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RESEARCH ARTICLE

Effect of *Terebinthus atlanticus* on Glucose Metabolism in Diabetic Rats

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ARTICLE HISTORY

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Abstract: ***Background*:** *Terebinthus atlanticus* (Anacardiaceae) is an important source of essential oil and phenolic compounds justifying its use in traditional medicine.

***Objective*:** The present work aimed to evaluate the antidiabetic and the antioxidant activities of the aqueous extract of the leaves of *Terebinthus atlanticus (T. atlanticus).*

***Methods*:** The current study evaluated the effect of a single and repeated (15 days of treatment) oral administration of the aqueous extract of the leaves of *T. atlanticus* (PALAE) on blood glucose levels in normal and streptozotocin(STZ)-induced diabetic rats. Furthermore, the effect of PALAE on glucose tolerance and histopathological examination of the liver was carried out.

***Results*:** A single oral administration of PALAE reduced blood glucose levels in normal ($p<0.05$), and STZ diabetic rats ($p<0.0001$), 6 and 4 hours after administration, respectively. Furthermore, this extract had an optimal effect ($p<0.0001$) in both normal and STZ diabetic rats at the 15th and 7th day of treatment. This extract was also shown to prevent significantly the increase on blood glucose levels 120 min after glucose administration, in both normal ($p<0.05$), and diabetic ($p<0.01$) treated rats when compared to the control group. In addition, the histopathological analysis highlighted the positive effect of *T. atlanticus* on pancreas and liver.

***Conclusion*:** The study demonstrates the antihyperglycemic effect of the aqueous *T. atlanticus* extracts in diabetic rats which should be mediated through the amelioration of the oxidative stress as well as an improvement in liver histology.

Keywords: Glucose tolerance, histopathological changes, streptozotocin, *T. atlanticus*, diabetes mellitus, gastrointestinal disorders.

1. INTRODUCTION

The WHO estimated that 80% of the population from developing countries rely on traditional medicine for their primary health effects [1, 2]. Diabetes mellitus is a metabolic syndrome affecting carbohydrates proteins and fats assimilation caused by a variable interaction between hereditary and environmental factors [3, 4]. Several medicinal plants and their extracts or different formulations are used for the management of diabetes mellitus. The low incidence of side effects and low cost are considered as major benefits of herbal medicines.

Terebinthus atlanticus, commonly called "*El Betoum*, *Botma"* in Morocco, belongs to the family of Anacardiaceae [5-7]. This tree is an important source of essential oil and phenolic compounds justifying the use of its various parts including oleoresin in traditional medicine as antiseptic and anti-inflammatory agent [8-13]. Indeed, different parts of the *Terebinthus* species including resin, leave, fruit, and aerial parts have widely been used in traditional medicine of many countries for different reasons. According to our ethnobotanical survey in Tafilalet region (Morocco), *Terebinthus atlanticus* is used as a remedy to treat cardiac and gastrointestinal disorders, hair loss and dandruff, kidney disorders, and hypertension [14]. In addition, *Terebinthus atlanticus* has been considered as a cure for diabetes, pains and skin diseases [14]. The extracts of *Terebinthus* species have demonstrated to exhibit anti-atherogenic, hypoglycemic, antioxidant, anti-inflammatory, anti-insect and antimicrobial activities [15-17]. Moreover, it has been proven that some extracts possess stimulant and diuretic properties and they are used as a urinary and respiratory antiseptic [18]. On the other side, Peksel *et al*., (2010), reported the antiacetylcholinesterase and antioxidant activities of extracts of leaves of *Terebinthus atlanticus* [19, 20]. A recent study demonstrated that *T. atlanticus* leaf significantly decreased lipid profile and atherosclerotic biomarkers [21]. Our study is conducted to evaluate

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the antidiabetic effect of *T. atlanticus* leaves aqueous extract (PALAE). In addition, its effect on glucose tolerance and liver histopathological changes, as well as antioxidant potential was evaluated.

2. MATERIAL AND METHODS

2.1. Plant Material

Terebinthus atlanticus specimens were collected from Tafilalet region (a semi-arid area of Morocco) in the period between March and April 2017. The specimens were air-dried at 40°C and placed in the herbarium of the Faculty of Sciences and Techniques at Errachidia.

2.2. The Aqueous Extract

The aqueous substance was prepared as it has been described previously [22-24]. The dose administrated of lyophilized aqueous extract was 50 mg/kg.

2.3. Experimental Animals

The study was performed in adult male Wistar rats weighing about 100 to 150 g kept under usual environmental conditions with full access to water and food.

2.4. Effect of PALAE on Glucose Tolerance in Rats

The glucose tolerance test was performed in normal and diabetic rats as it has been described previously [22-24].

2.5. Antidiabetic Effect of *T. atlanticus*

The study of the antidiabetic effect of PALAE has been performed as it has been described previously [22-24].

2.6. Histopathology

The histological analysis of pancreas and liver has been performed as it has been described previously [22-24].

2.7. Determination of DPPH (1-1-diphenyl 2-picryl hydrazyl) Radical Scavenging Activity

The *in vitro* DPPH radical scavenging activity of the aqueous *T. atlanticus* extract has been performed as it has been described previously [22-24].

2.8. Statistical Analysis

Data were expressed as mean ± S.E.M. Statistical differences among the means studied were assessed by two-way

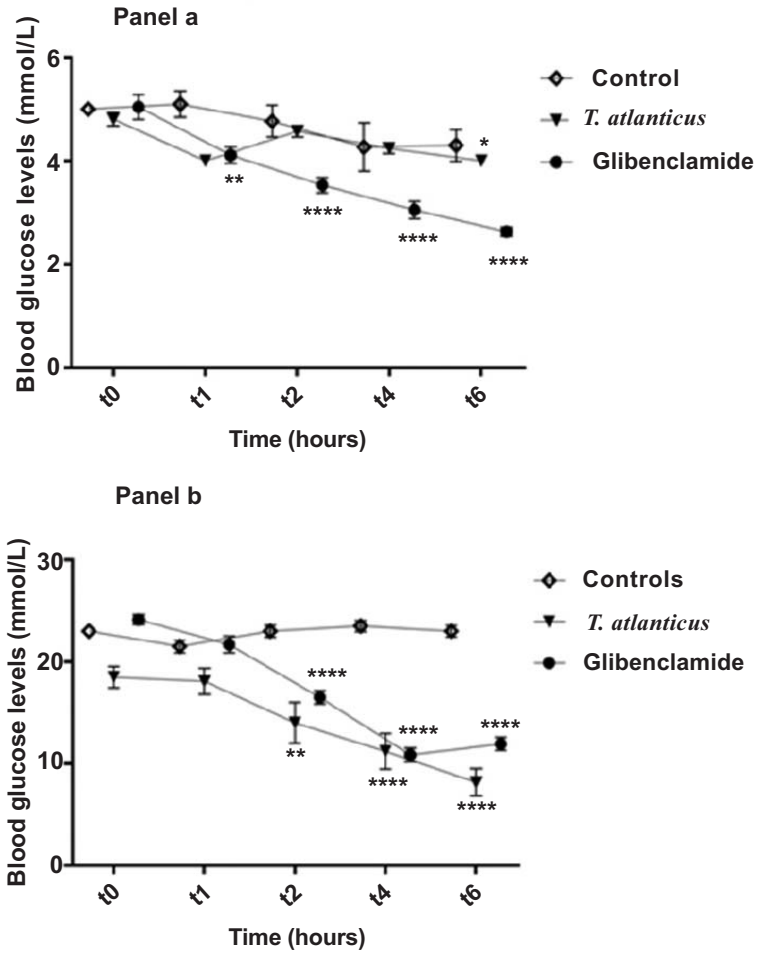

Fig. (1). Plasma glucose levels over 6 h after single oral administration of PALAE (50 mg/kg) in normal (**Panel a**) and diabetic rats (**Panel b**). Data are expressed as means ± SEM, n = 6 rats per group. *p < 0.05; **p < 0.01;***p < 0.001; and ****p < 0.0001 when compared to baseline values.

ANOVA followed by Bonferroni multiple comparisons test with GraphPadPrism 6 software. Differences were considered to be significant when $p<0.05$.

3. RESULTS

3.1. Single Oral Administration

Fig. (**1**) depicts the effect of a single oral administration of PALAE on plasma glucose levels in normal and STZ-induced diabetic rats. In normal rats, a single administration of PALAE (50 mg/kg) caused a significant reduction in blood glucose levels after 6 hours of administration ($p<0.05$). In diabetic rats, a single administration of PALAE caused a significant decrease ($p<0.01$) in blood glucose levels after 2 hours of treatment. This effect was more pronounced at the fourth hour of treatment ($p<0.0001$), and it was maintained until the end of the test ($p<0.0001$). By contrast, a significant decrease ($p<0.01$) in blood glucose levels was reported from the first hour to the sixth hour of treatment ($p<0.0001$) in Glibenclamide-treated normal rats. However, in diabetic rats, Glibenclamide caused a significant reduction in blood glucose levels from the 2nd hour ($p<0.01$) to the 6th hour ($p<0.0001$) of treatment.

3.2. Repeated Oral Administration

Fig. (**2**) shows the change in blood glucose levels during 15 days of daily oral administration of PA LAE at a dose of 50 mg/kg in normal and STZ-induced diabetic rats. During 15 days of treatment, PALAE exhibited a significant reduc-

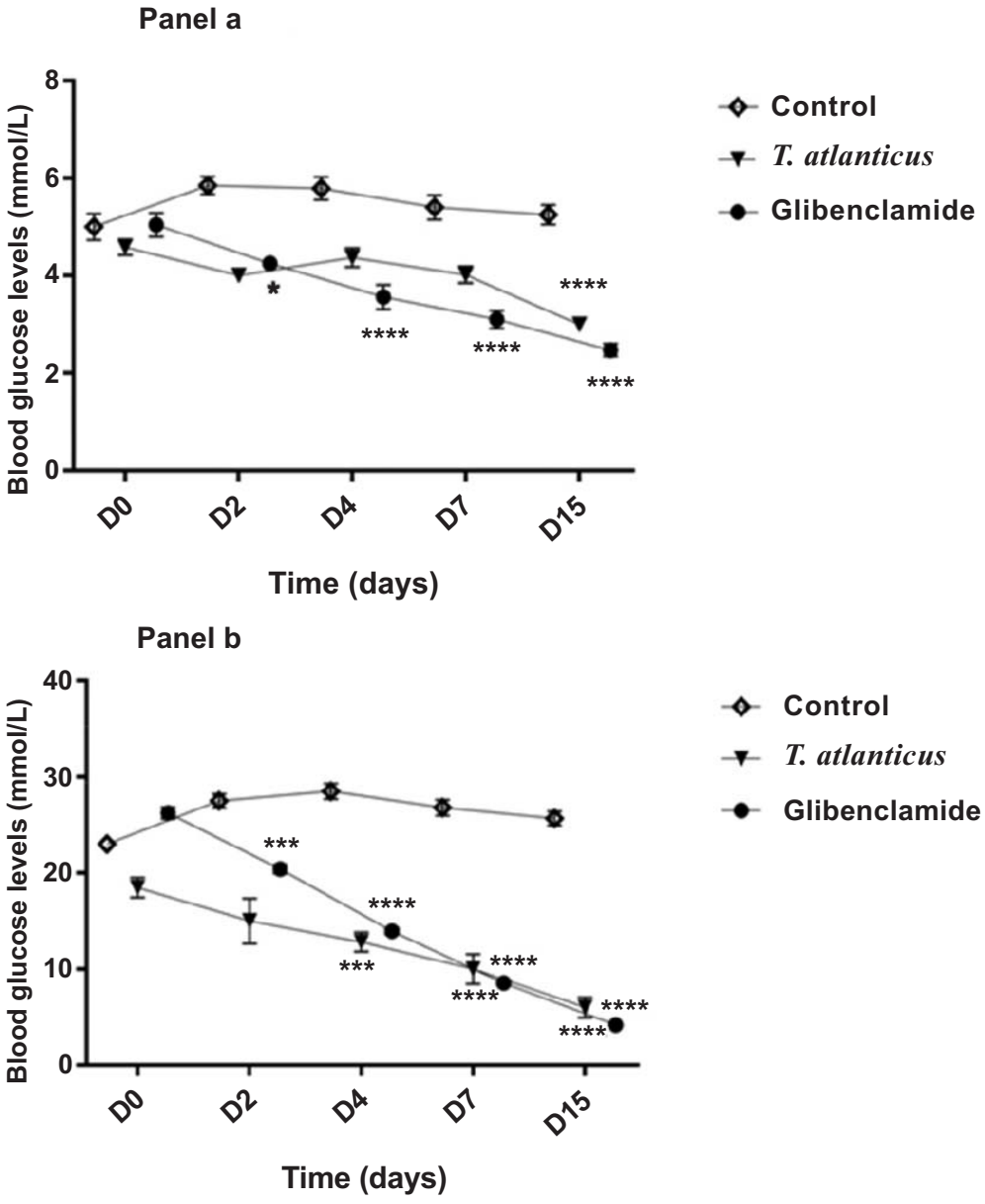

Fig. (2). Plasma glucose levels after daily single oral administrations of PALAE (50 mg/kg) for 15 days in normal (**Panel a**) and diabetic rats (**Panel b**). Data are expressed as means ± SEM, n = 6 rats per group. *$p<0.05$; **$p<0.01$; ***$p < 0.001$; and ****$p<0.0001$ compared with baseline values.

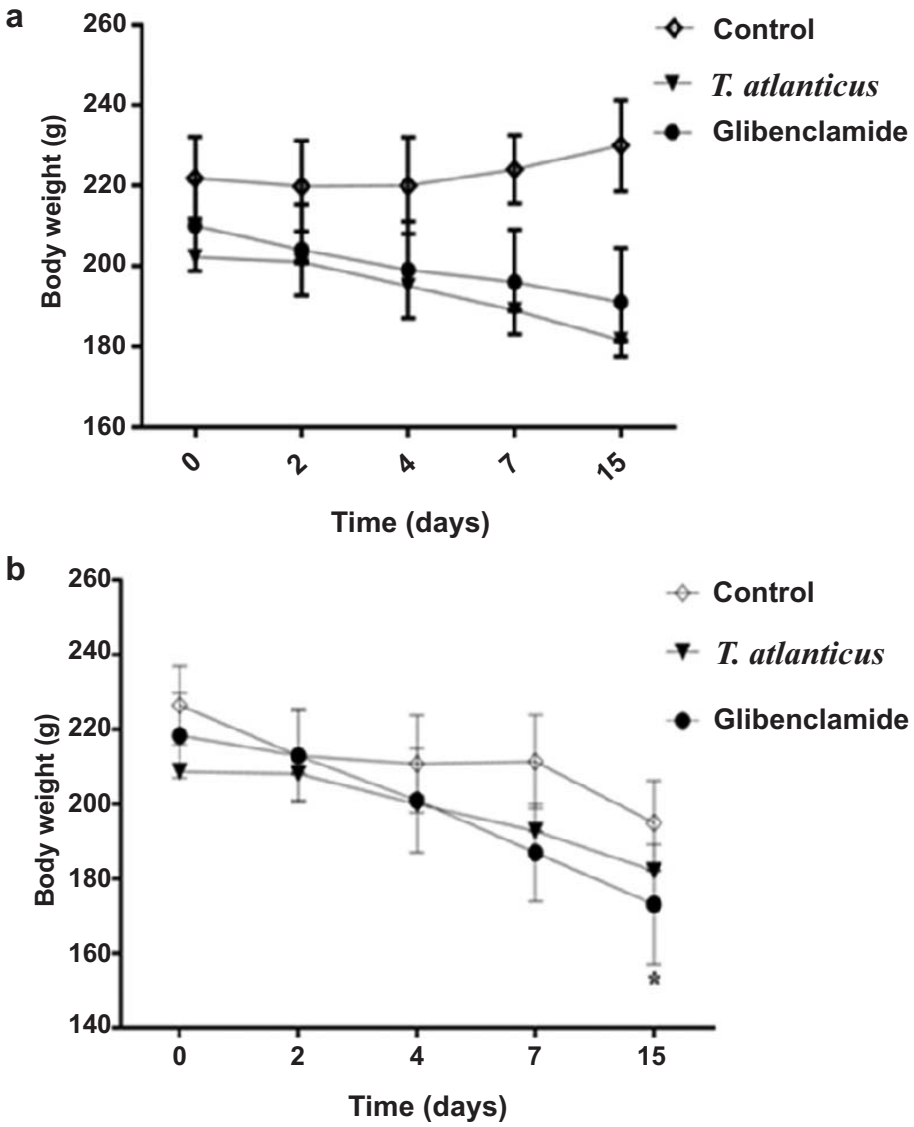

Fig. (3). Body weight change after once daily repeated oral administration of PALAE (50 mg/kg for 15 days in normal (**Panel a**) and diabetic rats (**Panel b**). Data are expressed as mean ± SEM, n = 6 rats per group. *p<0.05; **p< 0.01; ***p<0.001; and ****p<0.0001 compared with baseline values (the start of treatment).

tion (p<0.0001) of blood glucose levels at the 15th day of treatment in normal rats. In a glibenclamide-treated group, a significant decrease has been observed from the second day of treatment (p<0.05). This effect was more pronounced from the fourth day until the end of treatment (p<0.0001). In untreated normal rats, no significant alteration was detected during this test.

In STZ-diabetic rats, PALAE-treated group showed a significant decrease (p<0.001) of blood glucose levels from the fourth to the 15th day of treatment (p<0.0001). In STZ-diabetic rats treated by Glibenclamide, a significant reduction was noted from the second day (p<0.001) to the 15th day of treatment (p<0.0001).

3.3. Body Weight

Effect of leaves aqueous extract of *T. atlanticus* on the body weight in normal and STZ rats after 15 days of treatment is shown in Fig. (**3**). In normal rats, a slight decrease of body weight has been noticed (p<0.05) after the treatment with PALAE but in diabetic rats, no significant change was observed. In addition, a significant change of body weight (p<0.05) was noticed in glibenclamide-treated diabetic groups at the end of treatment.

3.4. Oral Glucose Test Tolerance

Treatment with PALAE 30 min before glucose administration (2 g/kg) produced in normal rats a significant reduction in the high blood glucose levels, 120 min of the glucose load (p<0.05). Furthermore, in glibenclamide-treated normal rats, a significant reduction in blood glucose levels (p<0.01) was noticed after 60, 90 and 120 min of administration. However, in STZ-diabetic rats, oral administration of PALAE (50 mg/kg) revealed a more significant reduction (p<0.01). While no significant change was observed in glibenclamide-

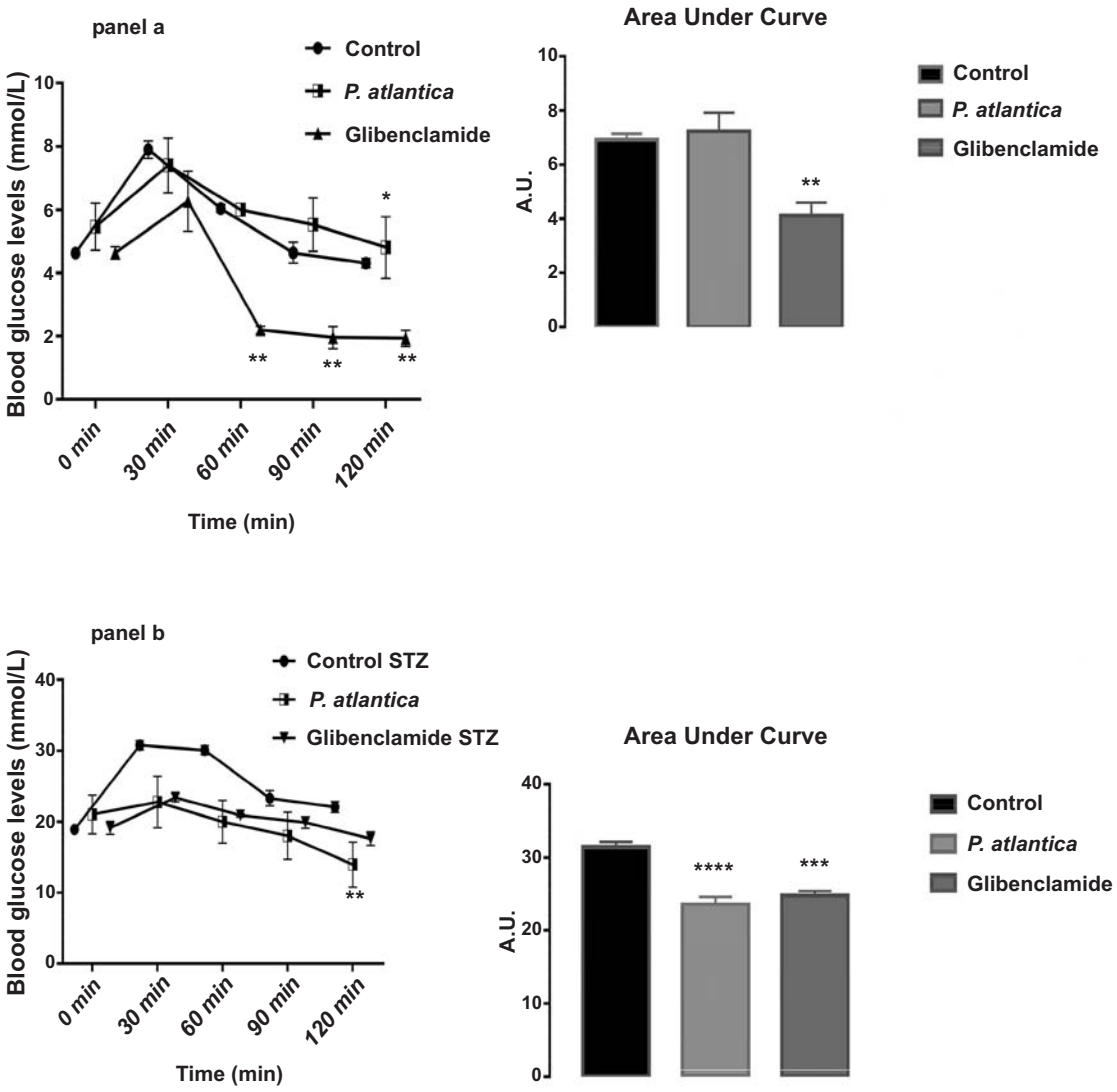

Fig. (4). Effect of the aqueous *T. atlanticus* (*P. atlantica)* extract (50 mg/kg) on oral glucose tolerance in normal and Area Under Curves (**Panel a**), and in STZ-diabetic rats and Area Under Curves correspondents (**Panel b**). Values are means ± SEM; n=6. (*) $p<0.05$; (**) $p<0.01$; (***) $p<0.001$ *vs*. control.

treated diabetic rats. It was also reported that PALAE provoked a decrease at the level of the area under the curve AUC ($p<0.0001$) as compared with untreated control diabetic group, whereas, no change was produced in normal rats during this test (Fig. **4**).

3.5. Histopathological Changes in the Liver and Morphometric Analysis

Table **1** represents quantitative data of histopathological slides of the liver in diabetic rats treated with *T. atlanticus* or Glibenclamide. The results showed that the number of hepatocytes counted in an area of 40000 μm^2 was increased in diabetic rats treated with PALAE (27 hepatocytes) when compared to diabetic untreated rats (16 hepatocytes). Then, the diameter of the core of diabetic rats treated with *T. atlanticus* was larger (28.48±4.13) in comparison to the diabetic control rats (23.48±0.48). Fig. (**5A**) illustrates the histopathological changes in the liver of diabetic rats 15 days after oral treatment with *T. atlanticus* (50 mg/kg) or Glibenclamide (5 mg/kg). A remarkable change in liver morphology has been shown in diabetic control (Fig. **5B**), characterized by microvesicular and macrovesicular vacuolation, which disappears with the chronic treatment with PALAE. Indeed, injuries and inflammations were remarkably cicatrized in STZ-diabetic treated with PALAE and sinusoids have recovered their normal form and size (Fig. **5C**) that leads to the improvement of the liver architecture in STZ-diabetic treated rats group (Fig. **5C**).

3.6. DPPH (1-1-diphenyl 2-picryl hydrazyl) Radical Scavenging Activity

Plotted graph of scavenging activity against the concentrations of the samples showed that the IC50 value of PALAE was equal to 32.34±4.54 µg/ml. However, the synthetic antioxidant (BHT) has revealed an IC50 of 2.46±0.17 µg/ml. Consequently, leaves aqueous extract prepared from

Table 1. Morphometric analysis of hepatocytes of diabetic rats treated with *T. atlanticus* (50 mg/kg) and the control groups.

-	Number of Hepatocytes	Diameter of the Cores (µm)
Normal control	27	25,29 ± 2,50
STZ control	16	23,48 ± 0,48
Glibenclamide STZ	27	27,60 ± 2,11
***T. atlanticus* LAE STZ**	27	28,48±4,13

Values are expressed as means ±SEM. (*) p<0.05; (**); p<0.01; (***) p<0.001 and ****p<0.0001 when compared to control diabetic.

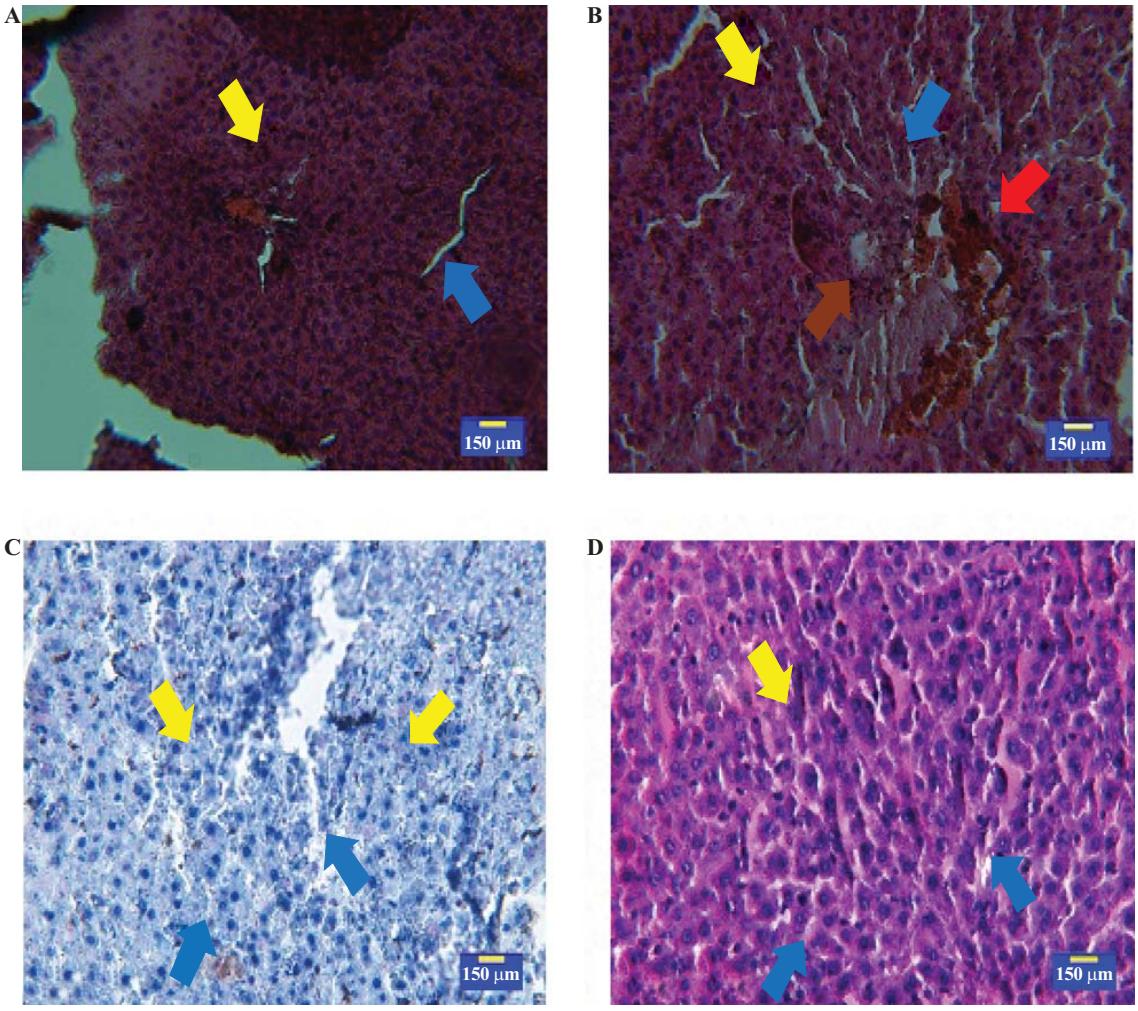

Fig. (5). Effect of orally administered PALAE on liver histology. Representative images of liver in (**A**) normal; (**B**) STZ induced diabetic rats; (**C**) diabetic rats treated with 50 mg/kg/day PALAE and; (**D**) diabetic rats treated with glibenclamide (5 mg/kg/day). Images were taken under 40 ×magnification. Yellow arrow indicates hepatocytes, blue arrow indicates sinusoids, the brown one indicates central vein and the red one indicates injuries provoked by intoxication resulting from STZ.

leaves of *T. atlanticus* showed a strong antioxidant activity compared to synthetic antioxidant BHT (Fig. **6**).

4. DISCUSSION

About 200 species have shown anti-diabetic properties. Traditionally, these plants were used widely as a complementary alternative medicine for the treatment of diabetes [26]. In this study, the antidiabetic and the antioxidant effect of *T. atlanticus* leaves aqueous extract was evaluated in normal and STZ-induced diabetic rats. During clinical trials, Glibenclamide is used as a reference drug because it has been reported to be potent a second-generation sulfonylurea drug that promotes glucose control by acting both on insulin secretion and action [27-29].

The results demonstrate that PALAE (50 mg/kg) exerted a significant hypoglycemic effect in normal and STZ-

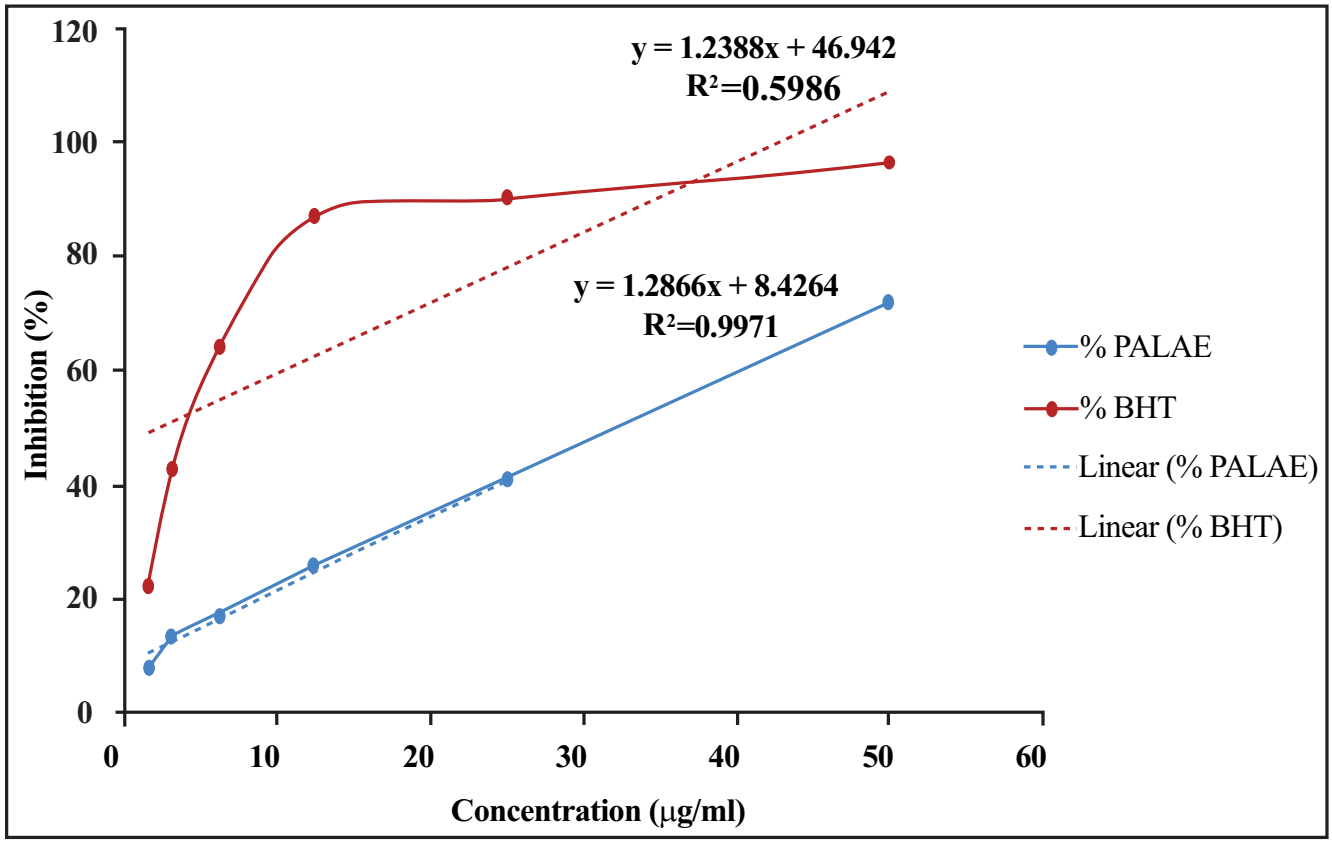

Fig. (6). DPPH radical scavenging activity of *T. atlanticus* (PALAE).

induced diabetic rats. The choice of the dose of 50 mg/kg was based on a preliminary pharmacological screening; the doses 5, 10, 20 mg/kg of the plant did not show any blood-glucose-lowering effect. Despite the counter-regulatory factors that are physiologically involved in response to hypoglycemia, such as glucagon, cortisol, adrenaline, PALAE significantly reduced the blood glucose levels in normal rats after 6 hours of treatment ($p<0.05$). In addition, the study demonstrates that PALAE induced a potent antihyperglycemic effect in diabetic rats during both a single and repeated oral treatments.

Various mechanisms involved in the lowering blood glucose activity can explain the antidiabetic effect of *T. atlanticus* in STZ-induced diabetes, like inhibition of hepatic glucose production [30] or a decrease of intestinal carbohydrate absorption. This extract may act also through the activation of signaling pathways leading to the improvement of insulin secretion by beta cells [31-33], or inhibition of aldose-reductase and alpha-glucosidase [34]. On the other hand, there are many reports suggesting the direct link between oxidative stress and the onset of diabetes and related complications [35, 36]. In type 1 diabetes, reactive oxygen species (ROS) have been shown to be involved in the destruction of pancreatic β-cells and the further development of insulin-dependent diabetes mellitus [37, 38]. In this study, *T. atlanticus* exhibits antioxidant *via* scavenging the free radicals that are highly elevated in diabetes. A similar study proved that both methanolic and ethyl acetate extracts prepared from leaves of *T. atlanticus* showed a strong antioxidant activity compared to synthetic antioxidant BHT. The IC50 value of methanolic and ethyl acetate extracts was equal to 2.41±0.01 µg/mL and 4.12±0.01 µg/mL, respectively [19].

Additionally, the effect of aqueous *T. atlanticus* extract on glucose tolerance was tested in both normal and STZ-induced rats. Oral glucose test tolerance aimed to show the body's capacity to use glucose. In normal rats, a significant reduction in blood glucose levels was marked after 120 min of the glucose load ($p<0.05$). A significant decrease in blood glucose levels was also observed in STZ-diabetic rats treated with PALAE ($p<0.01$). Consequently, PALAE prevented the increase in blood glucose levels after glucose load in both normal and STZ-diabetic rats. This finding suggests that this increase in levels of glucose tolerance may be linked to increased secretion of insulin as well as amelioration of insulin sensitivity [39].

Degenerative damages induced by diabetes are characterized by histopathological changes in the liver as it is shown in untreated diabetic rats. This involves disorganization in hepatocytes as well as disordered liver architecture nuclear pyknosis and enlarged sinusoids with thickened vein walls. These liver damages could be due to the effect of STZ according to other studies [40]. The PALAE seems to improve these damages along with glibenclamide treatment and its effect. The liver is considered a non-insulin dependent organ with an important role in lipid and glucose homeostasis [41].

The biological activity of *T. atlanticus* species can be attributed to a variety of compounds. Previous phytochemi-

cal studies showed that *Terebinthus* species are rich in monoterpenes [42, 43], tetracyclic triterpenoids [44], flavonoids [45-47] and other phenolic compounds including gallic acid [48, 49]. More precisely, catechin, epicatechin, gallic acid methyl ester and gallic acid were identified in leaves and galls of *T. atlanticus* [50]. This last bioactive polyphenol is known to possess antihyperglycemic and insulin secretagogue properties in streptozotocin-induced insulin-deficient diabetic rats [51, 52]. It was also reported that gallic acid possesses a beneficial action on pancreatic beta cells and protects them from impairment such as a major compound in *Cyamopsis tetragonoloba* [53]. Previous studies showed a significant alpha-amylase and α-glucosidase inhibitory activities of *T. atlanticus* leaves *in vitro* [54] that can support our finding. In contrast, *T. atlanticus* had not shown an antidiabetic effect in the same model according to the study presented by Hamdan *et al*. in 2004 [55]. However, it is difficult to compare these results, because several factors can influence the content of phenolic compounds. Recent studies have shown that extrinsic factors such as geographical and climatic factors, genetic factors, but also the degree of maturation of the plant and the duration of storage may exert a strong influence on the polyphenol content [56].

CONCLUSION

In conclusion, the present study demonstrates that *T. atlanticus* showed considerable *in vivo* antidiabetic effect which supports its use in traditional medicine for the prevention and treatment of diabetes**.** However, additional studies targeting mechanisms of action and safety are required.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the regional committee of Faculty of Sciences and Techniques (FSTE/2015), Errachidia, Morocco.

HUMAN AND ANIMAL RIGHTS

No humans were used in this study. All animal research procedures followed were in accordance with the standards of Guide for the Care and Use of Laboratory Animals.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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