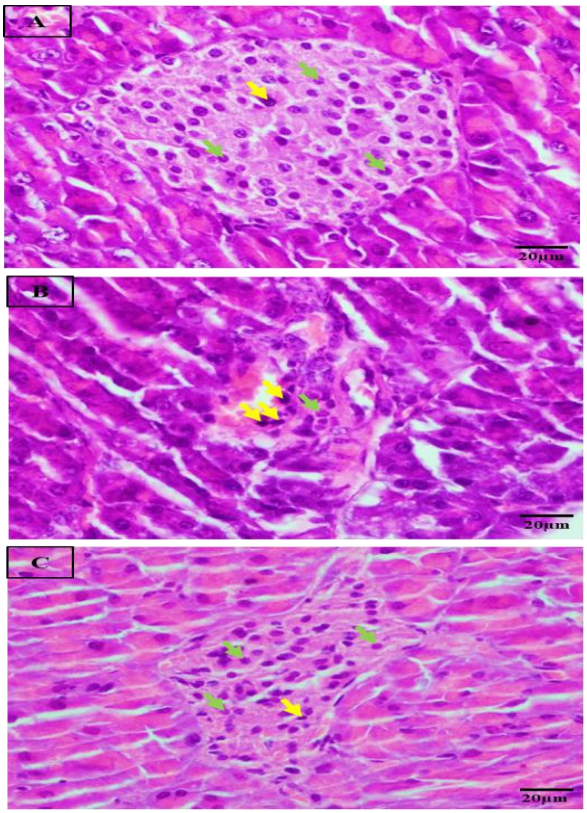

Figure 4. Effects of MT corm on histopathological changes of pancreatic tissue in different groups. (A) non-DM mice, (B) DM mice, (C) DM mice fed with Mentawai taro corm flour (MT 25%). Green arrows indicate normal cells; yellow arrows indicate degenerated cells (hematoxylin and eosin stained, 400x magnification).

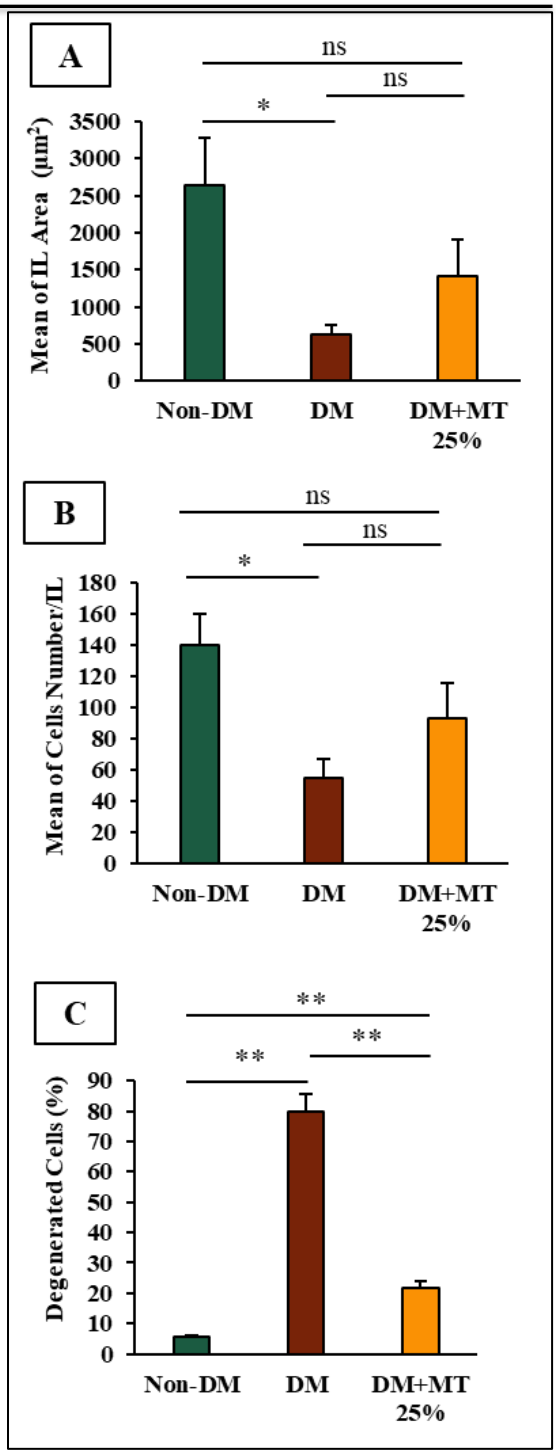

Figure 5. Effect of MT on (A) area of islet Langerhans (IL), (B) number cells of IL, (C) number of degenerated islet cells of the pancreas. Non-DM (healthy mice); DM (diabetes mellitus mice); MT 25% (25% of Mentawai taro flour in the diet); * and ** indicate statistically significant differences between groups by ANOVA and subsequent post-hoc test at P<0.05 and P<0.01, respectively; ns (not significant).

In Fig. 5A, it was observed that the DM mice group had a significantly decreased area of the Islet of Langerhans compared to the healthy mice (non-DM group) (*P<0.05). Administration of 25% Mentawai taro corm tended to increase the area of the Islet of Langerhans in diabetic mice compared to untreated DM mice, although the difference was not statistically significant (ns).

Analysis of the number of cells within the islet (Fig. 5B) indicated that DM mice had fewer cells in the Islet of Langerhans compared to non-DM mice (*P>0.05). Treatment with 25% Mentawai taro corm showed a trend towards increasing the number of cells in the Islet of Langerhans, although this difference was not statistically significant (ns). Furthermore, assessment of cell degeneration within the islet (Fig. 5C) revealed that the DM mice group had a significantly higher percentage of degenerated cells compared to the non-DM mice (**P<0.01). Treatment with 25% Mentawai taro corm significantly decreased the percentage of degenerated cells within the Islet of Langerhans in diabetic mice (**P<0.01).

Discussion

Previous studies have shown that alloxan-induced beta-cell damage occurs in the pancreatic islets of Langerhans (Solikhah *et al*., 2022; Woldekidan *et al*., 2021). This damage is characterized by a reduction in the area of the islets of Langerhans and a decrease in the number of normal cells within them. Alloxan is a toxic diabetogenic agent that specifically targets pancreatic beta cells. When administered to test animals, alloxan induces diabetes in these animals (Solikhah *et al*., 2022). The administration of alloxan affects the degradation of beta cells in the islets of Langerhans, which are responsible for insulin production in the body (Kumar *et al*., 2012). This effect is due to the specific action of alloxan in damaging pancreatic beta cells. The mechanism of alloxan involves the formation of reactive oxygen species, which generate superoxide radicals through a redox cycle. These highly reactive hydroxyl radicals rapidly damage pancreatic beta cells (Kumar *et al*., 2012; Longkumer *et al*., 2021).

Alloxan disrupts the cellular oxidation process by depleting calcium ions from the mitochondria, leading to the development of homeostatic disturbances that ultimately result in pancreatic cell death (Longkumer *et al*., 2021). Metabolic disorders and diabetes are associated with impaired mitochondrial function in pancreatic beta cells caused by oxidative stress (Dludla *et al*., 2023; Haythorne *et al*., 2019). Moreover, dysfunctional mitochondria in insulin-producing pancreatic beta cells can trigger apoptosis in these cells by generating free radicals (Sha *et al*., 2020; Diane *et al*., 2022). Key factors contributing to the loss of islets, which play a role in the development of type 1 and type 2 diabetes, include inadequate enzymatic antioxidant defense mechanisms and inefficiency in the cell regeneration process to repair oxidative DNA damage caused by free radicals (Ikegami *et al*., 2021).

Beta-cell damage in the pancreas leads to increased blood glucose levels. Blood glucose levels depend on the capacity of pancreatic beta cells to synthesize and release insulin. This hormone plays a crucial role in maintaining blood sugar balance in the circulatory system (Röder, 2016). The islets of Langerhans in the pancreas are affected by alloxan, a pro-oxidant that exhibits cytotoxic properties toward beta cells (Longkumer *et al*., 2021). The formation of free radicals by alloxan impairs pancreatic function and reduces insulin secretion, thereby damaging beta cells (Lenzen, 2021). The imbalance between glucose uptake into cells and insulin production by the pancreas results in elevated blood sugar levels, leading to hyperglycemia (Stoner, 2017).

Damage to pancreatic beta cells also reduces glucose and insulin tolerance in mices, as evidenced by high AUC (Area Under the Curve) values. This study aligns with previous research showing that blood glucose levels increase after the administration of glucose at 2g/kg body weight (Santoso *et al*., 2023). Typically, after glucose administration, blood glucose levels return to normal within 2 hours (Dimitriadis *et al*., 2021). The gradual decrease in blood glucose observed in diabetes mellitus may indicate impaired insulin response in muscle and adipose tissue due to elevated glucose concentrations (Haythorne *et al*., 2019). Additionally, diabetes mellitus involves disruptions in both insulin resistance and secretion, leading to a hyperglycemic state. This condition can result in

hyperinsulinemia and pancreatic beta-cell damage. Reduced insulin secretion by pancreatic beta cells impairs glucose uptake by cells and tissues, causing elevated blood glucose levels (Swisa *et al*., 2017).

Mentawai taro (MT) preparation has been proven to have antidiabetic effects by reducing fasting blood sugar levels in diabetic rats. This effect is attributed to the fiber and resistant starch present in MT corms (Santoso, 2022). The mechanism of action of fiber involves lowering blood glucose levels. Specifically, dietary fiber, especially water-soluble fiber, increases the viscosity of food, forming a gel-like substance that resists digestion by digestive enzymes. This increased viscosity slows gastric emptying and delays food digestion. As a result, nutrient absorption, including glucose, is reduced. The delayed digestion and slower gastric emptying contribute to prolonged satiety, which reduces food intake (Dimitriadis *et al*., 2021).

Consequently, reduced glucose absorption and decreased food intake contribute to the normalization of blood glucose levels. Another aspect of the fiber mechanism is that dietary fiber, which cannot be broken down by digestive enzymes, enters the colon intact. In the colon, undigested fiber is fermented by bacteria, producing Short-Chain Fatty Acids (SCFAs). The production of SCFAs stimulates the release of hormones such as Glucagon-Like Peptide-1 (GLP-1), Gastric Inhibitory Polypeptide (GIP), and Peptide YY (PYY). These hormones enhance insulin sensitivity and ultimately lead to a decrease in blood glucose levels (Giuntini *et al*., 2022).

Resistant starch has physiological effects similar to fiber, thus it can lower fasting blood sugar levels in diabetic mices. Resistant starch is a type of starch that escapes digestion by digestive enzymes (such as α-amylase) in the human small intestine and instead undergoes fermentation by gut microflora (Bojarczuk *et al*., 2022). The reduced digestibility of resistant starch makes it more difficult for digestive enzymes to convert it into simple sugars. This property helps regulate blood sugar levels and reduces the risk of elevated blood glucose levels (Pugh *et al*., 2023).

Additionally, Mentawai taro (MT) preparations also contain flavonoids, which are antioxidants with antidiabetic properties and exhibit anti-inflammatory effects. Flavonoids improve diabetes mellitus conditions by scavenging reactive oxygen species (ROS), which are free radicals. By reducing ROS activity in the body, flavonoids mitigate oxidative and inflammatory processes, promoting the regeneration or repair of insulin receptor cells and pancreatic beta cells. This ultimately results in a decrease in blood glucose levels. Flavonoids are polyphenolic compounds found in plants that exert antidiabetic effects through various mechanisms. They enhance insulin secretion, regulate glucose metabolism in hepatocytes (liver cells), and increase glucose uptake in skeletal muscle and adipose tissue. One mechanism of action is by inhibiting sodium-dependent glucose transporters (SGLT1), thereby reducing glucose entry into the bloodstream (Al-Ishaq *et al*., 2019).

Furthermore, flavonoids inhibit gluconeogenic enzymes, thereby reducing the rate of the gluconeogenesis pathway. In addition, flavonoids enhance glucose uptake by cells through Glucose Transporter Type 4 (GLUT-4), ultimately reducing the amount of glucose entering the bloodstream. As antioxidants capable of scavenging free radicals, flavonoids also have significant antidiabetic potential (Al-Ishaq *et al*., 2019). Additionally, flavonoids have been shown to regenerate cells in the islets of Langerhans (Dias-Soares *et al*., 2017). These compounds can counteract insulin deficiency, making them beneficial for diabetes mellitus caused by insulin absence or damage to insulin receptors (Al-Ishaq *et al*., 2019; Vinayagam *et al*., 2015).

Conclusion

In conclusion, the administration of 25% Mentawai taro corm flour in the diet has demonstrated efficacy in lowering fasting blood glucose levels and improving insulin and glucose tolerance in alloxan-induced mice. Additionally, the consumption of Mentawai taro corm flour effectively restored the damaged pancreatic structure caused by alloxan, reducing the number of degenerating islet cells. Therefore, Mentawai taro shows promise in effectively managing hyperglycemia and pancreatic degeneration in diabetes.

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