



Dose-Dependent Amelioration of Diabetic Dyslipidemia and Hyperglycemia by *Ruellia tuberosa* L. Leaf Extract

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Abstract | *Ruellia tuberosa* L. leaf extracts (RTLE) contain bioactive compounds that exhibit significant antihyperglycemic and antihyperlipidemic effects in diabetic models by enhancing glucose uptake, modulating lipid metabolism, influencing hepatic detoxification enzymes, and insulin signaling pathways. These multifaceted actions support RTLE's potential as a natural therapeutic agent for managing the metabolic disorders of diabetes mellitus. This research focuses on investigating the beneficial effect of RTLE on glucose levels and lipid profiles in alloxan-induced diabetic rats. The diabetic rats model (n = 25) were divided into five groups and received the following treatments: P0 (Normal saline oral), K- (Alloxan injection + normal saline oral), K+ (Alloxan injection + 50 mg/kg Metformin), P1 (Alloxan injection + 200 mg/kg RTLE), and P2 (Alloxan injection + 400 mg/kg RTLE). Blood glucose levels were measured from the tail vein, and a blood sample for lipid profile analysis was drawn from the heart via cardiac puncture. This study showed that animals treated with RTLE at 400 mg/kg BW showed decreased glucose levels and stabilized lipid profiles. The leaf extract of *Ruellia tuberosa* L. improves hyperglycemia and hyperlipidemia in diabetic rats by inhibiting α -amylase, enhancing glucose uptake, and modulating genes involved in glucose and lipid metabolism.

Keywords | Alloxan, Diabetes, Hyperglycemia, Hyperlipidemia, *Ruellia tuberosa* L. Leaf extract

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by high blood glucose levels, resulting from impaired carbohydrate and lipid metabolism due to deficiencies in insulin secretion (Wondafrash *et al.*, 2020; Solikhah and Solikhah, 2021). Type 1 diabetes mellitus (T1DM) is an autoimmune disease because of decreased insulin production from pancreatic beta cells, leading to their destruction, insulinopenia, hyperglycemia,

and impairment of insulin-dependent mitochondrial function (Castellanos *et al.*, 2020). Bad Glucose control and insulinopenia can lead to several complications in diabetic patients, including dyslipidemia, neuropathy, and nephropathy due to high levels of reactive oxygen species (ROS) (Beverly and Budoff, 2020; Madić *et al.*, 2021). Dyslipidemia is significantly correlated with obesity, cardiovascular disease, and several kinds of cancer (Vekic *et al.*, 2019; Ilmi *et al.*, 2024). Increased fasting triglycerides (TG), decreased high-density lipoprotein (HDL), raised

low-density lipoprotein (LDL), and tiny dense LDL are the hallmarks of diabetic dyslipidemia. Diabetic dyslipidemia is a cluster of potentially atherogenic lipid and lipoprotein abnormalities that are metabolically interrelated (Yanai *et al.*, 2019).

A study conducted between 1990 and 2019 found that the incidence of T1DM was 15 per 100,000 people in Asia and Europe, 20 per 100,000 people in the Americas, and 8 per 100,000 people in Africa. On the other hand, the International Diabetes Federation reports that over 96,000 new cases of T1DM are diagnosed annually in children and adolescents under 15 years of age (Forouhi and Wareham, 2019). Dog breeds at risk of developing DM vary between countries and regions (Wulandari *et al.*, 2023; Titisari *et al.*, 2025). For example, a study conducted in the UK found that Samoyed, Tibetan Terrier, and Cairn Terrier breeds were at risk of developing DM. In North America, Miniature Schnauzer, Miniature Poodle, Bichon Frise, Samoyed, and Cairn Terrier breeds were identified as at risk of developing DM. In Sweden, the breeds include the Australian Shepherd, Samoyed Terrier, Swedish Lapphund, Swedish Elkhound, and Border Collie. Other breeds identified as at risk for developing DM include Bernese Mountain Dogs, Boxers, Chesapeake Bay Retrievers, Golden Retrievers, Kerry Blue Terriers, and Miniature Poodles (Niaz *et al.*, 2018).

The most commonly prescribed oral medication for diabetic patients is metformin. It belongs to the class of drugs known as biguanides and is often considered a first-line therapy for managing diabetes. However, metformin can have side effects such as vomiting, nausea, bloating, and diarrhea. The use of metformin is not recommended for patients with hepatic disorders or severe renal impairment due to the potential risk of lactic acidosis (Triggle *et al.*, 2022). Alternatively, the management of diabetes mellitus can involve the use of nutraceuticals, dietary sources, or herbs with fewer adverse effects (Solikhah and Solikhah, 2023). Nutraceuticals, including polyphenols, terpenoids, flavonoids, sterols, alkaloids, pigments, and unsaturated fatty acids, have been linked to antioxidant, insulin-releasing activity, insulin secretion enhancement, metabolic, and cardiovascular effects (Vita *et al.*, 2019; Safira *et al.*, 2022).

Ruellia tuberosa L. is a medicinal plant that has been used for several decades in Southeast Asia as traditional medicine, including antioxidant, anti-inflammatory, and anticancer. The leaf of *Ruellia tuberosa* L., being the primary site of photosynthesis, contains a richer and more diverse array of bioactive compounds, including flavonoids, phenolics, and chlorophyll, compared to the roots and flowers (Ko *et al.*, 2019). Phytochemicals from RTLE, including alkaloids, steroids, tannins, flavonoids, glycosides, phenolics, and saponins, have been found to possess potential antioxidant and antidiabetic effects (Dutta *et al.*, 2020). Another study

showed that RTLE compounds squalene and steroids (stigmastrol and stigmast-5-en-3-ol). Phytochemicals in RTLE exhibit antioxidant, antitumor, anticancer, hypolipidemic, antidiabetic, antihyperlipidemic, and anti-inflammatory properties, making them useful for treating various internal diseases (Susilo and Farhan, 2023). The phytochemical composition of plants can vary depending on the species, growing conditions, and extraction method used. In this study, 96% ethanol was used as a polar solvent to extract phytochemicals from *Ruellia tuberosa* L. leaf because it is relatively safe and less toxic (Dewinta *et al.*, 2020).

Ruellia tuberosa L. leaf extract has been shown in several studies to have a beneficial impact on DM management (Tuong Vi *et al.*, 2022). Another study demonstrated that administering ethanolic leaf extracts of *Ruellia tuberosa* L. for 28 days to alloxan-induced diabetic rats significantly increased the weights of the testes and epididymis, improved sperm count, and decreased sperm abnormalities, effects that were associated with reduced blood glucose level (Wiratmini *et al.*, 2024). Therefore, this study was conducted to investigate the potential of RTLE as an herbal medicine for treating hyperglycemia and dyslipidemia in diabetes mellitus. The research was conducted by observing the effect of *Ruellia tuberosa* L. leaf ethanol extract on blood glucose levels and lipid profiles, including TG, TC, LDL, and HDL, in alloxan-induced rats, which serve as a model for diabetes.

MATERIALS AND METHODS

EXPERIMENTAL ANIMALS

Adult male Wistar rats (*Rattus norvegicus*) aged ± 3 months and with a body weight of around 180-200 grams. The rats were housed in wire and wooden cages with a size of (40 cm x 30 cm x 20 cm). Rat cages have good ventilation under standard conditions of temperature (23-25 °C) and relative humidity (40-60%), with a 12-hour light/dark cycle. The bottom of the cages is lined with a husk approximately 2 cm thick and is replaced every two days. Rats are maintained on a standard pellet diet (Pokphand Hi-Pro-Vite® 512-Bravo) and given twice a day with ad libitum access to water.

MATERIALS AND TOOLS

This study utilized *Ruellia tuberosa* L. leaves, which were collected from the Banyuwangi district, Banyuwangi Regency, East Java, Indonesia. *Ruellia tuberosa* L. leaf determination was carried out at UPT Materia Medica, Batu City. The other materials and tools were male Wistar rats strain, alloxan as diabetogenic agent, metformin as standard drug, 0.9% NaCl, normal saline, CMC-Na (Natrium Carboxymethyl Cellulose), aquadest, 10% saccharose water, water, Pokphand Hi-Pro-Vite®

512-Bravo feed, sawdust, 96% ethanol, beaker glass, electric grinder, rotary evaporator, strainer, stir bar, aluminum foil, 70% alcohol, glucometer (ACCU-CHEK® instant), glucose strip test (ACCU-CHEK® instant), centrifuge, blood serum lipid reagent (Agappe Diagnostic Ltd), Autochemistry Analyzer (PKL® PPC 125).

EXTRACTION OF *RUELLIA TUBEROSA* L. LEAF

Ruellia tuberosa L. leaves were extracted using the maceration method. Healthy leaves were cut into pieces (approximately 4 cm) and washed with running tap water. Then, clean leaves were dried at 40 °C for 72 hours in the oven. Dried *Ruellia tuberosa* L. leaves were ground with an electric grinder into a fine powder. *Ruellia tuberosa* L. leaf powder was soaked in 96% ethanol at a ratio of 1:10 (w/v) for five days in an impermeable room and stirred every 6 hours. After five days, *Ruellia tuberosa* L. extract was filtered using Whatman No. 1 paper and concentrated using a rotary evaporator at 50°C and 120 rpm until a thick extract was obtained (Susilo and Farhan, 2023). The final yield of the thick extract was approximately 10% w/w based on the dry weight of the leaf powder. The thick RTLE was placed in a beaker, covered with aluminum foil, and stored in the fridge to prevent damage and contamination. To make an appropriate concentration, thick extract was dissolved with 0.5% CMC-Na (Natrium Carboxymethyl Cellulose) (Solikhah et al., 2023).

DIABETES INDUCTION

Rat models were adapted for seven days before being induced by alloxan. A diabetic model rat was induced with alloxan. Freshly prepared alloxan monohydrate in 0.9% NaCl at a single dose of 150 mg/kg BW was injected intraperitoneally into rats that had been fasted for 12 hours. To prevent severe acute hypoglycemia caused by the rapid destruction of pancreatic beta cells following alloxan administration, normal water was replaced with 10% sucrose water for up to 48 hours. This supplementation provides an immediate source of glucose, stabilizing blood sugar levels and reducing the risk of fatal hypoglycemic shock during the critical early phase of diabetes induction. Rats were fasted for approximately 12 hours before blood glucose measurement, which was performed 72 hours after

alloxan injection. Diabetes was confirmed at fasting blood glucose levels ≥ 200 mg/dL, and continued with treatment.

EXPERIMENTAL DESIGN

Wistar rats that had been adapted for 7 days were then weighed to confirm successful adaptation before the start of experimental treatments. A total of 25 rats were randomly assigned to five groups (n = 5 per group) using a simple randomization method to ensure unbiased allocation and equal group sizes for the study (Table 1). Wistar rats were fasted for 12 hours before being injected with alloxan. All treatment groups of Wistar rats were given a single dose of alloxan injection of 150 mg/kg BW dissolved in 0.9% NaCl intraperitoneally, except for the control group (Solikhah et al., 2022). Rats injected with alloxan were given water containing 10% sucrose to prevent severe hypoglycemia. Three days after alloxan injection, the blood glucose levels of rats were measured via the tail vein. Rats are categorized as diabetic if their fasting blood glucose levels ≥ 200 mg/dL and were subsequently used for the administration of extracts and treatments (Solikhah and Solikhah, 2021).

BLOOD GLUCOSE DETERMINATION

Blood was collected from the tail vein of rats after a 12-hour fast. Fasting blood glucose was measured using ACCU-CHEK® Instant and glucose strips three days after alloxan injection to confirm the induction of diabetes mellitus (blood glucose ≥ 200 mg/dL). This measurement was recorded as the first day of the treatment period, serving as the baseline before any therapeutic interventions. Blood glucose was measured again on day 14th following the treatment period to assess treatment effects.

BLOOD COLLECTION AND MEASUREMENT OF SERUM LIPID

After 14 days of administration of RTLE, on day 15th, all rats were anesthetized after a 12-hour fast. Rat's blood was drawn from the heart via cardiac puncture. Blood samples were centrifuged at 5000 rpm for 20 minutes twice to obtain serum samples. Serum lipid profiles (TG, LDL, HDL, and TC) were measured using an autochemistry analyzer (PKL® PPC 125).

Table 1: Experimental design groups.

Group	Treatment
P0	Normal saline
K-	Alloxan 150 mg/kg BW injection + normal saline
K+	Alloxan 150 mg/kg BW injection + metformin 50 mg/kg BW
P1	Alloxan 150 mg/kg BW injection + 200 mg/kg BW RTLE
P2	Alloxan 150 mg/kg BW injection + 400 mg/kg BW RTLE

The treatment groups contain of normal control (P0), diabetes control (K-), diabetic treated with metformin as a standard drugs (K+), diabetic treated with 200 mg/kg of RTLE (P1), and diabetic treated with 400 mg/kg of RTLE (P2). All the group of rats received the treatment once a day for 14 days.

STATISTICAL ANALYSIS

Data results are expressed with mean $\pm$ standard deviation (SD). The statistical significance between means was analyzed using one-way ANOVA, followed by the Duncan post hoc test to elucidate significant means on SPSS version 23. The p-value ($p < 0.05$) was considered statistically significant between groups.

RESULTS

The diabetic animal models exhibited classic symptoms of diabetes, including polydipsia, polyuria, and polyphagia. Water intake in diabetic rats increased compared to that of normal rats. The physical appearance of the animals and physiology can occur in diabetic animals, including acute weight loss, decreased activity, a rough coat, increased urination, and diarrhea.

GLUCOSE LEVELS

Glucose levels in alloxan-induced diabetic rats (groups K-, K+, P1, P2) were significantly elevated 72 hours after alloxan injection. According to the One-Way ANOVA analysis with a 95% confidence level, the diabetic groups showed a significant difference in glucose levels compared to the normal group ($p < 0.05$). Following 14 days of RTLE supplementation in diabetic rats (P1 and P2), a marked reduction in glucose levels was observed. This reduction was further examined using Duncan's test (Table 2).

Table 2: Blood glucose levels (mg/dL) in Wistar rats on day 1 and day 14 of the treatment period.

Group	Mean glucose data (mg/dL) $\pm$ SD	
	1 st	14 th
P0	85,4 $\pm$ 1,52 ^a	92,8 $\pm$ 2,17 ^a
K-	256,2 $\pm$ 62,35 ^b	475,6 $\pm$ 89,26 ^c
K+	249,4 $\pm$ 51,83 ^b	218,6 $\pm$ 64,17 ^b
P1	441,4 $\pm$ 129,36 ^c	237,6 $\pm$ 130,04 ^b
P2	395,4 $\pm$ 190,84 ^{bc}	151,6 $\pm$ 49,16 ^{ab}

All values are expressed as means $\pm$ SD ($n = 5$). Means with different superscript letters within a column are significantly different ($p < 0.05$) according to Duncan's test. Groups: normal control (P0), diabetes control (K-), diabetic + metformin (K+), diabetic + 200 mg/kg BW RTLE (P1), diabetic + 400 mg/kg BW RTLE (P2); all treated once daily for 14 days.

Based on, Table 2 the P0 group showed the normal glucose blood levels on day 1 (85.4 mg/dL) and day 14 (92.8 mg/dL). The diabetic group with no treatment (K-) in this study has a significantly elevated blood glucose levels, indicating hyperglycemia. Diabetic rats treated with RTLE doses of 200 mg/kg BW (P1) and 400 mg/kg BW (P2) showed a glucose levels on day 14, approaching normal. The P2 group (151.6 mg/dL) had a greater hypoglycemic effect

on day 14, with levels approaching normal compared with the P1 group (237.6 mg/dL) (Table 2). The glucose blood levels of diabetic rats treated with metformin 50 mg/kg BW (K+) showed a slight decline on day 14 (218.6 mg/dL) but were still not approaching normal compared to the P2 group. This result showed a positive effect of RTLE (400 mg/kg BW dose) toward hyperglycemia inhibition in alloxan-induced rats (Table 2).

Compared with day 1, the P0 group showed a slight increase (8.7%) in blood glucose levels on day 14. The diabetic group without treatment (K-) showed an increase in blood glucose levels on day 14 (85.6 %), confirming the diabetic state. The (K+) group showed a slight decrease in blood glucose levels on day 14 (12.3%). In the P1 group, there was a decrease on day 14 (46.2%). In the P2 group, there was a decrease on day 14 (61.7%). Treatments P2 and P1 were more effective at reducing blood sugar than the K+ (metformin) treatment. The best reduction in blood sugar was shown in treatment P2, with a reduction of up to 61% compared to the first day (Table 2).

LIPID PROFILE

One-way ANOVA at a 95% confidence level revealed that different doses of *Ruellia tuberosa* L. extract (RTLE) had a significant impact on the average levels of triglycerides (TG), low-density lipoprotein (LDL), total cholesterol (TC), and high-density lipoprotein (HDL) in rats ($p < 0.05$). A post hoc Duncan's test was conducted to further explore these differences, with the findings summarized in Table 3. The analysis revealed that administration of RTLE at a dose of 400 mg/kg BW significantly lowered TG, LDL, and TC levels while increasing HDL levels.

Table 3: Lipid profile of the 14th day Wistar rats.

Group	Lipid profile			
	TG (mg/dL)	LDL (mg/dL)	TC (mg/dL)	HDL (mg/dL)
P0	66.00 $\pm$ 1.23 ^a	60.00 $\pm$ 3.08 ^a	74.00 $\pm$ 1.00 ^{ab}	52.40 $\pm$ 2.07 ^b
K-	76.40 $\pm$ 2.40 ^b	83.00 $\pm$ 1.58 ^c	89.00 $\pm$ 2.74 ^c	45.00 $\pm$ 3.00 ^a
K+	75.60 $\pm$ 1.14 ^b	59.20 $\pm$ 3.83 ^a	76.40 $\pm$ 1.14 ^b	48.20 $\pm$ 2.04 ^a
P1	75.80 $\pm$ 3.76 ^b	81.60 $\pm$ 7.70 ^c	75.00 $\pm$ 2.45 ^{ab}	48.00 $\pm$ 3.24 ^a
P2	69.20 $\pm$ 3.11 ^a	74.20 $\pm$ 4.91 ^b	72.60 $\pm$ 1.34 ^a	59.60 $\pm$ 2.96 ^c

All values are expressed as means $\pm$ SD ($n = 5$). Means with different superscript letters within a column are significantly different ($p < 0.05$) according to Duncan's test. Groups: normal control (P0), diabetes control (K-), diabetic + metformin (K+), diabetic + 200 mg/kg BW RTLE (P1), diabetic + 400 mg/kg BW RTLE (P2); all treated once daily for 14 days.

Compared with normal rats (P0), diabetic rats without treatment (K-) exhibited significantly higher TG, LDL, and TC levels, while their HDL levels decreased significantly. There was no significant difference in the changes in TG

(75.80 ± 3.76 mg/dL) and LDL (81.60 ± 7.70 mg/dL) between the group treated with 200 mg/kg BW RTLE (P1) and the untreated diabetic rats (TG = 76.40 ± 2.40 mg/dL; LDL = 83.00 ± 1.58 mg/dL). In contrast, diabetic rats given metformin (K+) had a significant decrease in LDL (59.20 ± 3.83 mg/dL), which was nearly normal (60.00 ± 3.08 mg/dL) (Table 3).

The most improvements were observed in diabetic rats treated with 400 mg/kg BW RTLE (P2), which showed significant reductions in serum TG (69.20 ± 3.11 mg/dL), LDL (74.20 ± 4.91 mg/dL), and TC (72.60 ± 1.34 mg/dL) compared to diabetic controls (K-). The TC level in this group was the lowest among all experimental groups. On top of that, HDL jumped up significantly in P2 to 59.60 ± 2.96 mg/dL, beating out both the diabetic rats at 45.00 ± 3.00 mg/dL and even the normal ones at 52.40 ± 2.07 mg/dL. Overall, giving RTLE at 400 mg/kg BW for 14 days helped stabilize lipid profile in diabetic rats (Table 3).

DISCUSSION

This study has shown the potential antihyperglycemic and antihyperlipidemic effects of RTLE on alloxan-induced diabetic model rats. Various phytochemical compounds in RTLE, including flavonoids, saponins, alkaloids, polyphenols, tannins, stigmasterol (steroids), niacin, and vitamin E, can act as antioxidants (Ighodaro *et al.*, 2017; Susilo and Farhan, 2023). The components of RTLE have been observed to have antidiabetes and antihyperglycemic activity. Antioxidant compounds from the RTLE phytochemical can decrease ROS activity.

GLUCOSE LEVELS

Alloxan-induced diabetes is a standard model for evaluating the glycemic-control potential of therapeutic compounds and plant extracts in experimental studies. This oxidative stress is implicated in damaging pancreatic beta cells, contributing to the development of diabetes in animal models exposed to alloxan. The toxic and diabetogenic effects of alloxan are underlined by its selective inhibition of glucose-stimulated insulin secretion via inactivation of glucokinase and selective necrosis of the beta cells via induced ROS (Solikhah *et al.*, 2020). Inhibition of glucokinase activity by alloxan can inhibit glucose oxidation and ATP production, leading to the suppression of the ATP signal that stimulates insulin secretion (Solikhah *et al.*, 2022; Prameswari *et al.*, 2023). GLUT2 facilitates alloxan transport to pancreatic beta cells because glucose and alloxan share a similar molecular structure. Alloxan can inactivate glucokinase via disulfide bond formation because glucokinase contains two sulfhydryl groups (-SH). Alloxan in the pancreas has a complex redox cycle. Initially, alloxan forms dialuric acid through an oxidation process

(Rosso *et al.*, 2009).

Furthermore, dialuric acid is reduced to alloxan and then reoxidized to dialuric acid (Lenzen, 2008). Complex redox mechanisms from alloxan generate ROS such as superoxide radical anion and hydroxyl radical through the autooxidation of dialuric acid as a reduction product (Sharma *et al.*, 2023). Toxicity ROS leading to DNA fragmentation and lipid peroxidation in beta cells (Safitri *et al.*, 2021). Damage to pancreatic beta cells results in dysfunction of beta cells and insulin insufficiency, which are the hallmarks of hyperglycemia (Sudhakaran *et al.*, 2022).

The blood glucose test of this study found that the diabetic group treated with metformin showed a decline from day 1 (249.4 ± 51.83 mg/dL) to day 14 (218.6 ± 64.7 mg/dL), which was 12.3% from day 1. Based on the results of the experiment, it was shown that diabetic rat treated with RTLE dose 400 mg/kg BW was the best treatment in decreasing the blood glucose levels. It was shown on day 14 that it decreased by about 61% compared to day 1 (Table 2). This result also shows better performance compared to the same treatment with a lower dose (200 mg/kg BW). On day 14, the blood glucose levels in the group receiving 200 mg/kg BW RTLE decreased by 46.2%. Based on these results, it is demonstrated that RTLE provides the most effective treatment for reducing blood glucose levels with a dose of 400 mg/kg. It is also shown that RTLE dose 400 mg/kg BW has a significant antihyperglycemic effect approaching normal control in this study, compared with metformin and RTLE 200 mg/kg BW (Table 2).

LIPID PROFILE

In diabetes mellitus, hyperglycemia is associated with dyslipidemia. Dyslipidemia is the major independent predictor of atherosclerosis and cardiovascular disease (CVD) in diabetic patients (Kane *et al.*, 2021). Dyslipidemia is characterized by high TC, LDL, and low HDL. The abnormal high level of serum lipid is mainly due to lipase enzyme activity (Berberich and Hegele, 2022). Insulin from pancreatic beta cells regulates lipase enzymes, such as inactivated lipoprotein lipase (LPL) and activated hormone-sensitive lipase (HSL).

Insulin deficiency activates HSL, which increases the release of non-esterified fatty acids (NEFAs) from triglycerides stored in adipose tissue. High levels of NEFA are associated with increased hepatic triglyceride production and secretion of apolipoprotein B (apoB) (Schofield *et al.*, 2016). Furthermore, diabetic patients lost their inhibitory effect from insulin on hepatic apo B production and triglyceride secretion in VLDL. The VLDL secreted contains more TG. Hypertriglyceridemia is a condition characterized by an accumulation of large VLDL and its lipolytic products in the circulation.

Reduced catabolism of VLDL due to inactivated LPL decreases the clearance rate of TG from the circulation, further augmenting the hypertriglyceridemia condition (Adiels *et al.*, 2007; Hlaing and Park, 2013). Laboratory tests in this study showed that the lowest TG levels were found in the standard control group, whereas the highest TG levels were found in the diabetes group. The diabetic without treatment group had the highest TG compared to the normal control group and the treatment groups RTLE due to inactive LPL. This condition encourages the liver to produce more TG (Hlaing and Park, 2013).

The highest TC level was found in the diabetic without treatment group compared with other treatment groups (Table 3). Alloxan-induced diabetes leads to insulin deficiency, which can activate HMG-CoA reductase (Parhofer, 2015). Acetyl-CoA is converted to HMG-CoA, which is reduced to mevalonate. Insulin inhibits the production of mevalonate, a key intermediate in the cholesterol synthesis pathway (Tsuchiya *et al.*, 2010). This inhibition helps regulate cholesterol levels, demonstrating the complex interplay between insulin and lipid metabolism. Diabetic dyslipidemia is characterized by elevated serum concentrations of triglyceride-rich lipoproteins (TRLs), a high prevalence of small dense LDL particles, and low HDL levels (Hirano, 2018). The mechanism of LDL and HDL in diabetic dyslipidemia is not fully understood. Laboratory test results in this study showed that the diabetic without treatment group had high TC and low HDL levels compared with other treatments (Table 3).

The active constituents responsible for antihyperglycemics, such as flavonoids, alkaloids, tannins, and saponins, are against ROS that can damage pancreatic beta cells. The present study, published in 2019, showed antihyperglycemic activity from the root of *Ruellia tuberosa* L. on rats induced by multiple low doses of streptozotocin (Roosdiana *et al.*, 2019). The antihyperglycemic activity of RTLE was significant ($p < 0.05$) in decreasing blood glucose levels at a dose of 400 mg/kg BW (Table 2). Phytochemical compounds such as flavonoids, tannins, saponins, and alkaloids act as antioxidants. Antioxidants can reduce oxidative stress by neutralizing free radicals and preventing them from causing damage to cells. Stigmasterol, a bioactive compound identified in RTLE, has been reported to increase GLUT-4 translocation and enhance insulin secretion from the pancreas, contributing to improved glucose uptake and glycemic control (Wang *et al.*, 2017). Besides this mechanism, alternative pathways may also play significant roles in the hypoglycemic effects observed. These include inhibition of intestinal glucose absorption, which reduces postprandial glucose levels; enhanced peripheral glucose uptake by muscle and adipose tissues; and modulation of key enzymes involved

in glucose metabolism, such as glucokinase and glucose-6-phosphatase. The combined effect of these mechanisms likely contributes to the overall antidiabetic action of the extract, making it a promising candidate for diabetes management (Sharma *et al.*, 2023).

Diabetic standard drugs such as metformin were approved by the U.S. Food and Drug Administration (FDA) in 1994. Metformin is known to have an antihyperglycemic effect by stimulating insulin release from pancreatic beta cells and reducing the amount of glucose the liver releases into the body (Bailey, 2017). It achieves this mainly by inhibiting gluconeogenesis in the liver and enhancing peripheral glucose uptake by activating AMP-activated protein kinase (AMPK), which also leads to improved lipid metabolism. However, metformin is also associated with several side effects, including physical weakness, diarrhea, myalgia, gastrointestinal disturbances, upper respiratory tract infections, hypoglycemia, abdominal pain, and, in rare cases, lactic acidosis (Bouchoucha *et al.*, 2011). While metformin shows some lipid-lowering effects, such as increasing bile acid synthesis that enhances LDL cholesterol clearance, its action in diabetic dyslipidemia management remains limited. Importantly, long-term use of metformin may have adverse effects, including exacerbation of lipid abnormalities due to elevated bile acid levels. Furthermore, gastrointestinal side effects like nausea, diarrhea, and malabsorption can impair nutrient uptake, and vitamin B12 deficiency associated with prolonged metformin use can increase the risk of cardiovascular complications. These complexities highlight the need for cautious use of metformin and underscore the potential value of alternative therapies such as *Ruellia tuberosa* L. leaf extract, which has demonstrated both antihyperglycemic and antihyperlipidemic effects in diabetic models.

Diabetic rats were treated with a single dose of RTLE (200 and 400 mg/kg BW) and metformin (50 mg/kg BW) for 14 days. RTLE at a dose of 400 mg/kg BW was effective in regulating glucose levels and the lipid profile in diabetic rats. Phytosterols from RTLE contribute to its antidiabetic activity and modulation of lipid metabolism. Cirsimaritin, a flavonoid derivative, can increase insulin secretion after inducing DPP-4 inhibition, which in turn reduces VLDL catabolism via LPL (Benali *et al.*, 2022). Flavonoids also increase the LDL catabolism rate via LDL receptors. Flavonoids have been shown to inhibit oxidation and glycation of HDL. A recent study found that flavonoids in *Epimedium koreanum* extract have potent inhibitory activities against oxidation and glycation of HDL (Kim and Shim, 2019). Apigenin components prevent beta cells damage, cause insulin release, and raise glucose uptake signaling insulin pathway by increasing the concentration of GLUT-4 protein and facilitating GLUT4

NOVELTY STATEMENT

translocation in diabetic skeletal muscle rats (Barky *et al.*, 2020). Apigenin works by decreasing LDL oxidation and neutralizing free radicals. *In-silico* and *in-vivo* studies have shown that quercetin has the potential to inhibit HMG-CoA reductase, which causes hypercholesterolemia and dyslipidemia (Riyad *et al.*, 2023). Quercetin can regulate hepatic cholesterol metabolism by promoting cholesterol to bile acid conversion and cholesterol efflux in rats (Zhang *et al.*, 2016). Quercetin may also reduce fasting hyperglycemia by increasing insulin sensitivity through α -glucosidase inhibition and enhancing insulin signaling in diabetic rats (Srinivasan *et al.*, 2018). Squalene is a type of steroid lipid and has potential antidiabetic and lipid-lowering effects in diabetic rats. Additionally, a study found that squalene supplementation improved lipid profiles and reduced oxidative stress in DM patients (Mirmiranpour *et al.*, 2022). Vitamin E in RTLE is a physiologically essential antioxidant, preventing lipid peroxidation that involves the oxidative deterioration of fatty acids (Niki, 2021). Niacin can increase HDL levels by preventing the liver from removing apoA-I, thereby increasing apoA-I concentrations and the number of HDL particles (Zhang *et al.*, 2016). Saponins, alkaloids, and tannins, as secondary metabolites, exhibit antihyperlipidemic activity. Alkaloids and saponins have been shown to have pancreatic lipase inhibitory activity (Pereira *et al.*, 2017; Mahwish *et al.*, 2023). Saponins also significantly reduce hepatic glycogen and blood glucose levels while elevating the enzyme activities of glycolysis (Deng *et al.*, 2023). A previous study showed that tannins have a pronounced anti-hypercholesterolemic effect by enhancing reverse cholesterol transport and reducing intestinal cholesterol absorption in rats fed hypercholesterolemic diets (Tebib *et al.*, 1994).

CONCLUSION

The study's findings indicate that a 96% ethanol extract of RTLE affects the reduction of blood glucose levels, total cholesterol, triglycerides, LDL, and increases HDL. The results show that it may be developed into an antidiabetes and antihyperlipidemic medicine substitute. Based on the experiment, the dose of 400 mg/kg BW is the most efficient dose of RTLE in lowering blood sugar levels and restoring blood lipid levels after alloxan induction.

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This study provides new insights into the dose-dependent effects of *Ruellia tuberosa* L. leaf extract on both hyperglycemia and diabetic dyslipidemia in an alloxan-induced diabetic rat model. While previous studies have mainly focused on the antidiabetic potential of *Ruellia tuberosa* L., this research highlights its combined effects on glucose regulation and lipid metabolism by evaluating multiple lipid parameters, including triglycerides, total cholesterol, LDL, and HDL. The findings demonstrate that a 400 mg/kg body weight dose of *Ruellia tuberosa* L. leaf extract effectively improves metabolic abnormalities, suggesting its potential as a natural therapeutic candidate for diabetes management.

AUTHORS CONTRIBUTION

All authors contributed to the study. Tridiganita Intan Solikhah supervised the experiment. All authors read and approved the final manuscript.

GENERATIVE AI AND AI ASSISTED TECHNOLOGY STATEMENT

The authors declare that no generative AI and AI assisted technology was used in the creation of this manuscript.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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