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Therapeutic Effect of Pulai Bark Extract (*Alstonia scholaris* L. R. Br) on Body Weight of Streptozotocin-Induced Mice (*Mus musculus*)

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Abstract
Type 1 and type 2 diabetes mellitus are metabolic disorders characterized by elevated blood sugar levels (hyperglycemia) due to the body's inability to produce insulin effectively. Sustained hyperglycemia can affect various physiological parameters, including changes in body weight. *Alstonia scholaris* L. R. Br is a plant widely found in Southeast Asia. *Alstonia scholaris* stem bark extract contains bioactive compounds of flavonoids, saponins, and polyphenols that can be antidiabetic. This study aims to determine the therapeutic effect of pulai bark extract (*Alstonia scholaris* L. R. Br) on the body weight of mice (*Mus musculus*) induced by Streptozotocin. This research is experimental. A total of 18 mice were divided into 6 groups, namely the normal control group (KN), negative control group (K-), positive control group (K+), and DM mice group given the extract at a dose of 0.4 ml/mencit/day (P1), a dose of 0.8/ml/mencit/day (P2) and 1.6 ml/mencit/day (P3). Before treatment, all mice were weighed, and initial blood sugar levels were. After that, the K-, K+, P1, P2, and P3 groups were induced with streptozotocin mice at a dose of 0.3 ml for 14 days. Furthermore, suppose there is an increase in blood sugar levels. In that case, the K+ group is given the drug metformin, and the P1, P2, and P3 groups are given *Alstonia scholaris* stem bark extract at a predetermined dose. Data from the study were analyzed using an ANOVA test. The results showed that giving *Alstonia scholaris* stem bark extract can increase the body weight of DM mice.

INTRODUCTION

Diabetes Mellitus (DM) is a severe, chronic, and complex metabolic disorder caused by various acute and chronic factors (Hendrawan *et al*., 2023; Kaihena *et al*., 2024). It is a disease that leads to numerous complications and disproportionately affects people in developing countries, significantly influencing the socioeconomic conditions of the population. Approximately 25% of the global population is affected by DM (Datu *et al*., 2023; Syuaib et al., 2025). Indonesia has a notably high prevalence of DM, ranking seventh worldwide, with 10.7 million cases reported in 2013 (RISKESDAS, 2018). The World Health Organization has projected an increase in the prevalence of type II DM in Indonesia, from 8.4 million cases in 2000 to approximately 21.3 million by 2030 (PERKENI, 2021).

In Indonesia, DM is commonly referred to as penyakit gula or kencing manis. It is characterized by elevated blood glucose levels (hyperglycemia) resulting from an absolute or relative deficiency of insulin (Atmojo *et al*., 2016; Kaihena *et al*., 2024a). According to Aleydaputri and Kuswanti (2022), impaired insulin production may be caused by damage to the islets of Langerhans. Factors contributing to pancreatic cell damage include genetic

predisposition and environmental factors such as free radicals (Ayuni, 2020). An increase in reactive oxygen species (ROS) relative to antioxidants can trigger oxidative stress, possibly leading to β-cell damage in the pancreas (Moniharapon *et al*., 2023).

One of the hallmark symptoms of DM is significant weight loss, which occurs due to the body's inability to regulate glucose uptake into cells due to insulin deficiency (Balaji *et al*., 2019; Sarkar *et al*., 2019; Ukratalo *et al*., 2024). Siswantoro et al. (2018) state insulin typically facilitates glucose entry into body cells for energy production. This mechanism is impaired in DM patients, causing the body to utilize fat reserves as an alternative energy source, eventually leading to substantial weight loss.

DM patients commonly rely on synthetic drugs, which often cause side effects (Chaudhury *et al*., 2017). Examples include: (a) Metformin, a biguanide class drug, which may induce gastrointestinal disturbances such as nausea and vomiting (Zhai *et al*., 2016); (b) Dapagliflozin, known to cause urinary tract complications (Bhattacharjee & Agrawal, 2016); (c) Thiazolidinediones, such as pioglitazone, associated with edema and heart failure; and (d) Glibenclamide, a sulfonylurea, which can lead to hypoglycemia and constipation (Putra *et al*., 2017).

To mitigate these adverse effects, alternative therapies utilizing natural products have gained increasing attention (Pangemanan *et al*., 2023; Loilatu *et al.,* 2024; Tuhumuri *et al.,* 2025). One such potential antihyperglycemic agent is *Pulai* (*Alstonia scholaris* L. R. Br). This plant has long been used in traditional medicine to treat various ailments, including fever, hypertension, pain, postpartum fever, intestinal disorders, helminthiasis, dysentery, diabetes, and malaria. The bark of *Alstonia scholaris* contains secondary metabolites such as flavonoids, saponins, and polyphenols (Kakisina & Ukratalo, 2011; Ukratalo *et al*., 2023a).

Flavonoids are known to scavenge free radicals, functioning as natural antioxidants. Their antioxidant activity allows them to neutralize ROS and reactive nitrogen species (RNS) via their phenolic hydroxyl groups, thus preventing tissue damage and reducing inflammation (Prameswari & Widjanarko, 2014; Kartini *et al*., 2023; Widiasriani *et al*., 2024). Flavonoids also protect against pancreatic tissue damage induced by DNA alkylation, such as alloxan-induced diabetes, potentially restoring pancreatic morphology in mice (Lolok *et al*., 2020). Furthermore, flavonoids have demonstrated antidiabetic properties by promoting the regeneration of pancreatic β-cells and enhancing insulin secretion (Ukratalo *et al*., 2022).

Saponins exert their effect by inhibiting K-ATP channels, disrupting potassium ion (K^+) efflux, which leads to membrane depolarization of pancreatic β-cells. This depolarization opens Ca^{2+}-ATPase channels, facilitating the influx of calcium ions (Ca^{2+}) into the cytoplasm. The increased intracellular calcium activates calmodulin enzymes, triggering the exocytosis of insulin from vesicles for secretion (Indriana, 2018).

This study aims to investigate the therapeutic effects of *Alstonia scholaris* L. R. Br bark extract on the body weight of streptozotocin-induced mice (*Mus musculus*).

RESEARCH METHODS

Type of Research

This study was a laboratory-based experimental research.

Experimental Design

A Completely Randomized Design (CRD) was employed with six treatment groups and three replications. The mice were divided into the following groups: normal control group (NC), negative control group (NC-), positive control group (PC+), and three treatment groups of diabetic mice receiving *Alstonia scholaris* bark extract at doses of 0.4 ml/mouse/day (T1), 0.8 ml/mouse/day (T2), and 1.6 ml/mouse/day (T3).

Tools and Materials

The instruments used in this study included standard glassware, a rotary evaporator, a digital scale, a separating funnel, syringes, an analytical balance, a glucometer (Easy Touch), mouse cages, an oral gavage tool, a digital camera, an IBM SPSS Statistics version 25.0 software. Materials included *Alstonia scholaris* bark, *Mus musculus* (test animals), methanol, aluminium foil, streptozotocin (STZ), citrate buffer, metformin, mouse feed, rice husks, antiseptics, and tap water.

Experimental Procedure

Acclimatization

Before experimentation, all mice were acclimatized for seven days in cages measuring 21 × 21 cm, lined with 0.5–1 cm thick rice husk bedding to prevent infection from feces. The bedding was replaced every three days (Hendrajid et al., 2020). Mice were given AD2 feed and tap water in separate containers, both replenished daily (Ukratalo et al., 2023b).

Extraction Process

The bark of *Alstonia scholaris* was collected, washed, cut into small pieces, and air-dried at room temperature for two weeks. Once dried, the samples were ground into powder using a blender to obtain simplicia. 150 g of powdered bark was weighed and mixed with 250 ml of 96% methanol. The mixture was shaken at 120 rpm for three hours using a shaker and then left at room temperature for 24 hours. Filtration was performed using Whatman No. 42 filter paper to obtain the filtrate. The filtrate was then concentrated using a rotary evaporator at 60°C to produce a thick extract of *Alstonia scholaris*.

Dosage Determination of Alstonia scholaris Bark Extract

Based on human dosage estimation for a 70 kg individual (70/50 × 100 ml = 140 ml) and a conversion factor of 0.0026 g from humans to mice (20 g) (Elya et al., 2010), the mouse dosage was calculated as 0.0026 g × 140 ml = 0.4 ml. Therefore, three extract doses were administered: 0.4 ml/mouse/day (Dose I), 0.8 ml/mouse/day (Dose II), and 1.6 ml/mouse/day (Dose III).

Induction of Diabetes Using Streptozotocin

Diabetes was induced by intraperitoneal injection of streptozotocin at a dose of 500 mg/50 ml in 0.02 M citrate buffer, with a volume of 0.3 ml/g body weight, administered over 14 days.

Treatment of Experimental Animals

Before treatments began, initial body weight and fasting blood glucose levels were measured. In groups NC-, PC+, T1, T2, and T3, mice were induced with streptozotocin at 0.3 ml for 14 consecutive days. Mice with blood glucose levels >200 mg/dL were considered diabetic and subsequently reweighed. Mice in the PC+ group received metformin, while those in treatment groups T1, T2, and T3 were administered *Alstonia scholaris* bark extract at doses of 0.4 ml, 0.8 ml, and 1.6 ml per mouse per day. The treatment lasted for two weeks. In the final week, blood glucose levels and body weight were measured.

Data Analysis

Research data were analyzed using IBM SPSS Statistics version 25.0. Two-way ANOVA was applied with a 95% confidence level.

RESULTS AND DISCUSSION

Table 1 presents the average body weight of mice in each group—normal control (NC), negative control (NC-), positive control (PC+), and diabetic mice treated with *Alstonia scholaris* extract at doses of 0.4 ml/mouse/day (T1), 0.8 ml/mouse/day (T2), and 1.6 ml/mouse/day (T3) throughout the experiment.

Table 1. Average body weight of mice throughout the study

Treatment Group	Average Body Weight of Mice (g)			Mean ± SD
	Day 0	Day 14	Day 28	
Normal Control	21,34	21,48	21,49	**21,47 ± 0,57[a]**
Negative Control	21,56	20,97	20,54	**21,02 ± 1,12[b]**
Positive Control	21,31	21,12	21,53	**21,31 ± 0,97[c]**
Dose 0.4 ml/mouse/day	21,09	20,77	20,98	**20,94 ± 1,14[d]**
Dose 0.8 ml/mouse/day	21,78	21,52	21,70	**21,67 ± 1,29[e]**
Dose 1.6 ml/mouse/day	21,57	21,14	21,40	**21,37 ± 1,03[f]**

Note: Superscripts with the same letter indicate no significant difference (α < 0,05)

On Day 0, the mice across all groups showed relatively uniform body weights, with no significant differences among the groups. By Day 14, following streptozotocin (STZ) induction, the normal control group exhibited a slight increase in body weight. In contrast, the negative control, positive control, and all treatment groups (T1, T2, and T3) showed a decrease. However, by Day 28, while the negative control group continued to experience weight loss, the positive control and all treatment groups receiving methanolic *Alstonia scholaris* bark extract showed increased body weight.

Analysis of Variance (ANOVA) indicated that the administration of methanolic *Alstonia scholaris* bark extract significantly affected the body weight of mice ($p < 0.05$). Further analysis using the Least Significant Difference (LSD) test revealed that all treatment groups differed significantly from one another.

Table 2 summarises the differences in body weight for each group between Day 14 (post-induction) and Day 28 (post-treatment).

Table 2. Average body weight change in mice (g)

Perlakuan	Day 14 Difference	Day 28 Difference
Normal Control	0,07	0,006
Negative Control	-0,59	-0,43
Positive Control	-0,19	0,40
Dose 0.4 ml/mouse/day	-0,32	0,21
Dose 0.8 ml/mouse/day	-0,26	0,18
Dose 1.6 ml/mouse/day	-0,44	0,26

As shown in Table 2, the normal control group showed a slight increase in body weight on Day 14 (+0.07 g) and a negligible change on Day 28 (+0.006 g). The negative control group exhibited a relatively significant decrease in body weight throughout the study period. The positive control group experienced weight loss on Day 14 (–0.19 g) but gained weight by Day 28 (+0.40 g). In the treatment groups, the mice receiving 0.4 ml of extract/day lost 0.32 g on Day 14 but gained 0.21 g by Day 28. The group receiving 0.8 ml/day showed a weight reduction of 0.26 g on Day 14 and an increase of 0.18 g on Day 28. Meanwhile, the 1.6 ml/day group lost 0.44 g on Day 14 and gained 0.26 g on Day 28.

Based on the results presented in Table 1, it was observed that in the negative control group (NC-) and diabetic mice treated with *Alstonia scholaris* bark extract at doses of 0.4 ml/mouse/day, 0.8 ml/mouse/day, and 1.6 ml/mouse/day, body weight decreased following streptozotocin (STZ) induction. Hasibuan *et al*. (2021) stated that one of the common symptoms in diabetic patients is rapid and significant weight loss within a relatively short period.

The decrease in body weight in diabetic mice was presumably due to their inability to utilize glucose as an energy source, resulting from insulin deficiency. This condition was caused by STZ-induced damage to pancreatic β-cells responsible for insulin production. Due to insulin deficiency, glucose cannot enter cells effectively, prompting the body to obtain energy through lipolysis (Ukratalo *et al*., 2023). Rinawati *et al*. (2020) further explained that weight loss in diabetic experimental animals is also triggered by increased glycolysis. Glucose excretion stimulates pancreatic cells, which leads to increased glucagon activity. As a result, stored body fat is utilized as an energy source, causing significant weight loss.

On Day 28, body weight was increased in the positive control group treated with metformin. This result was likely due to metformin's mechanisms of action, which include enhancing insulin activity, reducing hepatic glucose production, and decreasing intestinal glucose absorption. These effects contribute to lowering blood glucose levels, ultimately leading to increased body weight in mice. Metformin is a key medication for patients with type 2 diabetes, as it helps lower blood glucose levels and improves insulin sensitivity, thereby reducing the risk of complications associated with hyperglycemia. Type 2 diabetes is when the body becomes resistant to insulin or does not produce enough insulin to regulate blood glucose levels effectively.

In addition to its glucose-lowering effects, metformin has been shown to offer other health benefits for individuals with type 2 diabetes (Foretz *et al.,* 2019). For instance, it may help reduce blood pressure, lower the risk of cardiovascular diseases, and improve lipid

profiles by reducing triglyceride and LDL cholesterol levels. Metformin is widely considered a first-line therapy for type 2 diabetes and is typically prescribed as part of a comprehensive treatment plan that includes dietary modifications and physical activity (Baptista *et al.,* 2018; Grammatiki *et al.,* 2021). In some cases, it may be combined with other medications to enhance glycemic control further. However, it is important to note that metformin is not a cure for type 2 diabetes and may not be effective for everyone (Sanchez-Rangel & Inzucchi, 2017). Additionally, it may cause side effects such as gastrointestinal discomfort, which could limit its use in specific individuals. Nevertheless, for many patients with type 2 diabetes, metformin remains an essential and effective option for improving glycemic control and reducing the risk of complications (Ahmad *et al.,* 2020).

The results of the ANOVA test indicated that administration of *Alstonia scholaris* bark extract at doses of 0.4 ml, 0.8 ml, and 1.6 ml per mouse per day significantly affected body weight gain in diabetic mice. This increase in body weight was likely associated with enhanced appetite following extract administration. The observed weight gain due to increased appetite aligns with findings by Denashurya (2016), who suggested that one of the factors influencing body weight is the animal's positive energy balance. When energy intake (input) exceeds energy expenditure (output), energy accumulates, increasing body weight.

The improved appetite may be attributed to bitter-tasting compounds, particularly saponins, found in the bark of *Alstonia scholaris*. Saponins are secondary metabolites that help regulate appetite and promote adequate caloric intake. Moreover, saponins can modulate the release of hormones related to satiety and hunger (Deng *et al*., 2023). Saponins also exhibit antidiabetic activity by acting as α-glucosidase enzyme inhibitors. This enzyme is responsible for converting carbohydrates into glucose; therefore, inhibiting blood glucose levels contributes to a hypoglycemic effect (Nafiu & Ashafa, 2017; Elouafy *et al,* 2023).

Additionally, *Alstonia scholaris* bark contains flavonoids with antioxidant activity that can accelerate metabolic processes in experimental animals (Datu *et al*., 2023). Flavonoids also function as antioxidants that can neutralize hydroxyl radicals responsible for damaging pancreatic β-cells in the islets of Langerhans, thereby optimizing insulin production.

CONCLUSION

The administration of *Alstonia scholaris* bark extract increased the body weight of diabetic mice. This finding indicates that *Alstonia scholaris* bark extract has the potential to mitigate weight loss associated with diabetes mellitus and may serve as an alternative therapeutic agent to support recovery or manage side effects related to diabetic conditions.

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