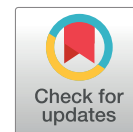


Hypoglycemic activity of *Moringa oleifera* extract in streptozotocin-induced diabetic rats



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ABSTRACT

Background: Diabetes mellitus, particularly Type 2 (T2DM), is a global health concern characterized by high blood glucose levels and insulin resistance.

Objective: This study aims to explore the hypoglycemic potential of *M. oleifera*, a plant that thrives in Central Sulawesi, using a rat model of T2DM.

Method: Healthy male Wistar rats (weight 200-300 g, aged 9-11 weeks) were used in the experiment. The rats were divided into five groups: normal control (healthy), negative control (diabetic without treatment), positive control (diabetic treated with 9 mg/200 g metformin), treatment 1 (diabetic treated with 400 mg/kg BW *M. oleifera* extract), and treatment 2 (diabetic treated with 800 mg/kg BW *M. oleifera* extract). Fasting blood glucose levels were measured enzymatically using the Glucose GOD FS kit from DiaSys. Data were analyzed using ANOVA followed by post-hoc analysis.

Results: The fasting blood glucose levels significantly differed among the groups (ANOVA, $p = 0.0426$). The normal control group maintained stable glucose levels (108.3 ± 8.34 mg/dL pre-test and 106.6 ± 29.67 mg/dL post-test). The negative control group showed a marked increase in glucose levels (185.3 ± 36.28 mg/dL to 268.6 ± 17.63 mg/dL). The positive control group (metformin) significantly reduced glucose levels (386.8 ± 64.22 mg/dL to 230.8 ± 25.82 mg/dL). Treatment 1 (400 mg/kg BW) reduced glucose levels from 292.2 ± 0.98 mg/dL to 218.1 ± 13.74 mg/dL, and treatment 2 (800 mg/kg BW) showed a substantial reduction from 287.3 ± 85.30 mg/dL to 145.3 ± 28.30 mg/dL. However, the Bonferroni post-hoc analysis indicated no significant differences between pre-test and post-test levels within each group.

Conclusion: The *M. oleifera* extract exhibited a hypoglycemic effect in diabetic rats, with the higher dose (800 mg/kg BW) showing a more pronounced effect.

Keywords: *Moringa oleifera*, hypoglycemic activity, diabetes, Wistar rats, metformin, blood glucose levels

Introduction

Diabetes mellitus (DM) is a metabolic condition characterized by elevated blood glucose levels due to issues with insulin production, insulin receptor sensitivity, or both [1]. A comprehensive analysis of 102 prospective studies on vascular disease risk factors found that diabetes doubles the risk of developing vascular disease [2]. Prolonged DM over an extended period can lead to macrovascular and microvascular complications, such as liver disease, high triglyceride levels, kidney disease, and nerve damage [3]. Furthermore, diabetes is

associated with a greater risk of severe COVID-19 and higher mortality rates [4]. COVID-19 patients with diabetes are significantly more likely to experience severe infection and death compared to those without the condition [5]. This underscores the need for further research on DM.

The worldwide prevalence of DM is exceptionally high. In 2021, an estimated 537 million people globally had DM, which is expected to rise to 783 million by 2045 [6]. In 2019, Indonesia ranked seventh globally, with 10.7 million individuals affected by DM [7], which increased to 19.5 million

by 2021. Projections suggest that this number will further rise to 28.6 million by 2045 [6]. The rapid increase in diabetes cases is concerning and requires enhanced strategies for treatment and prevention.

Type 2 diabetes mellitus (T2DM) is characterized by insulin insensitivity due to insulin resistance and diminished insulin production, ultimately leading to pancreatic beta cell dysfunction. This condition impairs glucose transport to the liver, muscle, and fat cells while also increasing fat breakdown in the presence of hyperglycemia. As a result, glucagon and hepatic glucose levels rise without being suppressed by food intake, further elevating blood glucose levels. The combination of insufficient insulin and insulin resistance leads to hyperglycemia [8]. Therefore, effective glycemic management is crucial.

Diabetes medications are crucial in managing blood glucose levels and preventing complications. Sodium-glucose co-transporter-2 (SGLT2) inhibitors are effective in lowering glucose levels in individuals with type 2 diabetes mellitus (T2DM); however, they pose risks such as urogenital infections, ketoacidosis, bone fractures, and potentially increased LDL cholesterol levels [9]. Metformin, the most commonly prescribed first-line medication for T2DM, is generally considered safe but can cause gastrointestinal issues [10]. While these medications effectively manage diabetes, it is important to carefully consider their side effects to optimize patient outcomes. Alternatively, plant-based compounds and natural angiotensin-converting enzyme (ACE) inhibitors are promising treatments with potentially fewer side effects [11–17].

In the last few decades, various antidiabetic agents have been developed derived from active plant ingredients known as phytopharmaceuticals, and one promising one is *Moringa oleifera*. It is a rich source of diverse bioactive compounds, including phenolic compounds [18], dietary fiber [19], carotenoids [20], flavonoids [21], alkaloids, glycosides, and terpenes [22]. Several research results show its ability to lower blood glucose levels both in animal models [23–26] and human studies

[27–29], as well as protect pancreatic β -cells from oxidative stress [24,26,30] and improve insulin sensitivity [31]. *M. oleifera*'s hypoglycemic activity in diabetic patients is a result of its multifaceted actions, including increasing insulin secretion and sensitivity [30,32], reducing glucose absorption [25,33], mitigating oxidative stress [34], and providing anti-inflammatory benefits [24].

Plant-based compounds show considerable potential for managing diabetes due to their wide range of bioactive properties and fewer side effects than synthetic medications. However, more rigorous and standardized human clinical trials are essential to confirm their efficacy and translate the successes seen in animal models into effective human treatments. Combining traditional medicinal knowledge with modern pharmacological research could lead to the development of new antidiabetic therapies. This study aims to explore the hypoglycemic potential of *M. oleifera*, a plant that thrives in Central Sulawesi, using a mouse model of T2DM. This basic research seeks to develop plant-based therapies for diabetes and leverage the natural resources unique to the Central Sulawesi region.

Methods

Preparation of *M. oleifera* extract

We obtained fresh *M. oleifera* leaves from the Sigi region in Central Sulawesi, Indonesia. The leaves were washed with water, drained, and dried in the open air and indirect sunlight. Once the leaves became brittle, they were crushed into a powder.

Extraction was done by percolation (humidification, immersion, and percolation). The moringa powder was placed into a percolator column with aquades for 24 hours. The percolator tap was then run at 20 drops per minute and evaporated in a vacuum at 50°C at a rotation of 90 rpm. The extract was transferred to a porcelain dish in a digital oven at 45°C to dry to a fixed weight. The bioactive components in the *M. oleifera* extract were examined using services from Biofarmaka, a division of the Bogor

Agricultural Institute. High-performance liquid chromatography (HPLC) and phytochemistry tests were employed to analyze the bioactive compounds in the *M. oleifera* extract.

Animals

The Wistar male rats, aged between 6 to 8 weeks and weighing 200 to 300 grams, were obtained from the Faculty of Pharmacy. They were housed in cages, with two rats per cage, and maintained under a light-dark cycle of equal duration, with constant environmental conditions. The rats were fed a standard diet and had free access to water. The study has been approved by Ethical Committee of the Medical Faculty, Universitas Tadulako, under ethical number 7684/UN28.1.30/KL/2022.

Type 2 DM rat model

Diabetic conditions were determined by hyperglycemia and hypercholesterolemia. Hypercholesterolemia was induced through a high-fat diet (HFD), with the rats being adapted to the diet for the first seven days, followed by an eight-week HFD induction period. Once the rats had developed hypercholesterolemia (total cholesterol >144 mg/dL), they were injected with streptozotocin (STZ) to induce hyperglycemia. The STZ dosage was 30 mg/kg body weight (BW) and was administered intraperitoneally in a 0.1 mL sodium citrate buffer (pH 4.5). Five days after the STZ injection, the rats with fasting blood glucose (FBG) ≥ 126 mg/dL and a total cholesterol level >144 mg/dL were considered to have developed type 2 diabetes [35].

Experimental design

We performed an experiment using healthy male Wistar rats weighing 200-300 grams and aged 9-11 weeks. The rats exhibited characteristics such as non-standing hair, pure white fur, clear red eyes, and active movement. The experimental design consisted of five groups, with two rats in each group: a normal control group with healthy rats, a negative control group with

untreated diabetic rats, a positive control group with diabetic rats treated with 9 mg/200 g of metformin, a treatment group where diabetic rats received 400 mg/kg BW of *M. oleifera* extract, and another treatment group where diabetic rats were administered 800 mg/kg BW of *M. oleifera* extract. The treatments were conducted for a duration of four weeks.

Blood sampling and plasma separation

Blood was drawn from the retro-orbital sinus, a specific location, in an amount of approximately 2 milliliters. This was done the day before the treatment (pre-test) and after the final treatment (post-test). The blood samples were collected from the rats in each group. The blood was stored in tubes containing EDTA, an anticoagulant. The blood plasma was then obtained by centrifuging the tubes, which separated the plasma from the other blood components. The collected plasma was then analyzed to measure the fasting blood glucose level.

Biochemical analyses

The fasting blood glucose level was determined using an enzymatic colorimetric assay from the Glucose GOD FS kit provided by DiaSys. This kit employs the glucose oxidase (GOD) reaction, which involves a reagent containing a phosphate buffer, glucose oxidase, 4-amino antipyrine, D-glucose, and peroxidase. A 10 μ L sample, blank, or standard, was combined with 1000 μ L of the reagent, incubated for 20 minutes at 20-25°C, and the concentration was measured by reading the absorbance against the blank within 60 minutes.

Statistical analysis

Data analysis on glucose used a completely randomized design ANOVA analysis of variance at a 95% confidence level, with a statistical significance level of $p < 0.05$. If the significance level was $p < 0.05$, the Bonferroni test was used for further tests. The statistical tests were performed by Graph Prism 9.

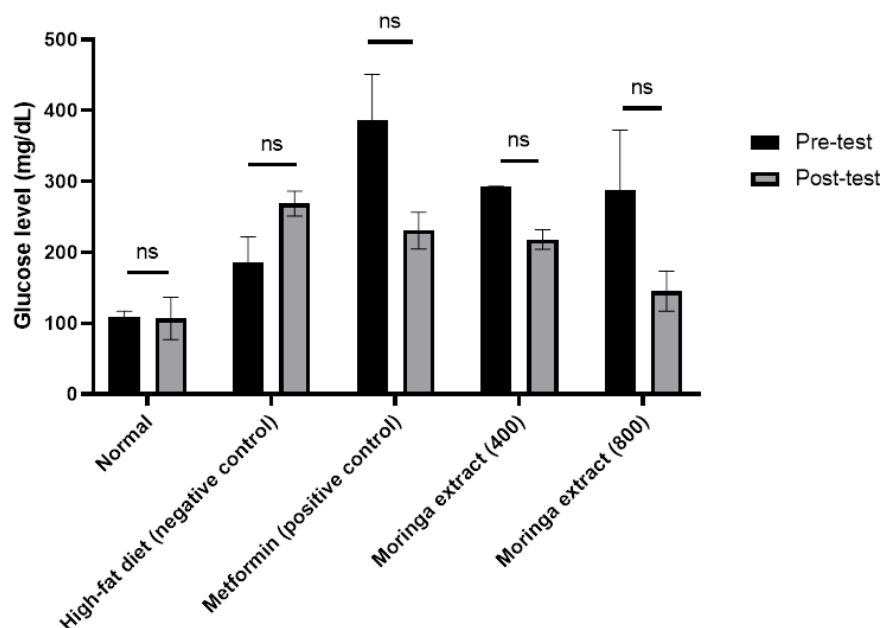


Figure 1. The glucose levels before and after *M. oleifera* extract treatment. Data are expressed as mean $\pm$ standard error of the mean (SEM). p-value < 0.05, *: significant difference between means of glucose at pre-test and post-test. ns: not significant

Results

Figure 1 shows that in the normal group, glucose levels remained consistent, as expected. Induction with a high-fat diet and STZ increased glucose levels, as shown in the negative control group. The increase in glucose levels in the negative control group suggested diabetes progression. The metformin (positive control) group showed an apparent reduction in glucose levels. The moringa extract treatment groups substantially reduced glucose levels.

A two-way ANOVA analysis revealed a significant difference between the pre-test and post-treatment conditions. A comparative analysis between the groups was performed using the Bonferroni test. The Bonferroni test results showed no significant difference between pre-test and post-treatment glucose levels despite the overall ANOVA indicating significant differences among groups (Figure 1).

Discussion

This study investigated the hypoglycemic effects of *M. oleifera* extract in diabetic male Wistar rats and compared its efficacy to metformin. The results demonstrated that *M. oleifera* extract significantly reduced fasting blood glucose levels in diabetic

rats, with a higher dose (800 mg/kg BW) showing a more pronounced effect. This finding aligns with previous research indicating the antidiabetic potential of *M. oleifera*.

The study found that the treatment groups experienced a significant reduction in blood glucose levels, from 292.2 ± 0.98 mg/dL to 218.1 ± 13.74 mg/dL for the 400 mg/kg BW group and from 287.3 ± 85.30 mg/dL to 145.3 ± 28.30 mg/dL for the 800 mg/kg BW group. This suggests that *M. oleifera* possesses potent hypoglycemic properties. These results were similar to a previous study by Mohammed et al. (2019), which reported a non-significant reduction in fasting blood glucose levels and improved hepatic insulin sensitivity in diabetic rats treated with 300 mg/kg of moringa for four weeks [36]. Another study showed that *M. oleifera* leaves decreased blood glucose and reduced glutathione and malondialdehyde (lipid peroxidation products in pancreatic tissue) [37], possibly due to the presence of flavonoids, saponin, steroids, and tannins. The antihyperglycemic effect of *M. oleifera* is likely attributed to the inhibition of α -glucosidase, pancreatic α -amylase, and intestinal sucrose by its flavonoid compounds, such as quercetin and kaempferol, leading to lower postprandial hyperglycemia and hemoglobin A1C (HbA1C) [38].

The standard antidiabetic drug metformin effectively lowered blood glucose levels from 386.8 ± 64.22 mg/dL to 230.8 ± 25.82 mg/dL. The higher dosage of the *M. oleifera* extract (800 mg/kg BW) produced a comparable reduction, suggesting its potential as an alternative or supplementary treatment to metformin. This supports the findings of a previous study by Ndong et al. (2007), which observed similar hypoglycemic effects of *M. oleifera* in diabetic models. The study also reported that *M. oleifera* has a beneficial impact on glucose intolerance, and this effect might be mediated by the presence of quercetin-3-glucoside and fiber in the *M. oleifera* leaf powder [39].

The Bonferroni analysis did not find any significant differences between the pre-test and post-test results, contradicting the findings of the ANOVA test. This inconsistency could be attributed to various factors, such as the sample size, the data variability, and the Bonferroni correction's conservative nature. The small sample size may not have detected significant differences within each group after the adjustment. Additionally, the high variability in glucose measurements within the groups could have obscured any significant differences. While reducing the risk of false-positive results (type I errors), the Bonferroni correction also increases the risk of false-negative results (type II errors), potentially failing to identify a genuine effect.

The hypoglycemic activity of *M. oleifera* may be attributed to several mechanisms. It may enhance pancreatic β -cell function [40], increase insulin secretion [41], and improve peripheral glucose uptake by enhancing the activity of glucose transporters [36]. The antioxidant properties of *M. oleifera* also play a crucial role in mitigating oxidative stress, which is known to impair insulin signaling pathways [34]. This multifaceted approach to glucose regulation supports the traditional use of *M. oleifera* in managing diabetes and its complications.

Conclusion

The results of this study demonstrate the hypoglycemic effects of *M. oleifera* extract in diabetic

rats, although the efficacy was still not comparable to metformin. These findings are supported by previous studies, showing the potential of *M. oleifera* as a natural antidiabetic agent. However, the lack of significant differences in pre-test and post-test comparisons within groups highlights the need for further research with larger sample sizes and alternative post-hoc analyses. Future studies should also explore the mechanisms underlying the hypoglycemic effects of *M. oleifera* and its broader metabolic benefits.

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Declaration of interest

The authors declare no conflicts of interest.

Authors contributions

Conceptualization, R.A. and T.S.; Methodology, R.A. and T.S.; Investigation, R.A., L, and R.B.; Writing – Original Draft, R.A., L, and T.S.; Writing – Review & Editing, R.A.; Resources, R.A., T.S., and R.B.; Funding Acquisition, R.A., T.S., and R.B.; Supervision, R.A., T.S., and R.B.

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