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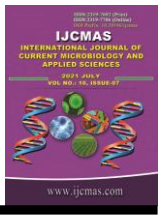

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Type 1 diabetes mellitus: therapeutic correction trial with the aqueous extract of the leaves of *Tapinanthus dodoneifolius* (Loranthaceae)

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A B S T R A C T

Tapinanthus dodoneifolius (Loranthaceae) is an epiphytic parasitic plant used in the treatment of cholera, asthma, hypertension, and diabetes. The general objective of this study was to evaluate the antidiabetic properties of the aqueous extract of the leaves of *T. dodoneifolius* (Loranthaceae) in the Wistar rat. Type 1 diabetes was induced by intraperitoneal injection of streptozotocin into the single dose of 60 mg/kg. Seventy-two hours later, rats with blood glucose ≥ 200 mg/dL were selected and treated for 28 days with distilled water, glibenclamide (3 mg/kg) and aqueous extract of *T.dodoneifolius* at doses of 125, 250 and 500 mg/kg. Body weight, blood sugar, and food and water intake were measured during treatment. At the end of treatment, serum insulin level, lipid profile and oxidative stress parameters were assessed. Results showed that administration of the extract of *T. dodoneifolius* leaves at doses of 250 and / or 500 mg/kg prevented drastic loss of body weight and reduced food and water consumption in diabetic rats. Blood glucose, TC, TG, LDL-c, and MDA were also reduced and HDL-c, GSH, and CAT and SOD activity increased after administration of the extract of *T. dodoneifolius* (250 and 500 mg/kg) in diabetic rats. At the end of this work, it appears that the aqueous extract of the leaves of *T. dodoneifolius* has anti-diabetic, lipid-lowering, and antioxidant properties, thus supporting the use of this plant by traditional healers for the treatment of diabetes and some of its complications.

Introduction

Diabetes mellitus is a chronic metabolic disease that occurs when fasting glycaemia greater than or equal to 126 mg/mL (American Diabetes Association, 2010). It represents a real public health problem in the world. In fact, more than 425 million people suffered from diabetes in 2017 (ADA, 2010). This number is projected to almost double by 2030 (International Diabetes Federation, 2019). According to estimates by the World Health

Organization, diabetes could become the seventh leading cause of death in the world by 2030. Type 1 diabetes is characterized by the destruction of the ß cells in the pancreas that produce insulin. It most often occurs before the age of 20 and accounts for 10 to 15% of diabetes mellitus. Uncontrolled permanent hyperglycemia can lead to long-term production of reactive oxygen species and damage to organs such as the eyes, nerves, kidneys and blood vessels (Standards of Medical Care in Diabetes, 2016).

The treatment of diabetes is based on strict diet, oral medication, and daily injection of insulin.

Daily injections of insulin requires a large financial means. Moreover, the choice of oral antidiabetic drugs depends on the patient's profile, lifestyle, level of glycemic control, access to medication and economic status. Due to these many limitations, the potential of natural products for the treatment of metabolic syndrome-related disorders is under exploration. Numerous plant extracts have been used in traditional folk medicine to treat hyperglycemia Efuntoye *et al.,* 2010). *Tapinanthus dodoneifolius* DC Danser (Loranthaceae) is extensively used as medicinal plant in traditional medicine in Africa in the treatment of malaria, hypertension, cholera, asthma, epilepsy, cancer, and diabetes (Ekhaise *et al.,* 2010 ; Nasri and Rafieian-Kopaei, 2014). Phytochemical screening showed the presence of anthraquinones, saponins, flavonoids, alkaloids, and tannins from *Tapinanthus dodoneifolius*(Deeni and Sadiq, 2002 ; Ekhaise *et al.,* 2010 ; Baso and Mudi, 2017). However, very limited information is available on *in vivo* antidiabetic, antidyslipidaemic, antioxidant activities of *T. dodoneifolius*.Thus, the aim of this study was to contribute to the valuation of *T. dodoneifolius*in the treatment of diabetes mellitus and its complications.

Materials and Methods

Chemicals and reagents

Glibenclamide, metformin, potassium dichromate, ketamine and diazepam were bought at the pharmacy in the Far North region, Cameroon. Streptozotocin, rat insulin ELISA and biochemical kits were purchased from Sigma-Aldrich, Saint. Louis, USA.D-glucose and sodium chloride were purchased from Edu-Lab Biology Kit, Bexwell, Norfolk PE38 9GA, UK. All chemicals and drugs were obtained commercially in analytical grade.

Harvest and identification of plant material

Fresh leaves of *Tapinanthus dodoneifolius* were collected from Kaélé, Cameroon, in July 2018. A sample of the plant has been identified and authenticated in the National Herbarium of Cameroon under the number 6925NHC. Subsequently, the collected leaves were washed with tap water, dried at room temperature, and then crushed to obtain the powder.

Preparation of the extract

Seventy five gram (75) of powder of *T. dodoneifolius* were introduced into 500 mL of distilled water previously brought to the boil. After 30 min, the resulting infusion was filtered using No. 1 filter paper and the filtrate was evaporated in an oven at 45 ° C for 48 hours. This allowed us to obtain 13.6 g of crude extract with an extraction yield of 4.53%.

Phytochemical screening

Phytochemical screening was carried out for aqueous extract of *T. dodoneifolius* leaves using standard procedures to determine the presence of phenols, flavonoids, tannins, alkaloids, anthraquinones, terpenoids,

saponins, glycosides, alkaloids, and steroids (Pandey and Tripathi, 2014).

Animal material

Male albino Wistar rats aged 8 to 12 weeks and weighing between 150 g and 250 g were used in the experiment. They were provided by the animal house of the Department of Biological Sciences at the University of Ngaoundere (Cameroon).

All the animals were placed in polypropylene cages at room temperature with a 12/12 h cycle (light/dark). They had free access to water and standard diet. They were acclimatized for 1 week prior to experimentation. The experimental protocols were conducted in accordance with internationally accepted principles for laboratory animal use and were approved the Institutional Animal Ethics Committee (IAEC).

Induction of diabetes

After a 24-hour non-water fast, diabetes was induced in rats by the intraperitoneal injection of a single dose (55 mg/kg body weight) of streptozotocin diluted in citrate buffer (0.1 mol/L, pH 4.5).One hour after, all animals received oral D-glucose solution (5%) to avoid hypoglycemic shock. Seventy-two hours (72 h) after induction, their blood glucose was taken at the tail vein using test strips and glucometer (One Touch Ultra Easy) for blood glucose testing. Rats with fasting glucose greater than or equal to 126 mg/dL were considered diabetic and used for the experiment (Miaffo *et al.,* 2019).

Distribution and treatment of animals

Thirty (30) rats were randomly divided into 6 groups of 5 rats each. These rats received the various treatments for 28 days as follows:

Group 1 (normal control) received 10 mL/kg bw of distilled water *per os*;

Group 2 (diabetic control) received 10 mL/kg bw of distilled water *per os*;

Group 3 (standard control) received 3 mg/kg bw of the glibenclamide *per os*;

Groups 4, 5 and 6 received the extract at the respective doses of 125, 250, and 500 mg/kg bw *per os*.

Fasting blood glucose, body weight, food and water intake were assessed on days 0, 7, 14, 21, and 28 of treatment.

Collection of blood and organs

At the end of the treatment period, the animals were fasted for 24 hours with free access to water. Then they were anesthetized by an intraperitoneal injection of the combination of ketamine (50 mg/kg) and diazepam (10 mg/kg).The abdominal cavity was opened and blood was collected in tubes without anticoagulant and centrifuged at 3000 rpm for 20 min at 4 ° C. The supernatant obtained was taken and stored at -20 °C for the assay of the biochemical parameters. After collecting the blood samples, the pancreas was removed and stored in 10% formalin for histological section.

Assessment of biochemical parameters

Blood glucose level was measured using a glucometer (One Touch Ultra Mini) and strips. Serum insulin was determined according to the enzyme-linked immuno-sorbent (ELISA) method using a commercial kit. Total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), malondialdehyde (MDA), glutathion (GSH), and superoxide dismutase (SOD) and catalase

(CAT) activities were determined in serum using standard kits.

Histological analysis of the pancreas

Pancreas were fixed in 10% formalin and embedded in paraffin. The paraffin-embedded tissue specimens were sliced into 4 mm thickness sections, which were stained with hematoxylin and eosin (H&E, 100x) and examined using a light microscope (Scientico STM-50).

Statistical analysis

All results were expressed as mean ± SEM (Standard Error of Mean). Statistical analyses were evaluated by one-way ANOVA followed by Turkey posttest using Graph Pad Prism Software Version 5.0. Statistical significance was accepted at $p < 0.05$.

Results and Discussion

Phytochemical screening

Qualitative phytochemical analysis indicated the presence of flavonoids, saponins, phenols, tannins, terpenoids, glycosides, and anthraquinones and the absence of absence of alkaloids and steroids in the aqueous extract of *T. dodoneifolius* (Table 1).

Body weight, food and water consumption

Figure 1 shows the effects of the different treatments on the body weight (A), food consumption (B) and water intake (C) of rats treated with the aqueous extract of *T. Dodoneifolius* leaves for 28 days. It emerges from this figure that the body weight of the rats of the diabetic control group significantly decreased on days 14 ($p < 0.05$), 21 ($p < 0.01$), and 28 ($p < 0.001$) of the treatment, in comparison with that of the normal control group. However, compared to the diabetic control group, a significant increase in body weight was observed in rats treated at the dose of 500 mg/kg of extract on days 21 ($p < 0.05$) and 28 ($p < 0.01$).Likewise, on day 28 of the experiment, body weight significantly increased ($p < 0.05$) in animals receiving glibenclamide and the extract at the dose of 250 mg/kg.

Rats in the diabetic control group exhibited significantly elevated food consumption on the 21st ($p < 0.05$) and 28th ($p <0.01$) day of treatment, compared to the normal control group. Compared to untreated diabetic animals, rats given glibenclamide and doses of 125 and 250 mg/kg of extract showed no significant difference in food consumption throughout the treatment. In contrast, a significant decrease ($p < 0.05$) in food consumption was noted in animals treated with the extract at a dose of 500 mg/kg at the last week of treatment (Figure 1).

Water consumption significantly increased in the diabetic control group rats on days 7 ($p <0.05$), 14 ($p <0.01$), 21 ($p <0.001$) and 28 ($p <0.001$) of treatment, compared to that of the normal control group. Compared to the diabetic control group, on the 28th day of treatment, a significant decrease ($p <0.01$) in water consumption was noted with glibenclamide. Doses of 250 and 500 mg/kg of extract induced a significant decrease in water intake on days 14 ($p <0.05$), 21 ($p <0.01$), and 28 ($p<0.01$) of treatment (Figure 1).

Fasting blood glucose and fasting serum insulin

On the first day of treatment, the blood glucose level of all animals receiving gliben clamide and *T. dodoneifolius* extract significantly ($p < 0.001$) increased, compared to the normal control group (Figure 2). During the 28 days of treatment, the blood glucose level of diabetic control group animals

significantly ($p < 0.001$) remained high, compared with that of the rats of the normal control group. However, compared to the diabetic control group, the blood glucose level significantly decreased with glibenclamide ($p < 0.01$) and the extract at doses of 250 ($p < 0.05$) and 500 mg/kg ($p<0.05$) on day 7 of treatment. In addition, from the 14th to 28th day, glibenclamide and the different doses of the extract caused a significant ($p <0.001$) drop in blood glucose in the animals.

The effect of the aqueous extract of the leaves of *T. dodoneifolius* on the blood insulin level of diabetic rats shows a significant ($p < 0.001$) decrease in insulinemia in untreated diabetic rats, compared to the normal control group (Figure 2).However, compared to the diabetic control group, the insulin level significantly increased in the animals receiving glibenclamide ($p < 0.01$) and the extract at doses of 250 ($p < 0.05$) and 500 mg/kg ($p < 0.05$).Furthermore, no significant difference in insulin level was noted at the dose of 125 mg/kg of extract.

Lipid parameters

Table 1 shows the effect of *T. dodoneifolius* extract on the lipid parameters of diabetic rats. In fact, the level of total cholesterol, triglycerides and LDL cholesterol significantly ($p < 0.001$) increased in the animals of the diabetic control group, compared to the normal control group. On the other hand, the HDL cholesterol level significantly ($p < 0.05$) decreased in the animals of the diabetic control group.

However, the extract at doses of 125 and 250 mg/kg caused a significant decrease ($p < 0.05$) in cholesterol level, compared to the diabetic control group. This decrease was greater ($p < 0.001$) with glibenclamide and the dose of 500 mg/kg of extract (Table 2). A significant decrease ($p < 0.05$) in triglyceride level was observed in animals given glibenclamide and the dose of 125 mg/kg extract. This decrease was greater ($p < 0.01$) with doses of 250 and 500 mg/kg of extract. Furthermore, glibenclamide and *T. dodoneifolius* extract at doses of 250 and 500 mg/kg resulted in a significant decrease ($p < 0.001$) in LDL cholesterol level, compared to the diabetic control group. This decrease was less significant ($p < 0.05$) with the dose of 125 mg/kg. In contrast, there was a significant increase ($p < 0.05$) in HDL cholesterol level in rats treated with glibenclamide and the extract at doses of 250 and 500 mg/kg. Furthermore, no significant difference in HDL cholesterol was noted at the dose of 125 mg/kg (Table 2).

Oxidative stress parameters

Table 3 shows the effect of the aqueous extract of the leaves of *T. dodoneifolius* on the level of MDA, GSH, and CAT and SOD activity in rats. It emerges from this study that the rats of the diabetic control group showed a significantly ($p <0.001$) high level of MDA, and a significantly ($p < 0.001$) low level of GSH and the activity of CAT and SOD, compared to the normal control group.

However, it was observed that the MDA level significantly decreased ($p < 0.001$) in the rats receiving glibenclamide and the doses of 250 and 500 mg/kg of extract. Likewise, the dose of 125 mg/kg of extract induced a significant decrease ($p < 0.01$) in MDA level. In contrast, the rats treated with glibenclamide and the extract at doses of 250 and 500 mg / kg showed a significantly $p < 0.01$) elevated level of GSH, compared to the diabetic control group. The level of GSH did not change significantly in rats treated at the dose of 125 mg/kg (Table 3). A significant increase in CAT activity was also noted with glibenclamide ($p < 0.05$) and the extract at doses of 250 ($p < 0.05$) and 500 mg/kg ($p < 0.01$), compared to the diabetic control group.

It was also noted that there is no significant difference in the activity of catalase between the animals receiving the dose of 125 mg/kg and those of the diabetic control group (Table 3). A significant increase ($p < 0.05$) in SOD activity was observed in rats treated with glibenclamide and at doses of 125 and 250 mg/kg of extract, compared to the diabetic control group. This increase was greater ($p < 0.01$) at the dose of 500 mg/kg of extract.

Histological sections of pancreas tissue

Figure 3 represents the histological section of the pancreas of diabetic rats. It emerges from this figure that the rats of the normal control group show a normal architecture of the pancreas (endocrine pancreas, well-differentiated exocrine pancreas and well-developed pancreatic islands). On the other hand, in the rats of the diabetic control group, a reduction in the size of the islets of the pancreas was observed. Administration of the extract and glibenclamide prevented destruction of the islets of Langerhans in the pancreas.

Plants are important sources of chemical compounds, some of which can influence carbohydrate metabolism (Amiri *et al.,* 2015).Certain secondary metabolites of plant origin have hypoglycaemic, lipid-lowering and antioxidant properties (Amiri *et al.,* 2015). In the present work, phytochemical studies revealed the presence of chemical compounds such as polyphenols, tannins, saponins, flavonoids, triterpenes, glycosides, and anthraquinones in the aqueous extract of the leaves of *T. dodoneifolis*. Some of these compounds such as terpenoids, polyphenols, saponins, and flavonoids are known for their ability to lower blood sugar by inhibiting glucose transporters and the activity of alpha-glucosidase enzymes (Fontana *et al.,* 2011). Saponins also act as antihyperlipidemic, antioxidants, and cardioprotectors agents (Hooper *et al.,* 2008). The possible pharmacological effects obtained in the present study would be partly due to these bioactive molecules contained in the aqueous extract of *T. dodoneifolius* leaves.

One of the main characteristics of type 1 diabetes is severe loss of body mass (Oliveira *et al.,* 2013). In the present study, significant loss of body weight was noted in untreated diabetic rats. This drastic weight loss is probably due to an insulin deficiency which leads to a decrease in the absorption of amino acids by the tissues with a consequent reduction in protein synthesis. Moreover, numerous studies suggest that the loss of body weight in diabetics can be explained by an increase in lipid and protein catabolism due to carbohydrate deficiency (Sathishsekar and Subramanian, 2005). In contrast, in the treated diabetic groups, administration by gavage of glibenclamide and the aqueous extract at daily doses of 250 and 500 mg/kg for 4 weeks resulted in an increase in the body weight of the animals. The ability of the extract to protect diabetic rats from weight loss appears to be due to its ability to lower blood sugar as well as its protective effect on protein turnover and / or amelioration of disorders associated with diabetes mellitus (Balamurugan *et al.,* 2014).

Polyphagia and polydipsia are symptoms of diabetes mellitus that are caused by insulin deficiency or lack of insulin use by target organs. These parameters essentially inform us about the reestablishment of insulin secretion as well as the degree of glucose utilization by the cells Rodríguez *et al.,* 1997). In the present study, a significant increase in food and water intake was noted in untreated diabetic animals. The exaggeration of food consumption indicates that the body cannot use glucose, although it is abundantly provided that it draws on its reserves of lipids and proteins for its energy metabolism (Sami *et al.,* 2017). The

increased water intake in diabetics is caused by high blood sugar overflowing into the urine resulting in dehydration. In contrast, administration of glibenclamide and *T. dodoneifolius* extract at doses of 250 and / or 500 mg/kg resulted in reduced food and water consumption in diabetic rats. The decrease in food and water intake in the groups treated with the extract could be due to the drop in blood sugar observed in these groups, which could indicate the insulinomimetic or insulin-secreting action of the extract of *T. dodoneifolius* (Muniappan *et al.*, 2014).

The two pathophysiologies of diabetes mellitus are insulin deficiency and insulin resistance. The administration of streptozotocin causes partial destruction of pancreatic β cells and therefore a decrease in serum insulin level. In fact, diabetogenic agents have a pathological effect interfering with the physiological function of the β cells of the pancreas; they lead to selective destruction of these cells, thus inducing chronic hyperglycemia (Szkudelski, 2001).

The present study indicates that oral administration of the extract at doses of 250 and 500 mg/kg to diabetic rats resulted in a significant decrease in blood glucose level, and an increase in insulin level as did glibenclamide. These results are attributable to the chemical compounds (flavonoids, phenols, and glycosides) present in the extract, which have the ability to mimic the action of insulin or to stimulate its secretion by the β cells of the islets of Langerhans (Tanko *et al.*, 2008; Khurshid Alam *et al.*, 2018). Another possible mechanism of action of the extract is the regeneration of pancreatic β cells. This is further confirmed by the results of histological sections of the pancreas which showed an increase in the number and size of the islets of Langerhans after administration of the aqueous extract of the leaves of *T. dodoneifolius*.

Diabetes mellitus is also associated with hyperlipidemia which causes profound disturbances in the concentration and composition of lipids and lipoproteins.

These abnormalities represent an important risk factor for cardiovascular disease (Woo *et al.*, 2008). Hyperlipidemia is a recognized complication of diabetes mellitus characterized by high concentrations of TC, TG, and phospholipids and changes in the composition of the lipoprotein (Ravi*et al.*, 2005). In the present study, a significant increase in TC, TG and LDL-c was observed, and a significant decrease in HDL-c in diabetic animals. In contrast, in animals treated with glibenclamide and extract of *T. dodoneifolius* (125, 250, and 500 mg/kg), a significant decrease in the level of TC, TG, and LDL-cand an increase HDL-c level was observed, compared to diabetic control groups.

These results are similar to those obtained by Miaffo *et al.*, (2014) with *Combretum molle*. The extract of *T. dodoneifolius* is said to have either mimicked the action of insulin in adipose tissue or to stimulate its secretion in the pancreas. It probably works by decreasing the biosynthesis of cholesterol specifically by decreasing the activity of the enzyme 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMG-CoA reductase). In addition, the extract would have reduced the level of serum triglycerides by decreasing the synthesis of fatty acids, increasing the catabolism of LDL and producing triglyceride precursors such as acetyl-CoA and glycerol phosphate (Eddouk**s** *et al.*, 2005). Limaye *et al.*, (2003) have shown that secondary metabolites such as flavonoids, saponins, and phenols have lipid-lowering activity. The observed antidyslipidemic effect could be due to the presence of these classes of chemical compounds in the aqueous extract of the leaves of *T. dodoneifolius*.

Table.1 Chemical compounds present in the aqueous extract of the leaves of *Tapinanthus dodoneifolius*

Chemical compounds	Extract
Flavonoids	+
Phenols	+
Tannins	+
Saponins	+
Alkaloids	-
Terpenoids	+
Glycosides	+
Steroids	-
Anthraquinones	+

+ : present - : absent

Table.2 Effects of aqueous extract of *T. dodoneifolius* leaves on lipid parameters in rats

Groups	Dose (mg/kg)	CT (mg/dL)	TG (mg/dL)	HDL-c (mg/dL)	LDL-c (mg/dL)
Normal control	-	89.78 ± 4.37	78.37 ± 5.76	38.22 ± 2.39	55.89 ± 2.28
Diabetic control	-	133.64±6.24***	113.27±5.54***	23.35±0.64*	104.64±6.15***
Glibenclamide	10	100.20 ± 4.77c	84.39 ± 7.06a	28.52 ± 1.20	69.80 ± 4.43c
Extract	125	110.62 ± 3.63a	86.94 ± 5.25a	30.87 ± 1.01a	82.35 ± 4.37a
	250	108.55 3.64a	81.63 ± 5.08b	33.69 ± 1.35a	27.71 ± 5.85c
	500	91.67 ± 5.29c	79.62 ± 4.46b	35.26 ± 1.20a	13.77 ± 1.10c

Each value represents the mean ± SEM; n = 5. **p < 0.01; *** p < 0.001 statistically significant difference from the normal control group. ap < 0.05; bp < 0.01; cp < 0.001 statistically significant compared to the diabetic control. CT: total cholesterol, TG: triglycerides, HDL-c: High density lipoprotein cholesterol, LDL-c: Low density lipoprotein cholesterol.

Table.3 Effects of aqueous extract of *T. dodoneifolius* leaves on antioxidant parameters in rats

Groups	Dose (mg/kg)	MDA (mg/dL)	GSH (mg/dL)	CAT (mg/dL)	SOD (mg/dL)
Normal control	-	7.54 ± 0.59	11.54 ± 1.12	15.56 ± 1.34	21.70 ± 2.11
Diabetic control	-	17.82 ± 1.59***	5.46 ± 0.75**	6.42 ± 0.82***	9.98 ± 0.92***
Glibenclamide	3	9.96 ± 0.83c	9.96 ± 0.73a	13.26 ± 1.40a	16.61 ± 1.99a
Extract	125	11.36 ± 1.37b	7.06 ± 0.84	9.92 ± 0.89	17.26 ± 0.52a
	250	9.61 ± 1.04c	10.66 ± 1.27a	12.52 ± 1.07a	16.28 ± 0.60a
	500	8.50 ± 0.68c	10.28 ± 1.18a	14.90 ± 1.50b	18.36 ± 1.04b

Each value represents the mean ± SEM; n = 5. **p < 0.01; *** p < 0.001 statistically significant difference from the normal control group. ap < 0.05; bp < 0.01; cp < 0.001 statistically significant compared to the diabetic control
MDA : malondialdehyde, SOD : superoxyde dismutase, CAT : catalase, GSH :reduced glutathion.

Fig.1

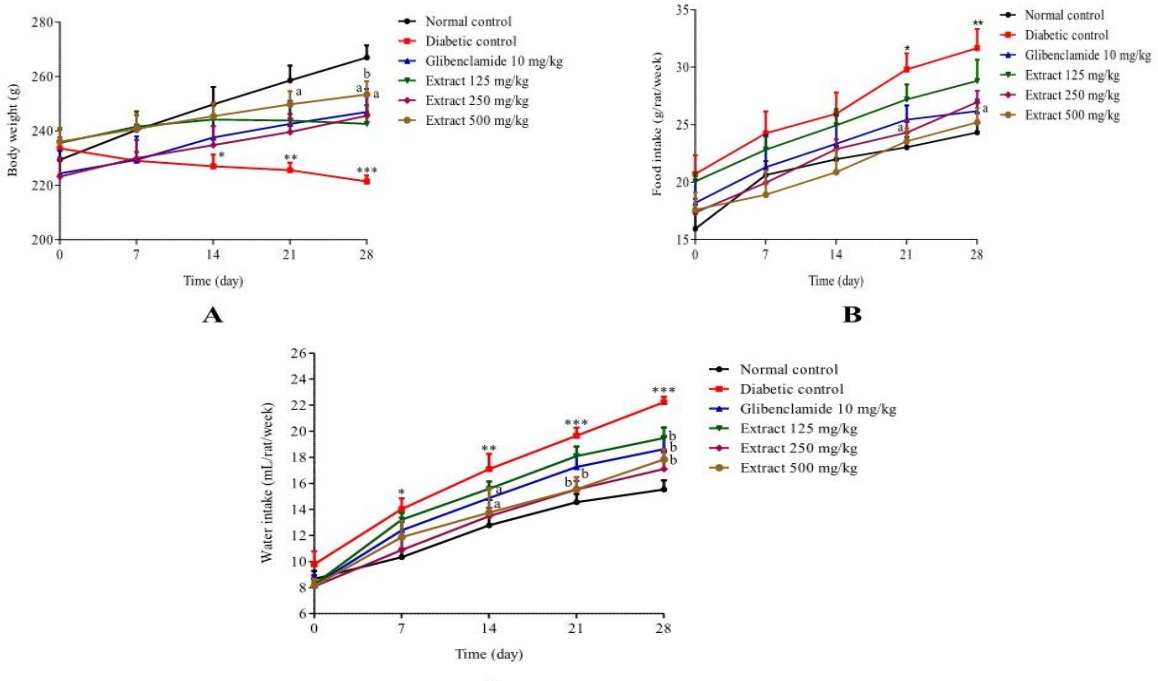

Fig.1 Effects of aqueous extract of *T. dodoneifolius* leaves on body weight (A), food consumption (B), and water intake (C) in animals. Each value represents mean ± SEM, n = 5. Data analysis was performed by two-way ANOVA followed by Bonferroni's post-hoc test. *P < 0.05; **P < 0.01; ***P < 0.001 compared to the normal control. ap < 0.05; bp < 0.01 compared to the diabetic control.

Fig.2

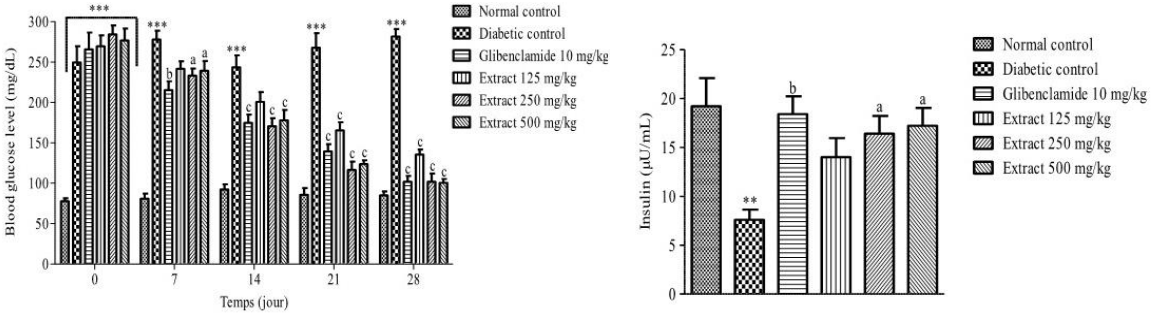

Fig.2 Effects of aqueous extract of *T. dodoneifolius* leaves on blood glucose level (A) and insulin level (B) in rats. Each value represents mean ± SEM, n = 5. Data analysis was performed by two-way ANOVA followed by Bonferroni's post-hoc test. ***p < 0.001; **p < 0.01 compared to the normal control. ap < 0.05; bp < 0.01; cp < 0.001 compared to the diabetic control.

Fig.3

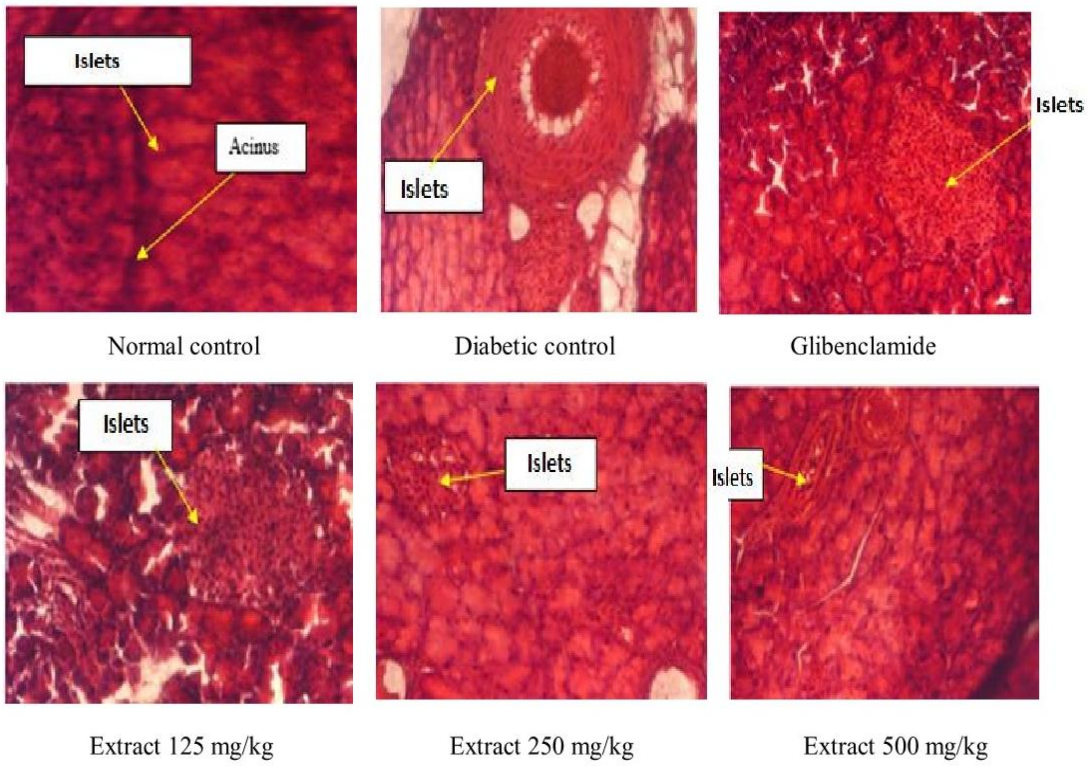

Fig.3 Effects of of aqueous extract of *T. dodoneifolius* leaves on pancreas histology.

Several studies have shown that oxidative stress plays an important role in the progressive development of diabetes and its complications (Kumar *et al.*, 2004). In the diabetic state, free radical generation can occur via increased glycolysis, intercellular activation of the polyol pathway, auto-oxidation of glucose, and glycation of non-enzymatic proteins (Sharma *et al.*, (2008). We noticed an increase in the level of MDA, and a decrease in the activity of antioxidant enzymes (CAT and SOD) and the concentration of GSH in diabetic rats. However, glibenclamide and / or the aqueous extract of *T. dodoneifolius* caused a decrease in the level of MDA and an increase in the activity of CAT, SOD, and the level of GSH. These results are similar to those of Webo *et al.*, (2019) and Mahamad *et al.*, (2020) with *Baillonella toxisperma* and *Cissus polyantha*, respectively. The extract is said to have prevented oxidative damage by scavenging and scavenging free radicals in order to restore the antioxidant parameters disrupted by streptozotocin. According to Patel *et al.*, (2014)and Abdelaziz *et al.*,(2015), phenols and flavonoids possess the antioxidant potential via their reducing power or their potential for donating or transferring electrons or hydrogen.

The oral administration of aqueous extract of *T. dodoneifolius*leaves in rats possess the hypoglycaemic and hypolipidemic effects, and protect tissues against damage induced by oxidative stress. These different pharmacological properties are thought to be due to the phytoconstituents presents in the extract. This study provides evidence for the ethnobotanical use of *T. dodoneifolius* extract as a treatment for diabetes mellitus.

To complete this work, more in-depth and detailed studies will be performed later to isolate and identify the main active compounds and their mechanisms of action.

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