

Full Length Research Paper

Pharmacological effects of the aqueous extract from the leaves of *Artabotrys thomsonii* Oliv. (Annonaceae) against diabetic hypertension induced by fructose/sucrose and streptozotocin (STZ) in Wistar rats

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The pharmacological effects of *Artabotrys thomsonii*, a vine traditionally used against diabetes mellitus, were evaluated in an insulin-resistant diabetes model. Diabetes and hypertension were induced in rats by daily oral administration of 10% fructose (by gavage) and 10% sucrose (in drinking water) for 21 days, followed by intraperitoneal (*i.p.*) injection of streptozotocin (STZ) (40 mg/kg) on day 22. 100, 200, and 400 mg/kg of the extract were then administered to the diabetic rats from day 49 to day 77. The insulin sensitivity test was also performed on day 29 and day 77. Blood glucose levels were measured every 7 days, while blood pressure was measured on day 49 and day 74. Serum and tissue biochemical parameters were determined at the end of the last treatment. Diabetic rats exhibited hyperglycemia, insulin resistance, hypertension, tachycardia, and dyslipidemia on day 77. Daily administration of plant extract for 28 days significantly improved ($p < 0.05$ - $p < 0.001$) hemodynamic, serum biochemical, and tissue parameters. Metformin was used as a positive control. Chemical analysis of the plant extract revealed the presence of five major classes of secondary metabolites, including alkaloids, terpenoids, flavonoids, saponins, and tannins. *A. thomsonii* could therefore be used to improve type 2 diabetes and its cardiovascular complications.

Key words: *Artabotrys thomsonii*, aqueous extract, diabetes and arterial hypertension, biochemical parameters.

INTRODUCTION

An endocrine epidemic affecting all social strata and potentially leading to an economic and even health crisis

is diabetes mellitus (Antoine, 2022). It is a metabolic pathology characterized by chronic hyperglycemia linked

to insulin deficiency and/or insulin resistance (Nezha and Siham, 2024). This pathology being a real public health problem on the rise all over the world, the International Diabetes Federation (IDF) reported that approximately 536.6 million peoples were affected by diabetes worldwide in 2021 (or 46% increase compared to 2019), with 24 million in Africa (or 134% increase compared to 2019) and around 620,800 cases in Cameroon (or around 6.4% of the Cameroonian population affected) (IDF, 2021).

Among the three main types of existing diabetes mellitus (type 1 diabetes, gestational diabetes, and type 2 diabetes), type 2 diabetes represents the most widespread form in the world, with 90 to 95% of cases recorded (Regufe et al., 2020). In addition, type 2 diabetes is a main risk factor for the development of cardiovascular complications such as angiopathies (microangiopathy and macroangiopathy), which can lead to diabetic hypertension (Jia et al., 2017; Jia and Sowers, 2021). Furthermore, the risk factors causing more than 70% of type 2 diabetics to suffer from hypertension are obesity, lack of physical activity, smoking, and diet enriched in lipids, fructose, and sucrose (Martemucci et al., 2024).

Moreover, environmental toxicants (endocrine disruptors) as well as synthetic toxicants (streptozotocin (STZ) and alloxan) are increasingly implicated in the pathogenicity of type 2 diabetes and its cardiovascular complications (Rashid et al., 2024). Thus, from an experimental point of view, having knowledge of these risk factors contributes to the development of animal models of type 2 diabetes, making it possible to improve understanding of the pathophysiology and to encourage studies on the discovery of new therapeutic targets. For this, the fructose, sucrose, fructose/STZ models are the most scientifically investigated (Salau et al., 2024). Indeed, excessive consumption of fructose or sucrose generates toxic products in the body that oxidize the insulin receptors, phosphorylate the serine-threonine residues, and dephosphorylate the tyrosine kinase residues of the insulin receptor, leading to hepatic and muscular insulin resistance (James et al., 2016). Subsequently, the injection of low-dose STZ stimulates the compensatory effect of this insulin resistance, in particular by promoting the apoptosis of pancreatic beta cells, leading to chronic hyperglycemia (Olatunji et al., 2021).

The chronic hyperglycemia that occurs mainly activates three metabolic pathways (the polyol pathway, oxidative stress and the protein glycation pathway) producing toxic compounds (sorbitol, free radicals and AGEs) which in turn damage the heart (cardiomyopathy), the kidneys

(nephropathy) and the endothelium of the artery (endotheliopathy), all being organs strongly involved in the maintenance of homeostasis of hemodynamic parameters (Morin et al., 2019; Hashimoto et al., 2020; Kassi et al., 2023). Thus, alterations of the endothelium reduce the bioavailability of nitric oxide (NO), thus limiting the vasorelaxation of vascular muscle fibers, leading to arterial hypertension (Jia et al., 2018). The oxidation of cardiac proteins by these toxic compounds disrupts cardiac electricity and leads to tachycardia (Lugat et al., 2018; Scheen, 2018). Nephropathy alters the functioning of the renin-angiotensin-aldosterone system, which disrupts the maintenance of the balance of blood pressure and heart rate (Monnier et al., 2023). To overcome hypertension secondary to type 2 diabetes, therapies based on oral antidiabetics (metformin or glibenclamide), sometimes in combination with antihypertensive medications, are strongly recommended (Ortega-Montiel et al., 2023).

However, these treatments are expensive, cause serious side effects, and are often ineffective in the face of multiple complications (Wander et al., 2024). Moreover, traditional pharmacopoeia offers natural plant-based therapies that are inexpensive, low-toxic, and effective. In addition, extracts of many plants have already shown their effectiveness against type 2 diabetes and its complications. These are *Pterocarpus soyauxii* Taub (Tchamadeu et al., 2022) for its insulin-sensitizing and antioxidant effects, *Morinda lucia* (Ulrich et al., 2016) for its antidiabetic and antioxidant effects, *Azadirachta indica* (Pingali et al., 2020) for its effects against type 2 diabetes and arterial hypertension, and *Rehmannia glutinosa* (Zaaba et al., 2023), known for its antidiabetic and anti-inflammatory effects. *Artabotrys thomsonii* Oliv is a vine belonging to the Annonaceae family, which is found in central Africa and which is traditionally used for the treatment of numerous pathologies (Nkounkou-Loumpangou et al., 2005). Furthermore, a study showed that the *A. thomsonii* leaves aqueous extract does not cause toxicity in acute and subacute administration (Pechi et al., 2024). In addition, a chemical study carried out on the *A. thomsonii* leaves extract revealed the presence of compounds, such as oxoberberine and oxodiscretamine (Nguemdjo et al., 2022) with antidiabetic and antihypertensive activities (Chelleng et al., 2024; Marchelak et al., 2025). Moreover, to the best of this study's knowledge, no scientific study aimed at evaluating the pharmacological properties of *A. thomsonii* against diabetic hypertension has yet been carried out.

The present work aimed to evaluate the antidiabetic and antihypertensive effects of *A. thomsonii* leaves aqueous extract in type 2 diabetic rats induced with

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fructose/sucrose and STZ.

MATERIALS AND METHODS

Chemicals

STZ was obtained from Nanjing Duly Biotech Laboratory Company (Nanjing Duly Biotech Co., Ltd, China), semi-lent insulin from Rotexmedica GmbH (Germany), metformin from Africure Pharmaceuticals (Cameroon), NaCl 0.9% from the safe inhalation pipe provision (S.I.P.P) laboratory (S.I.P.P, Cameroon), Accu-chek Performa blood sugar test strips from Roche Diagnostics (Mannheim, Germany), and all other reagents and chemicals from common commercial providers were used in this study.

Plant

A. thomsonii leaves were collected in Obak Mount, Center Region of Cameroon, in March 2022, and a plant sample was sent to the Cameroon National Herbarium, where the identification was made by comparison with a voucher specimen number 52237HNC.

Procedure of aqueous extraction of *A. thomsonii*

The leaves of the plant were dried at room temperature in a shaded room for four weeks and ground into powder using a grinder. 500 g of powdered leaves were added to the pot containing 2.5 L of distilled water and heated to boil for 30 min. After cooling to room temperature ($24 \pm 2^\circ\text{C}$), the mixture was filtered using Whatman No. 3 filter papers. The procedure was repeated with the residues, and the two filtrates obtained were mixed and evaporated at 40°C in an oven. The crude extract obtained (40 g) was stored at 4°C and used as *A. thomsonii* leaves aqueous extract (At) throughout the study.

The choice of the dose used was made from the traditional human dose (32.46 mg/kg) determined by following the traditional instructions for preparing the plant extract and translated into the rat dose as follows (Reagan-Shaw et al., 2008):

Rat dose (mg/kg) = [Human dose (mg/kg)] $\times$ k (with $k=6.2$).

Thus, the dose obtained in rats was adjusted to the fixed upper/lower value; its half and double were used for the study.

For rats' administration during the experimental period, the concentrated solution of the plant aqueous extract was prepared by dissolving a weighed quantity of the crude aqueous extract of the dried plant in distilled water to obtain 30 mg/mL of stock solution every 3 days.

Chemical analysis of the aqueous leaf extract of *A. thomsonii*

Qualitative chemical analysis

The crude extract was evaluated for the presence of secondary metabolites such as alkaloids (Dhawan and Gupta, 2017), terpenoids (Pandey and Tripathi, 2014), flavonoids (Trease and Ewans, 1989), saponins, and tannins (Wallis, 1985).

Animals

Adult male albino Wistar rats (02 months old and weighing 180-200 g) were used. They were raised in the animal room of the Faculty of Sciences of the University of Douala. They were housed in colony

cages (5 rats per cage), at ambient temperatures ($28 \pm 2^\circ\text{C}$, 2) and humidity (80-85%), on a 12-h light/dark cycle with free access to tap water and standard rat diet. Before measuring blood sugar levels, the rats were fasted for 2 h in the morning, with free access to water.

The experimental procedure was conducted in accordance with all guidelines for care and use of laboratory animals as described in the European Community Guidelines (EEC Directive 2010/63/EU of September 22, 2010) and after the approval for Animal Experimentation N°2459 CEI-UDO/10/2020/M by the Institutional Ethics Committee of the University of Douala.

Induction of type 2 diabetes mellitus

In this study, insulin resistance and type 2 diabetes were induced in rats using the method of Wilson and Islam (2012) with a slight modification. To induce insulin resistance, 10% fructose and 10% sucrose were administered daily to rats by gavage and in drinking water, respectively, for 21 days. Subsequently, type 2 diabetes was induced in insulin-resistant rats by a single intraperitoneal injection of STZ (40 mg/kg freshly prepared in ice-cold 0.9% saline solution) after 12 h of fasting on the 22nd day. The preparation of the STZ was carried out in the dark to avoid its denaturation. The control rats received 10 mL/kg of NaCl by the same route. After STZ injection, a 5% glucose solution was administered to the rats for 24 h, allowing them to resist the hypoglycemic shock which occurs after the STZ injection (Zafar and Naqvi, 2010). Seven days (Day 28) after STZ injection, rats presenting a postprandial blood sugar level of at least 200 mg/dL were considered diabetic and were observed for a period of 21 days in order to promote the occurrence of cardiovascular complications. Subsequently, these diabetic animals in the complication phase were used throughout the experiment.

Experimental design for evaluating subacute effects of *A. thomsonii* leaf aqueous extract on diabetic hypertension

In total, 30 rats were used: twenty-five type 2 diabetic rats were divided after randomization into five diabetic groups (5 rats in each group) and a single group of five non-diabetic rats. The rats were treated daily by gavage for 28 days, starting directly after the observation period, and distributed as follows:

- 1) Group 1: Normal control (NC), consisting of normal rats that received distilled water (10 mL/kg);
- 2) Group 2: Diabetic control (DC) composed of diabetic rats that received distilled water (10 mL/kg);
- 3) Group 3: Metformin (Met)-treated diabetic rats received the standard drug, metformin (Met, 200 mg/kg);
- 4) Groups 4, 5, and 6, consisting of diabetic rats, received the *A. thomsonii* extract solution at respective doses of 100, 200, and 400 mg/kg.

The different treatments (distilled water, metformin, and plant extract) were administered daily by gavage to the animals for 28 days.

After the induction process, the postprandial blood glucose levels and body weight of the rats were measured before the first administration of the treatment (Day 49) and weekly (respectively on days 56, 63, 70, and 77 called W8, W9, W10, and W11). Blood pressure and heart rate were measured before the first and last treatment on days 49 and 74, respectively. On day 77, an insulin sensitivity test was immediately performed after blood glucose determination. Immediately afterwards, the rats were anesthetized (by intramuscular injection of ketamine (50 mg/kg) and diazepam (10 mg/kg) and euthanized by beheading. Blood samples were then

Table 1. Qualitative chemical analysis of the aqueous leaf extract of *A. thomsonii*.

Compound type	Tests used	Results
Alkaloids	Dragendorff test	+
Saponins	Foaming test	+
Terpenoids	Salkowski test	+
Flavonoids	Shinoda test	+
Tannins	Gelatin-Salt test	+

(+): Presence of the desired secondary metabolite.

taken from the abdominal artery by laparotomy (Tchamadeu et al., 2017). The serum obtained after centrifugation of the blood (3000 g/10 min) was stored at -20°C to perform serum biochemical analyses. Organs such as the aorta, heart, kidneys, liver, and pancreas were removed and weighed. A portion of these organs was crushed and centrifuged, and the homogenates obtained were also stored at -20°C to perform the tissue assay of NO. The other part of the latter was preserved in a 10% formaldehyde solution to carry out the histopathological sections.

Histopathological analysis

The procedure described by Rahman et al. (2017) was followed for histological analysis by Hematoxylin-Eosin staining (H-E). Briefly, each organ (pancreas, liver, kidneys, heart, and aorta) previously fixed in formalin buffer 10% was embedded in paraffin, cut into sections of 5 μm using a microtome (Reichert-Jung 2030), and mounted on slides. Slides of each organ were stained with hematoxylin and - eosin (H-E) after deparaffinization, then photographed using an Olympus brand optical microscope (Leitzwetzlar, Germany 513) to detect any alterations compared with the control.

Statistical analysis

Results were expressed as mean $\pm$ SEM. The difference between the treated and control group was determined using a one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison post-test. The analysis was performed using PRISM Software (GraphPad Software, Inc., San Diego, CA, version 5.03). A p-value less than 0.05 was considered significant (Michel et al., 2020).

RESULTS

Qualitative chemical analysis of *A. thomsonii* leaves aqueous extract

Qualitative chemical analysis of *A. thomsonii* aqueous extract revealed the presence of secondary metabolites such as alkaloids, saponins, terpenoids, flavonoids, and tannins (Table 1).

Effects of the aqueous leaf extract of *A. thomsonii* on blood glucose in type 2 diabetic rats

Figure 1 shows that the variation in blood sugar levels of rats having received 10% fructose, 10% sucrose, and

STZ administered at a single dose of 40 mg/kg. The administration of diabetogenic toxins induced a significant increase ($p<0.001$) in the blood sugar levels of rats from the seventh week (W7) until the last week (W11) of the experiment compared to NC. *A. thomsonii* extract administered at doses of 100, 200 and 400 mg/kg significantly reduced ($p<0.01$ - $p<0.001$) the blood glucose levels from the first week (W8) of treatment to the fourth week (W11), compared to diabetic controls (Figure 1).

Effects of the aqueous leaf extract of *A. thomsonii* on insulin sensitivity in type 2 diabetic rats

The insulin sensitivity test showed that the administration of insulin to the different animals reduced blood sugar levels in all groups treated with the plant extract, metformin, and distilled water, unlike that of the DC group, whose glycemia more or less slightly decreased. However, this reduction was more rapid in the groups of rats treated with the extract at different doses and with metformin than in the group of DC rats. In general, the area under the blood glucose curve (AUC) in the different treatment groups showed elevated ($p<0.001$) blood glucose of 433.93% in DC rats compared to normal rats. However, the blood sugar levels of rats treated with the plant extract decreased ($p<0.001$) by 333.82, 352.25, and 345.03% at the respective doses of 100, 200, and 400 mg/kg, compared to DC rats. Likewise, metformin significantly lowered ($p<0.001$) blood sugar levels by 333.82% compared to DC. Doses of 200 and 400 mg/kg of plant extract showed a major insulin-sensitizing effect compared to metformin (Figure 2).

Effects of the aqueous leaf extract of *A. thomsonii* on hemodynamic parameters in type 2 diabetic rats

During the period after induction of diabetes mellitus in rats, pre-administered fructose/sucrose and STZ significantly maintained elevated diastolic (A), systolic (B), mean blood pressure (C) and heart rate (D), respectively at 48.46, 46.51, 46.48, and 92.98%, compared to normal controls. The plant extract administered daily for a period of 28 days in rats significantly ($p<0.05$ - $p<0.01$) reduced systolic, diastolic,

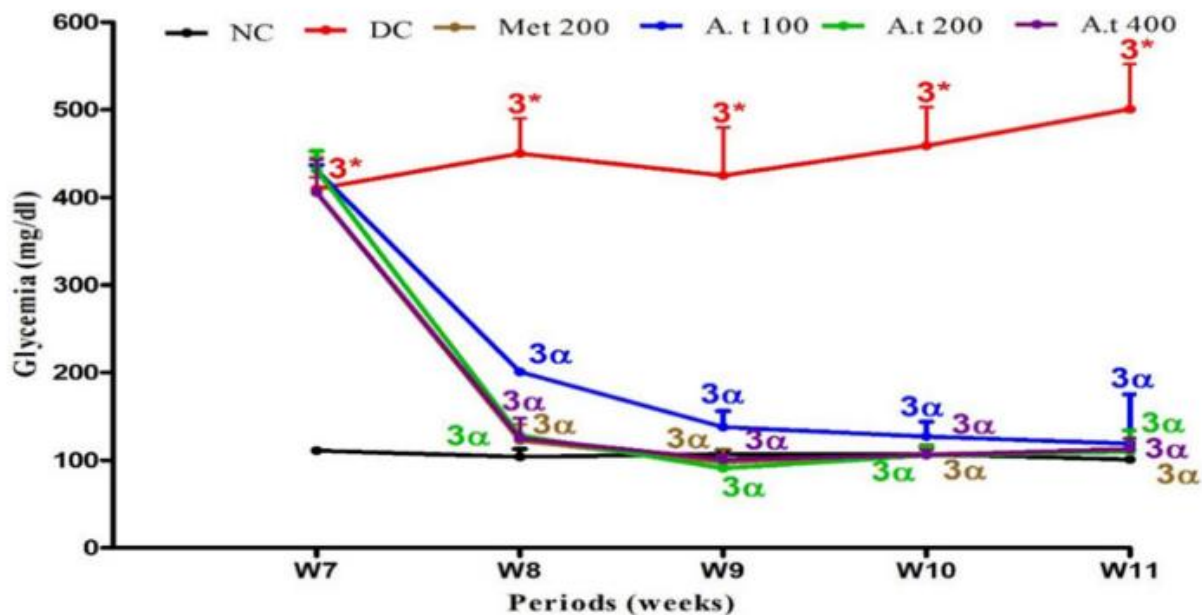


Figure 1. Variation of blood sugar levels in type 2 diabetic rats treated with *A. thomsonii* leaves aqueous extract. Each point represents the mean $\pm$ ESM, $n = 5$, $3^*p < 0.001$: significant difference compared to NC, $3\alpha p < 0.001$: significant difference compared to the diabetic control, NC = normal control, DC = diabetic control, Met 200: metformin administered at a dose of 200 mg/kg, and at (100, 200 and 400 mg/kg): *A. thomsonii* leaves aqueous extract administered at the indicated doses, and W: number of weeks.

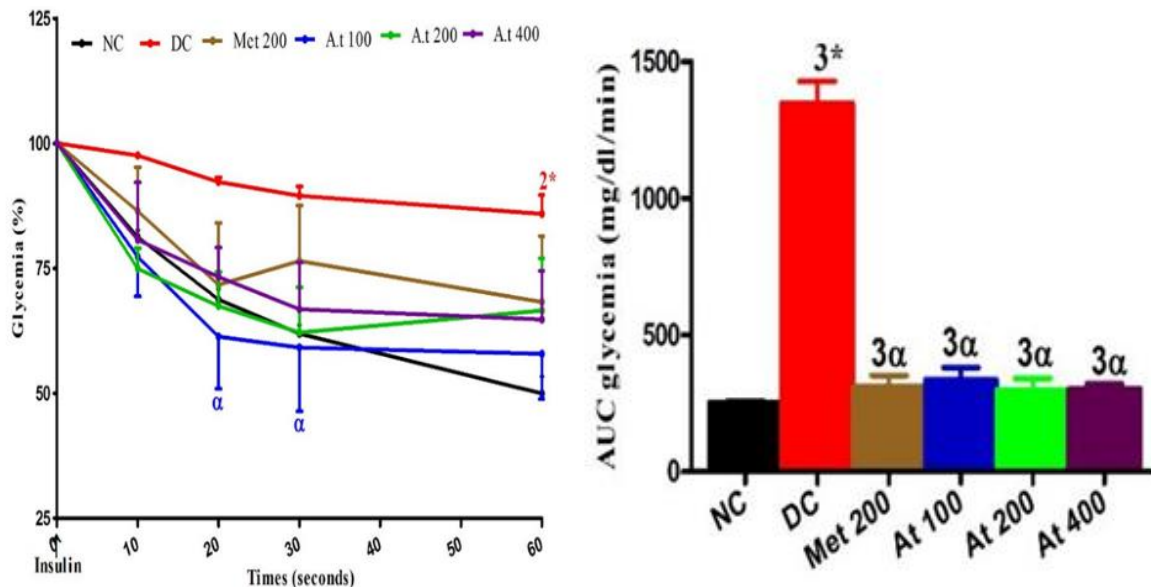


Figure 2. Variation of insulin sensitivity of type 2 diabetic rats treated with *A. thomsonii* leaves aqueous extract. Each point represents the mean $\pm$ SEM, $n = 5$, $2^*p < 0.01$: significant difference compared to EN, $\alpha p < 0.05$: significant difference compared to DC, NC: normal control, DC: diabetic control; Met 200: metformin administered at a dose of 200 mg/kg, and at (100, 200 and 400 mg/kg): *A. thomsonii* leaves aqueous extract administered at the indicated doses.

mean blood pressure, and even heart rate compared to hypertensive rats DC group. However, compared to

untreated diabetics, the plant extract at all doses tested (100, 200 and 400 mg/kg) reduced systolic blood pressure

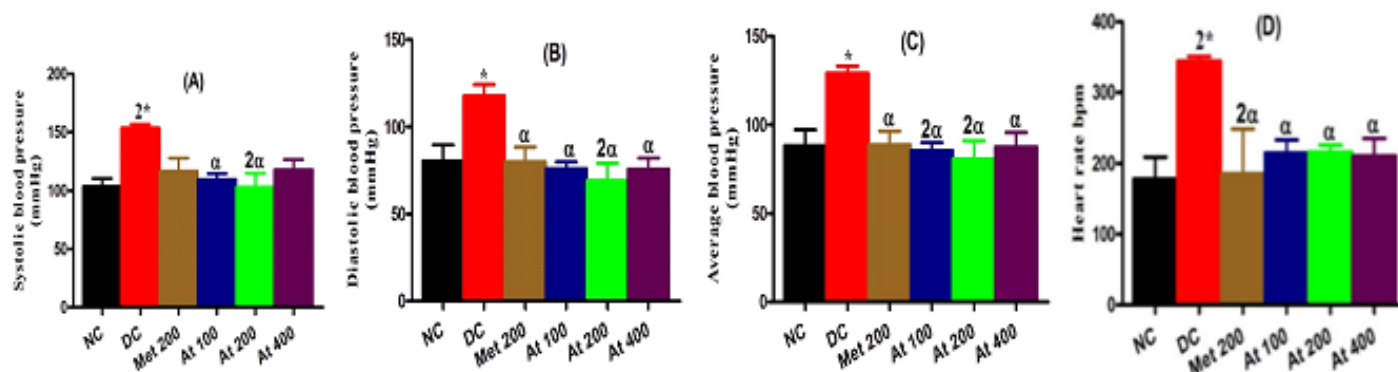


Figure 3. Variation of hemodynamic parameters of type 2 diabetic rats treated with *A. thomsonii* leaves aqueous extract. Each bar represents the mean $\pm$ SEM, $n = 5$; * $p < 0.05$, $2^*p < 0.01$: significant difference compared to NC, $\alpha p < 0.05$, $2\alpha p < 0.01$: significant difference compared to DC, NC = normal controls, DC = diabetic controls, Met 200: metformin administered at a dose of 200 mg/kg, and at (100, 200 and 400 mg/kg): aqueous extract of *A. thomsonii* leaves administered at the doses indicated.

pressure by 40.07, 49.08, and 30.33%, respectively; diastolic blood pressure of 55, 70.32, and 55.40%, respectively; mean blood pressure of 50.93, 59.84, and 47.48%, respectively; and heart rate of 60.18, 59.01, and 63.42%, respectively. Metformin administered at a dose of 200 mg/kg significantly ($p < 0.05$) reduced the systolic, diastolic, mean blood pressure, and heart rate of the treated animals, respectively, by 32.01, 47.25, 45, 44, and 85.69%, compared to the group of untreated animals (DC). It is interesting to note that the 200 mg/kg dose of the plant extract showed maximum effectiveness in reducing systolic, diastolic, and average blood pressure compared to the other two doses (100 and 400 mg/kg) and even compared to metformin (Figure 3).

Effects of the aqueous leaf extract of *A. thomsonii* on the body mass of type 2 diabetic rats

Figure 4 shows the evolution of the body mass of rats having received fructose/sucrose and STZ. From the 8 to 11th week of treatment, the body mass of the animals in the DC group, as well as that of those treated with the plant extract at all doses, increased compared to normal controls. However, this increase was only significant ($p < 0.05$) in rats of the DC group and in those treated with the plant extract at a dose of 100 mg/kg at the 11th week of experimentation, compared to the normal rats. A non-significant decrease in the body mass of rats treated with metformin was observed at the 11th week compared to normal rats and those treated with the plant extract.

Effects of *A. thomsonii* leaves aqueous extract on the relative organ mass of type 2 diabetic rats

Administration of fructose/sucrose and STZ did not modify the relative organ mass of diabetic rats compared

to normal controls. Only the animals that had received the plant extract at a dose of 100 mg/kg showed a significant decrease ($p < 0.05$) in the relative mass of the pancreas, compared to untreated diabetic rats. Likewise, daily administration of metformin did not modify the relative mass of the different organs compared to diabetic controls (Table 2).

Effects of the aqueous leaf extract of *A. thomsonii* on serum biochemical parameters in type 2 diabetic rats Effects on serum protein, creatinine, and urea

The administration of diabetogenic substances (fructose, sucrose and STZ) significantly (95.39%; $p < 0.001$) reduced the serum level of total protein, and significantly increased those of creatinine (52.94%; $p < 0.001$) and urea (133.33%; $p < 0.001$) in DC rats compared to NC rats. Compared to diabetic controls, the plant extract administered at all doses (100, 200, and 400 mg/kg) significantly increased the level of total proteins by 97.54, 91.41, and 96.01%, respectively. For this total protein parameter, metformin (200 mg/kg) significantly ($p < 0.001$) increased by 74.23%. On the other hand, a significant decrease in serum levels of creatinine at doses of 100 mg/kg (82%; $p < 0.001$), 400 mg/kg (46.77%; $p < 0.001$), and urea at doses of 100 mg/kg (143.47%; $p < 0.001$), 200 mg/kg (43.58%; $p < 0.001$) and 400 mg/kg (44%; $p < 0.01$) were observed. Metformin significantly ($p < 0.01$ - $p < 0.001$) reduced serum creatinine and urea levels of rats by 52.94 and 51.35%, respectively (Table 3).

Effects on serum ALAT/ASAT and PAL activities

A significant increase in serum activities of aspartate transaminase (AST) (50.96%; $p < 0.01$), alanine amino transferase (ALT) (44.83%; $p < 0.05$), and alkaline

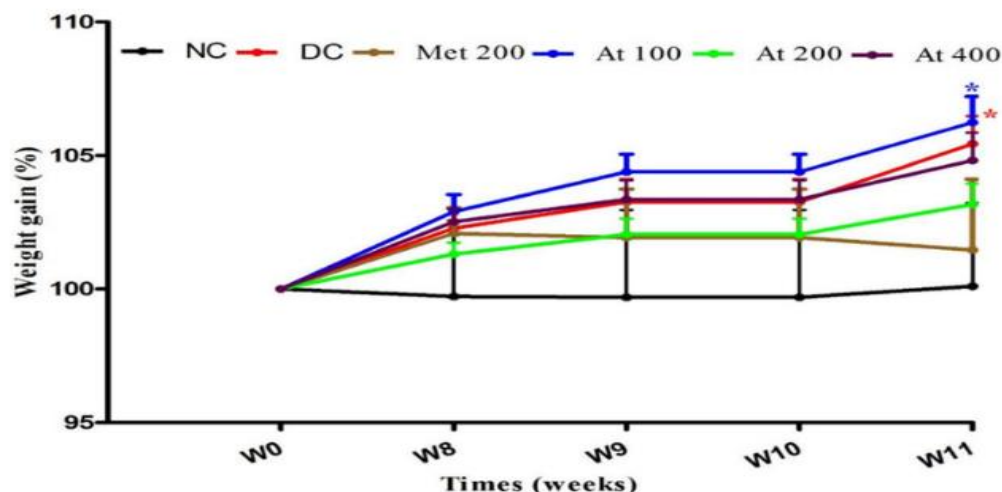


Figure 4. Variation of body mass of type 2 diabetic rats treated with *A. thomsonii* leaves aqueous extract. Each point represents the mean $\pm$ SEM, n: 5, *p<0.05: significant difference compared to NC, NC: normal control, DC: diabetic control, Met 200: metformin administered at a dose of 200 mg/kg, at (100, 200 and 400 mg/kg): *A. thomsonii* leaves aqueous extract administered at the indicated doses, and W: weeks.

phosphatase (ALP) (66.78%; $p<0.001$) in untreated diabetic rats was observed by comparison to normal rats. Compared to DC rats, the plant extract significantly reduced ALT activities at doses of 100 mg/kg (31.28%; $p<0.001$), 200 mg/kg (18.58%; $p<0.05$), and 400 mg/kg (21.70%; $p<0.01$). It also significantly reduced the activity of AST at doses of 100 mg/kg (38.71%; $p<0.05$), 200 mg/kg (45.71%; $p<0.01$), 400 mg/kg (52.48%; $p<0.001$), and of ALP by 51.24% ($p<0.01$) and 38.77% ($p<0.001$) at the respective doses of 100 and 200 mg/kg. In addition, the extract at a dose of 400 mg/kg, as well as metformin 200 mg/kg, did not induce significant variation in the serum level of ALP. Metformin caused a significant decrease in ALT and AST activities by 54.17 and 56.11%, respectively (Table 3).

Effects on serum α -amylase activities

In comparison to normal rats (NC), diabetic rats (DC) showed a significant increase in serum α -amylase activity by 45.82% ($p<0.01$). However, treatment with *A. thomsonii* extract at doses of 100 and 400 mg/kg significantly ($p<0.05$ - $p<0.01$) reduced this activity by 26.16 and 40.10%, respectively, compared to DC rats. Metformin (200 mg/kg) showed a decrease in α -amylase activity by 24.36% ($p<0.05$) compared to DC rats. Thus, the plant extract at a dose of 400 mg/kg showed greater efficacy than metformin (Table 3).

Effects on lipid profile

Untreated diabetic (DC) rats compared to normal rats

showed a significant increase in serum levels of triglycerides (169.02%; $p<0.001$), total cholesterol (82.85%; $p<0.001$), Low-density lipoprotein (LDL) cholesterol (31.39%; $p<0.05$), followed by a significant reduction in serum high-density lipoprotein (HDL) cholesterol level (137.50%; $p<0.01$). Overall, the 400 mg/kg dose of *A. thomsonii* extract showed maximum effect by significantly reducing serum levels of triglycerides (182.5%; $p<0.001$), total cholesterol (134.14%; $p<0.001$), and LDL-cholesterol (63.76%; $p<0.05$) compared to DC rats. The plant extract significantly increased serum HDL cholesterol levels, respectively, at the respective doses of 100 mg/kg (147.50%; $p<0.001$), 200 mg/kg (152.50%; $p<0.01$), and 400 mg/kg (127.50%; $p<0.01$) compared to DC rats. Metformin significantly reduced serum levels of triglycerides (68.95%; $p<0.001$), total cholesterol (82.99%; $p<0.001$), LDL cholesterol (37.04%; $p<0.05$), and increased serum HDL cholesterol levels non-significantly compared to DC rats. Furthermore, a significant increase in atherogenic index (AI) (311.67%; $p<0.001$) and insulin resistance index (RI) (503.37%; $p<0.001$), thus calculated from lipid parameters, was noted in DC rats compared to NC rats.

The plant extract at all doses (100, 200, and 400 mg/kg) significantly ($p<0.001$) reduced the atherogenic index by 392.51, 426.62, and 417.65%, respectively. Likewise, the RI was significantly ($p<0.001$) reduced following the administration of the plant extract at all doses, respectively by 460.78, 503.37, and 618.59% compared to the diabetic animals. Metformin significantly reduced AI (219.29%; $p<0.001$) and RI (272.39%; $p<0.001$) (Table 3).

Table 2. Effects of the aqueous leaf extract of *A. thomsonii* on the relative organ mass of type 2 diabetic rats.

Doses (mg/kg)	Relative mass (g)							
	Liver	Kidneys	Heart	Pancreas	Aorta	Thymus	Spleen	Brain
NC	2.50±0.19	0.24±0.01	0.31±0.02	0.28±0.03	0.05±0.01	0.12±0.01	0.44±0.05	0.75±0.05
DC	2.49±0.08	0.27±0.01	0.31±0.01	0.33±0.04	0.04±0.01	0.12±0.01	0.35±0.01	0.71±0.03
Met 200	2.22±0.09	0.26±0.01	0.30±0.01	0.25±0.01	0.04±0.01	0.12±0.01	0.31±0.02	0.74±0.02
At 100	2.57±0.09	0.25±0.01	0.28±0.01	0.16±0.02	0.04±0.01	0.09±0.01	0.29±0.02	0.63±0.01
At 200	2.12±0.06	0.22±0.01	0.28±0.01	0.27±0.02	0.04±0.01	0.09±0.01	0.31±0.01	0.65±0.01
At 400	2.41±0.08	0.24±0.01	0.29±0.01	0.23±0.02	0.03±0.01	0.09±0.01	0.35±0.02	0.62±0.01

Table 3. Effects of the aqueous leaf extract of *A. thomsonii* on serum biochemical parameters in diabetic rats.

Doses (mg/kg)	Prot (g/L)	Creat (mg/L)	Urea (g/L)	ALAT (U/L)	ASAT (U/L)	ALP (U/L)	α – amy (U/L)	TC (g/L)	TG (g/L)	HDL-C (g/L)	LDL-C (g/L)	RI	AI
NC	6.37±0.20	4.76±0.33	0.24±0.02	104±2.90	131±12.9	109±8.45	107±3.14	1.05 ±0.02	0.43±0.02	0.19±0.02	0.87±0.01	2.37±0.23	5.91±0.59
DC	3.26±0.19 ^{3*}	7.28±0.45 ^{3*}	0.56±0.03 ^{3*}	156±4.42 ^{3*}	190±4.66 [*]	181±6.92 ^{3*}	151±4.48 ^{3*}	1.93±0.03 ^{3*}	1.13±0.02 ^{3*}	0.08±0.01 ^{2*}	1.30±0.06 [*]	14.30±0.73 ^{3*}	24.33±1.20 ^{3*}
Met 200	5.68±0.20 ^{3a}	5.65±0.21 ^a	0.37±0.01 ^{2a}	133±3.92 ^a	139±11.4 ^a	162±2.90	126±7.01 ^a	1.05±0.03 ^{3a}	0.53±0.07 ^{3a}	0.14±0.01	0.83±0.03 ^a	3.84±0.44 ^{3a}	7.62±0.57 ^{3a}
At 100	6.44±0.09 ^{3a}	4.00±0.33 ^{3a}	0.23±0.02 ^{3a}	119±5.83 ^{3a}	137±11.4 ^a	120±8.37 ^{3a}	124±8.19 ^a	0.94±0.01 ^{3a}	0.49±0.02 ^{3a}	0.20±0.01 ^{2a}	0.91±0.04	2.55±0.21 ^{3a}	4.94±0.35 ^{3a}
At 200	6.24±0.10 ^{3a}	6.18±0.23	0.39±0.02 ^{2a}	132±3.97 ^a	130±4.76 ^{2a}	142 ±10.3 ^{2a}	130±6.33	0.89±0.02 ^{3a}	0.46±0.01 ^{3a}	0.20±0.01 ^{3a}	0.67±0.05 ^{3a}	2.37±0.19 ^{3a}	2.16±0.02 ^{3a}
At 400	6.40±0.22 ^{3a}	4.95±0.11 ^{3a}	0.40±0.03 ^{2a}	129±1.60 ^{2a}	125±4.40 ^{2a}	147±2.40 ^a	112±1.72 ^{2a}	0.83±0.02 ^{3a}	0.36±0.03 ^{3a}	0.18±0.01 ^{2a}	0.70±0.10 ^{3a}	1.99±0.10 ^{3a}	1.16±0.02 ^{3a}

Each value represents the mean ± SEM, n: 5. *p<0.05; ²p<0.01; ³p<0.001: significant difference compared to NC, ^ap<0.05; ^{2a}p<0.01, ^{3a}p<0.001: significant difference compared to DC. NC: normal controls, DC: diabetic controls, Met 200: metformin administered at a dose of 200 mg/kg, At (100, 200, and 400 mg/kg) aqueous extract of *A. thomsonii* leaves administered at the doses indicated. TC: total cholesterol, TG: triglyceride, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, ALAT: alanine amino transferase, ASAT: aspartate amino transferase, ALP: alkaline phosphatase, PROT: total proteins, CREAT: creatinine, α-amy: α-amylase, RI: resistance index, and AI: atherogenic index.

Effects of the aqueous leaf extract of *A. thomsonii* on tissue levels of cardiac and aortic NO in diabetic rats

The administration of different diabetogenic substances to rats in the DC group caused a significant decrease in tissue levels of cardiac NO (68.74%; p<0.001) and aortic NO (71.79%; p<0.001) compared to NC rats. Treatment with the aqueous extract of *A. thomsonii* at doses of 100, 200, and 400 mg/kg significantly (p<0.01) increased the NO level in the heart, respectively, of 162.67, 156.27, and 173.07% compared to erectile dysfunction (ED) rats. Likewise, aortic NO

significantly (p<0.01) increased has been respectively of 169.67%, 142.73%, and 201.11%. Metformin significantly increased the tissue level of cardiac NO (181.34%; p<0.01) and aortic NO (254.58%; p<0.05) (Figure 5).

Effects of the aqueous leaf extract of *A. thomsonii* on the histopathology of the pancreas, liver, kidneys, heart, and aorta of diabetic rats

The histopathology of the organs of DC rats showed alterations induced by diabetogenic

substances in the pancreas, liver, kidney, heart, and aorta compared to NC rats. The pancreas of normal rats presented an unaltered and well-differentiated endocrine and exocrine pancreas, unlike DC rats, whose circumference of the endocri pancreas was greatly reduced. Similarly, the liver of normal animals showed normal parenchyma with a portal vein, bile canaliculus, and well-differentiated hepatocytes. The liver of diabetic rats showed areas of leukocyte infiltration. Furthermore, the histological section of the kidney of NC animals shows normal renal parenchyma with a urinary space, a glomerulus, well-differentiated distal and proximal convoluted

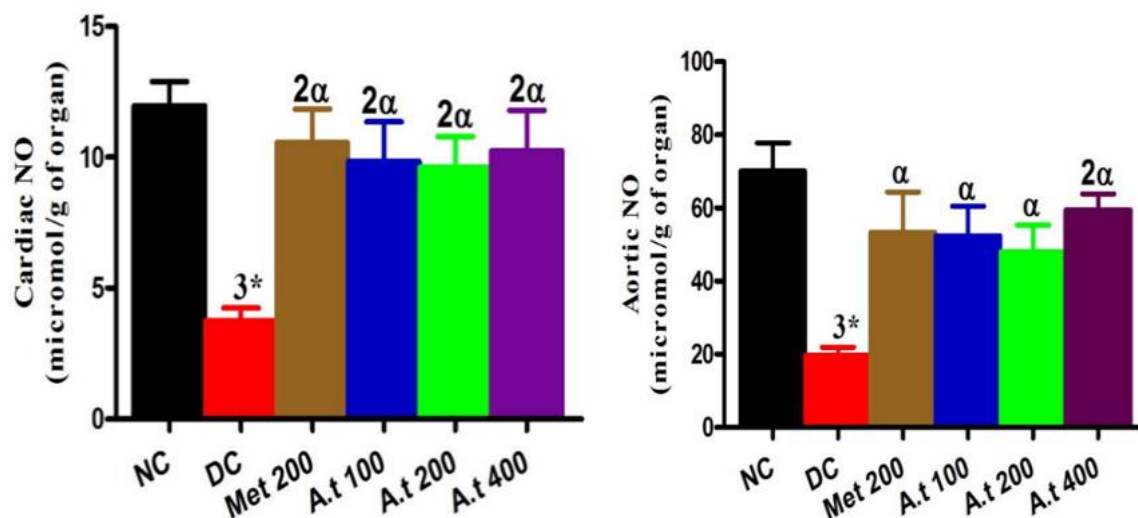


Figure 5. Variation in cardiac and aortic tissue NO levels of diabetic rats treated with *A. thomsonii* leaves aqueous extract. Each bar represents the mean $\pm$ SEM, n: 5, 3* p <0.001: significant difference compared to NC, α p <0.05, 2 α p <0.01: significant differences compared to DC, NC: normal controls, DC: diabetic controls, Met 200: metformin administered at a dose of 200 mg/kg, and at (100, 200 and 400 mg/kg): aqueous extract of *A. thomsonii* leaves administered at the doses indicated.

tubules, compared to DC rats, whose liver was invaded by leukocyte infiltration associated with a pushed mesangial expansion. For the heart, DC rats presented a disorganization of muscle fibers and leukocyte infiltration compared to normal control rats, which presented a normal structure of muscle fibers and well-differentiated cardiomyocyte nuclei. The alteration of the aorta of DC rats results in a thickening of the media compared to NC rats, which presented a normal structure and a well-differentiated tunic (intima, media, and adventitia). In general, it is important to note that the administration of the extract of *A. thomsonii* at all doses (100, 200 and 400 mg/kg), as well as metformin at a dose of 200 mg/kg improved all the alterations tissues induced by diabetogenic substances at the pancreatic, hepatic, renal, cardiac and aortic levels compared to the organs of normal control rats (Figure 6).

DISCUSSION

The primary mortality factor in type 2 diabetes is its cardiovascular complications, and its management is a major challenge (Wong and Sattar, 2023). To improve the latter, taking modern antidiabetic drugs presents notorious side effects and risks of toxicity to the organs. Scientific studies carried out on numerous plants with little prior toxicity (case of *A. thomsonii*) have shown pharmacological measures largely sufficient to reduce cardiovascular damage linked to diabetes (Pingali et al., 2020; Tchamadeu et al., 2022). Therefore, this work assessed the effects of *A. thomsonii* leaves aqueous extract on the cardiovascular function of type 2 diabetic

rats.

In pharmacology, the therapeutic effects of a natural substance or medicinal plant come from its composition of secondary metabolites or bioactive compounds. According to the results of qualitative phytochemistry, *A. thomsonii* contains secondary metabolites and compounds with multiple biological activities (antidiabetic, antihypertensive, antioxidant, anti-inflammatory, antibacterial, and bactericidal) identified through the literature (Nkounkou-Loumpangou et al., 2005; Nguemdjo et al., 2022).

The evaluation of the effects of the plant extract on blood sugar and insulin sensitivity could justify its antidiabetic potential. In this study, it was noted that the administration of fructose/sucrose and STZ caused hyperglycemia and a reduction in insulin sensitivity. Daily treatment with the plant extract for 28 days improved blood sugar and insulin sensitivity in rats at all doses (100, 200, and 400 mg/kg) compared to untreated diabetics. Scientific work has shown that a diet rich in sugar (fructose/sucrose) combined with a low dose of STZ injected via the Intraperitoneal (IP) route led to insulin resistance and chronic hyperglycemia in rats (Wilson and Islam, 2012; Olatunji et al., 2021). Indeed, fructose causes insulin resistance by initiating increased production of fatty acids in the body which accumulates mainly in the liver and in the muscle, thus causing the production of toxic metabolites (diacylglycerol, ceramides and acylcoenzyme-A) which oxidize insulin receptor substrates (IRS) receptors located in the muscle and liver which in turn disrupt insulin signaling (James et al., 2016). In addition, the degradation of administered sucrose releases fructose, which also accentuates this

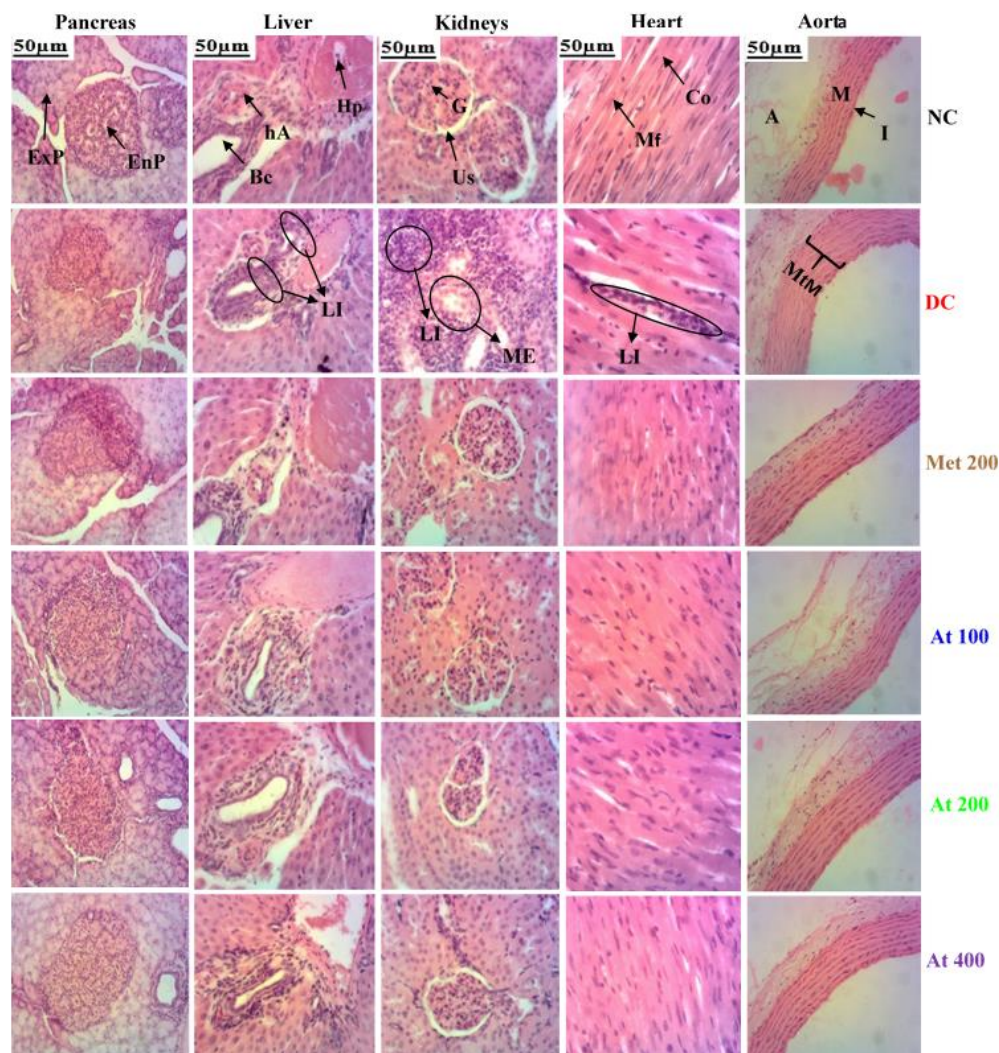


Figure 6. Photomicrographs showing the structure of the pancreas, liver, kidney, heart, and aorta of type 2 diabetic rats treated with *A. thomsonii* leaves aqueous extract. NC: Normal control, DC: diabetic control, Met 200: metformin 200 mg/kg, at (100, 200 and 400 mg/kg): *A. thomsonii* aqueous extract at the doses indicated, G: glomerulus, Us: urinary space, Co: core, Mf: muscle fiber; A: adventitia, M: media, I: intima, LI: leukocyte infiltration, Mt: media thickness, EXP: exocrine pancreas, EnP: endocrine pancreas, hA: hepatic arterial, Bc: bile canaliculus, Hp: hepatic portal vein, and ME: mesangial expansion.

these insulin-resistant rats caused chronic hyperglycemia (El-Emam et al., 2024). The improvement in insulin sensitivity and blood sugar levels of rats following treatment with *A. thomsonii* extract justifies the beneficial effects of the secondary metabolites it contains on the regulation of these parameters. Thus, the improvement in insulin resistance could be explained by the action of alkaloids, flavonoids, and terpenoids contained in *A. thomsonii*, which would have exerted their effects at the peripheral level by stimulating the sensitivity of the membrane receptors of target cells to the action of insulin (Shehadeh et al., 2021). Furthermore, this sensitivity to insulin action would be linked to the effect of

oxoberberine, a bioactive compound found in the leaves of *A. thomsonii* from a study by Nguemdjo et al. (2022). This compound appears to have acted by blocking the activity of tyrosine phosphatase 1B (PTP 1B). Muhammad et al. (2021) showed through an *in vitro* antidiabetic study that oxoberberine from *Berberis brevissima* and *Berberis parkeriana* inhibits the activity of PTP 1B. In addition, this improvement in insulin sensitivity by the plant extract would have caused increased use of glucose by the tissues, thus promoting a reduction in blood sugar. In addition, the reduction in serum levels of α -amylase observed in animals treated with *A. thomsonii* extract would have contributed to the

reduction in blood sugar. This inhibition of α -amylase activity would be linked to the alkaloids contained in *A. thomsonii*. Mohan et al. (2020) showed through an *in vitro* study that alkaloids contained from of *Artabotrys suaveolens* leaves methanolic extract inhibit the activity of this enzyme. Furthermore, the increase in the size of pancreatic β cells following the administration of the plant extract at all doses, as shown by the histopathology of the pancreas, would also have contributed to the improvement in blood sugar levels, thanks to the secretion of insulin in sufficient quantity. This increase in the size of pancreatic cells could be linked to the flavonoids contained in *A. thomsonii*, known for its effectiveness on the regeneration of damaged β cells (Benkhedir, 2023).

During the induction of type 2 diabetes in rats, the administration of fructose/sucrose and STZ induced an increase in body mass compared to normal controls. The increase in body mass would be linked to the obesogenic effects of fructose administered for 3 weeks. Indeed, prolonged administration of fructose and sucrose promotes an increase in fat synthesis in the liver and/or a modification of the structure of the intestine, favoring an increase in calorie absorption, leading to an increase in body mass (Febbraio and Karin, 2021). Administration of the plant extract at doses of 100, 200, and 400 mg/kg did not prevent the increase in body mass of rats from the 8th week until the 11th week of treatment compared to animals of the ED group. This result shows that the extract of *A. thomsonii* at the limit of the doses administered had no effect on the evolution of body mass.

One of the main factors that alters lipid metabolism in the body is insulin resistance (Wu, 2024). The results of this study show the presence of dyslipidemia in diabetic rats characterized by an increase in serum levels of triglyceride, total cholesterol, LDL-cholesterol followed by a decrease in HDL-cholesterol, contributing to a very high risk of developing insulin resistance (AR of at least 4 times normal) and coronary heart disease (AI of at least 7 times normal). Indeed, resistance to the action of insulin in these animals would have led to the activation of the enzyme (hydroxy-methyl-glutaryl coenzyme A reductase (HMG-CoA)) which ensures the synthesis of cholesterol and/or or a deactivation of the enzyme (7- α -hydroxylase) which ensures the reduction of the synthesis and expression of LDL receptors in hepatocytes (Fadhline et al., 2023). The treatment of diabetic rats with the plant extract significantly reduced the serum levels of triglycerides, total cholesterol, LDL cholesterol, and increased the level of HDL cholesterol, thus contributing to the reduction of the atherogenic risk and insulin resistance index compared to diabetic control rats. These beneficial effects of *A. thomsonii* extract on the lipid profile would result from the effectiveness of secondary metabolites (flavonoids and saponins), which, by improving the sensitivity of target tissues to insulin, would

have inhibited lipolysis and/or ameliorated the activity of enzymes involved in lipid metabolism (Arrisson et al., 2018; Sánchez-Velázquez et al., 2023).

Serum ALAT, ASAT, and ALP activity levels were significantly increased in untreated diabetic (DC) rats, indicating impaired liver function and cell necrosis in these animals (Bragança and Agiostra, 2017). Likewise, the decrease in serum levels of total proteins observed in DC rats compared to NC rats would indicate an alteration of hepatic protein metabolism in response to hepatic insulin resistance (Meex and Watt, 2017). These hepatic alterations are confirmed by the histopathology of the liver of DC rats, which presented leukocyte infiltrations indicating inflammation of the hepatocytes. Furthermore, it has been reported that the administration of fructose followed by the injection of STZ in rats causes hepatic lesions with infiltration of fats, with or without cirrhosis, contributing to the increase in ALAT, ASAT and of ALP, followed by a decrease in serum total protein levels (Yustisia et al., 2022). The extract of *A. thomsonii* administered at all doses (100, 200 and 400 mg/kg) in diabetic rats for 28 days significantly reduced the activity of ASAT, ALAT, ALP, significantly increased the serum total protein levels followed by restoration of normal liver structure (without leukocyte infiltration) compared to diabetic control rats. The decrease in the activities of these enzymes (ALAT, ASAT and ALP) shows that *A. thomsonii* contains secondary metabolites such as flavonoid compounds, which would have prevented damage and infiltration of fats into liver tissues (Bensaad et al., 2021). Similarly, Ulrich et al. (2016) showed that secondary metabolites, namely flavonoids contained in the *M. lucia* aqueous extract, protect the liver of rats intoxicated by STZ. The increase in protein levels would be due to the restoration of liver integrity and/or the improvement of insulin sensitivity, initiated by the *A. thomsonii* extract (Raghu et al., 2016).

The significant increase in urea levels and serum creatinine observed in diabetic control rats compared to normal control rats reflects an impairment of renal function (Lora, 2020). Furthermore, the kidney damage is visibly observed thanks to renal histopathology, which showed leukocyte infiltration and mesangial expansion induced by fructose/sucrose and STZ in DC rats compared to NC rats. It was reported by Aouadi et al. (2024) that chronic kidney damage results in increased serum creatinine and urea levels. The hypercreatininemia and hyperuremia that were observed in diabetic animals could be explained by the fact that chronic hyperglycemia would have activated the overproduction of reactive oxygen and nitrogen species, which would have triggered an inflammatory cascade leading to kidney damage (Zaaba et al., 2023). Administration of *A. thomsonii* extract at all doses improved serum levels of creatinine, urea, and prevented renal tissue alterations in treated diabetic rats compared to DC rats. The different compounds (flavonoids, saponins, and tannins) present

in the plant extract would have improved these parameters by protecting the integrity of the kidney, in particular by a reduction in the necrosis of renal cells linked to a reduction in blood sugar and the inflammation of kidney (Moin et al., 2023).

Administration of diabetogenic substances (fructose/sucrose and STZ) induced a significant decrease in tissue levels of cardiac and aortic NO in DC rats compared to NC rats. This reduction in tissue levels of NO indicates an alteration and dysfunction of the cardiac and aortic endothelium. Indeed, it is known that high fructose consumption contributes to elevated serum uric acid levels, which promote severe endothelial dysfunction leading to a crucial decrease in NO bioavailability (Mehmood et al., 2020). However, the increase in tissue NO levels following administration of *A. thomsonii* aqueous extract would suggest that the latter, through its bioactive compounds, would have improved insulin sensitivity, which would have favored the protection of the endothelium of the organs. In fact, oxoberberine was found in the leaves of *A. thomsonii* by Nguemdjo et al. (2022) and has been reported to stimulate the synthesis of nitric oxide synthase (NOS) (An et al., 2022). Likewise, oxodiscretamine (a compound probably contained in *A. thomsonii*) (Nguemdjo et al., 2022) stimulates endothelial NO production in hypertensive rats (Silva et al., 2009).

The tissue and biochemical alterations that occur during type 2 diabetes favor the development of arterial hypertension (Hashimoto et al., 2020). In this study, the administration of fructose/sucrose and STZ in diabetic rats induced a significant increase in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR), compared to NC rats. In addition, the histopathology of the organs of these hypertensive diabetic animals showed leukocyte infiltration in the heart and an increase in the thickness of the media of the aorta. In general, chronic hyperglycemia, hyperlipidemia, tissue, and histopathological alterations contributed significantly to the development of arterial hypertension. According to studies conducted by Jia and Sowers (2021), diabetic hypertension occurs as a result of inappropriate activation of the renin-angiotensin system, activation of the oxidative stress pathway, and inflammation pathway through insulin resistance and chronic hyperglycemia. To this end, inappropriate activation of the renin-angiotensin-aldosterone system promotes an increase in serine phosphorylation of insulin receptor substrate proteins by angiotensin II and aldosterone, which will decrease the activity of insulin signaling pathways and participate in the reduction of the activation of eNOS (endothelial nitric oxide synthase) by insulin, which will reduce vasodilation mediated by NO and promote an increase blood pressure (Brosolo et al., 2022). Moreover, the kidney and the heart, being organs that contribute to the regulation of arterial pressure and heart rate, the leukocyte infiltrations observed at the level

of the latter mark an inflammatory state that would have disrupted the homeostasis of the hemodynamic parameters. Furthermore, arterial hypertension and tachycardia could result from macroangiopathy linked to dyslipidemia. Indeed, hyperglycemia promotes the activation of pathways producing toxic substances that alter vascular lipid transporters (lipoproteins), which could initiate the development of atherosclerosis (Morin et al., 2019). Furthermore, the thickening of the media of the aorta observed in diabetic rats refers to hypertrophy and/or hyperplasia of the smooth muscle fibers that constitute this layer. Moreover, according to Boucly (2021), hyperplasia and hypertrophy of the media could promote the reduction of the vessel lumen, increase peripheral resistance, and lead to an increase in heart rate and blood pressure. Administration of *A. thomsonii* leaves aqueous extract at all doses improved systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, and aortic histopathologies in milked rats compared to DC rats. The beneficial pharmacological effects of the plant extract reported above on insulin sensitivity, glycemia, lipidemia, and organ histopathology would have contributed to the improvement of hemodynamic parameters (Serreli and Deiana, 2023). Additionally, Silva et al. (2009) showed that oxodiscretamine (a compound probably contained in *A. thomsonii*) (Chimeze et al., 2022), through its vasorelaxant and NOS stimulatory effects, reduces the blood pressure of hypertensive rats induced by the administration of L-NAME. Furthermore, the lipid profile and the atherogenic index improved following the administration of *A. thomsonii* extract at all doses would have contributed to the restoration of the hemodynamic parameters of type 2 diabetic rats. This would be linked to its possible antihyperglycemic and anti-inflammatory properties, which would have prevented the oxidation and stagnation of vascular free fatty acids, thus limiting the risks of formation of atheromatous plaques (Zhang et al., 2023). The absence of leukocyte infiltration in the kidney and heart of diabetic rats justifies the anti-inflammatory effects of *A. thomsonii* extract with respect to the organs involved in the regulation of hemodynamic parameters. This suggests the cardioprotective and nephroprotective effects of the plant extract.

Conclusion

Aqueous leaf extract of *A. thomsonii* administered at doses of 100, 200, and 400 mg/kg can have beneficial effects on insulin sensitivity, blood glucose, lipidemia, proteinemia, blood pressure, heart rate, tissue alterations, and histopathology in fructose/sucrose/STZ-induced type 2 diabetic rats. It may be useful for oral treatment, as an alternative to hypertension in type 2 diabetics. However, it would be important to evaluate the effects of extracts and secondary metabolites on key enzymes or target

proteins of type 2 diabetes and hypertension to elucidate the modes of action or mechanisms of action of the bioactive metabolites.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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