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RESEARCH ARTICLE

Anti-diabetic and Anti-oxidative Activities of Algerian *Oudneya africana* Extract in Alloxan Induced Diabetic Rats

Derouiche Samir[1,2]*,
Seghiri Iman[1],
Zebidi Maroua[1] and
Mehellou Zineb[1]

[1]Department of Cellular and Molecular Biology,
Faculty of the Sciences of Nature and Life,
El Oued University, 39000,
El Oued, Algeria

[2]Laboratory of Biodiversity and Application of Biotechnology in the Agricultural Field,
Faculty of the Sciences of Nature and Life,
University of El Oued,
El-Oued39000, Algeria

ABSTRACT

Background and Objectives: *Oudneya africana*is is a plant widely used in the treatment of a variety of diabetes disorders in Algerian traditional medicine. However, the underlying mechanism has remained unclear. This study focused on the research of the anti-diabetic and antioxidant effects of the aqueous extracts of the leaves of *Oudneya africana*. **Materials and Method:** The study carried out on 12 female rats of the Albino Wistar strain divided into three groups; healthy control group, untreated diabetic group, and the diabetic group treated with aqueous extracts of *Oudneya africana* (AEOa) (400 mg kg^{-1} b.wt.) for 21 days. Diabetes in rats was induced by Alloxan using a single peritoneal injection of 150 mg kg^{-1} dose. Body weight and blood sugar were measured regularly. After 21 days of treatment, the rats were sacrificed and some biochemical parameters were determined. **Results:** Results clearly showed that the treatment with aqueous extracts of *Oudneya africana* significantly decreases the blood glucose and improves the transaminases activities (TGO, TGP) of diabetic rats. On the other hand, the administration of the aqueous extract also decreases ($p>0.05$) the plasma level of uric acid, urea and creatinine. Decrease ($p<0.01$) in the concentrations of tissues MDA and an increase in the tissues GSH level was observed. On the other hand, histological examination of the pancreatic tissue shows that the aqueous extract of *Oudneya africana* has a protective effect on the structure and function of Langerhans β cells and improves the histological architecture of the islets of Langerhans. **Conclusion:** In conclusion, the present study suggests that *Oudneya africana* has a beneficial effect on the development of diabetes and these complications.

Key words: Diabetes, oxidative stress, *Oudneya africana*, pancreatic islet, alloxan

*Corresponding Author

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INTRODUCTION

Diabetes is a metabolic disease characterized by a disorder in the regulation of carbohydrate metabolism resulting in hyperglycemia[1]. According to the WHO, the number of diabetics in the world is estimated at 135 million with a forecast of 300 million people likely to be reached in 2025. In addition, diabetes mellitus is a metabolic disorder characterized by hyperglycemia and insufficient secretion or endogenous insulin action[2]. While exogenous insulin and other drugs can control many aspects of diabetes, many complications affecting the vascular system, kidney, retina, lens, peripheral nerves and skin are common and are extremely expensive in terms of longevity and quality of life[3]. Diabetes is generally accompanied by an increase in the production of free radicals or altered antioxidant defenses[4] which causes a state of oxidative stress which is widely involved in the development and progression of diabetes and its complications[5]. Through the creation of chemically and irreversibly abnormal biological molecules and the overexpression of certain genes[6], oxidative stress will be the essential initial cause of several diseases: diabetes, cancer, cataracts, amyotrophic lateral sclerosis, acute pulmonary distress syndrome, pulmonary edema, accelerated aging[7]. Plants are widely used in the treatment of a variety of disorders in Arab folk medicine[8]. They have been used for a long time as sources of medicine against various diseases, including diabetes mellitus.Among the most used medicinal plants and which are of great anti-diabetic and hypoglycemic interest for neighboring countries in Algeria (Tunisia and Maroco), this study based on *Oudneya africana*. The main objective of this work was to study the anti-diabetic and antioxidant effect of the aqueous extract of *Oudneya africana* in Wistar rats induced diabetic by alloxan.

MATERIALS AND METHODS

Study area: Research conducted for 3 months at January 5, 2019-March 25, 2019. The location of study is in the Laboratory of Molecular and Cellular Biology Department, University of El Oued, Algeria.

Chemicals and reagents: All chemicals used were of analytical grade and purchased from Sigma-Aldrich, Mo, USA. Commercials Kit obtained from Spinreact, Spin.

Collection, identification and extraction of plant material: Fresh leave of the plant were collected from a village in El Oued state, Algeria and was identified by a botanist at the herbarium in the Department of Biology, University of El Oued, Algeria. The leaves were washed with distilled water and used immediately. The extraction methods[9] were adopted using distilled water separately. After extraction, the solvents were removed using a rotary evaporator, to get gel-like extracts.

Animals: Adult females albino rats, weighing 160-190 g, were brought from the animal house of Pasteur institute, Algeria. They were placed in three groups of six rats in each and kept in animal's house of Molecular and Cellular Biology Department, University of El Oued, Algeria. Standard rats' food and tap water were available *ad libitum* for the duration of the experiments unless otherwise noted. Animals were acclimated for two weeks under the same laboratory conditions of photoperiod (12 h light/12 h dark) with a relative humidity 64.5% and room temperature of 22±2°C. The experimental procedures were carried out according

to the national institute of health guide-lines for animal care and approved by the ethics committee (No.: BCM 078/2019) of our institution.

Induction of diabetes: After fasting overnight, the induction of diabetes in diabetic groups was achieved by intraperitoneal injection of alloxan (Alloxan; Sigma, UK) freshly prepared in physiological water solution with a dose of 150 (mg kg^{-1} b.wt.). After the injection, the water bottles were replaced with bottles containing a 5% glucose solution to overcome the hypoglycemia induced by Alloxan.

Experimental design: The adult Wistar albino rats were randomly divided into three groups, each containing 4 rats:

Group I : Control group was given normal diet (served as a control)
Group II : Diabetic group given a normal diet (diabetic)
Group III : Diabetic treated groups were given a normal diet plus Aqueous Extracts of *Oudneya africana* (AEOa) (400 mg/kg/day) administered orally (diabetic+AEOa)

All the groups of animals had free access to water and diet. Body weight was monitored weekly.

Blood collection and preparation of tissue samples: At the end of 3 weeks of Aqueous Extracts of *Oudneya africana* (AEOa) treatment, rats were fasted for 16 h, decapitated and blood samples were transferred into ice cold centrifuge tubes. The serum was prepared by centrifugation, for 10 min at 3000 revolutions/min and utilized biochemical assays. The blood glucose was measured by glucometer, blood put in EDTA tubes used for the measurement of hematological parameters (FNS, Glycated HB). The pancreas from each rat was removed immediately and preserved in a sample bottle containing 10% formalin solution. The pancreas was processed by the paraffin technique. Sections of 5 µm thickness were cut and stained by hematoxylin and eosin for histological examination.

Serum Biochemical and hematological parameters: Biochemical markers were assayed according to standard methods. The levels of serum urea, creatinine, uric acid and total protein were estimated using commercial kits from Spinreact laboratories, Spain (urea, ref. 1001332; creatinine, ref. 1001113; uric acid, ref. 1001013 and total protein, ref. 1001291). The activities of Glutamate-Oxaloacetate Transaminase (GOT) and Glutamate-Pyruvate Transaminase (GPT) were determined using commercial kits from Spinreact (Girona, Spain) (refs: GOT-1001161, GPT-1001171). Hematological analysis (NFS) is performed by the autoanalyzer (mythic 18 Orpheuse). Glycosylated Haemoglobin (HbA1c) was analyzed from EDTA blood, using Turbiquickanalyser based on immunoturbidimetric method.

Tissues oxidative stress parameters

Tissues preparation: One gram of kidney tissue of each rat of different groups was used. After milling and homogenizing the tissues in TBS (50 mM Tris, 150 mM NaCl, pH 7.4), and centrifuged at 10,000×g for 15 min at 4°C, then the supernatant obtained was stored at -20°C while waiting for the determination of oxidative stress parameters.

Estimation of lipid peroxidation levels: The principle of this assay is based on the condensation of MDA in acidic and hot medium with thiobarbituric acid according to Yagi[10]. The reaction results in the formation of a pink complex between two molecules of thiobarbituric acid which can, therefore, be measured by Absorption spectrophotometry at 532 nm and the level of MDA in liver was expressed as nmol/mg protein.

Determination of reduced glutathione (GSH) level: GSH concentration was performed with the method described previously[11]. The complex formed between GSH and 5,5'dithiodis-2-nitrobenzoic acid (DTNB) releases thionitrobenzoic acid (TNB) which has an absorbance at 412 nm. Total GSH content was expressed as nmol GSH/mg prot.

Statistical analysis: Data were reported as Mean±SEM. Results comparisons were carried out by using one-way analysis of variance followed by the Student t-test to compare means among the groups. Differences were considered statically significant at $p<0.05$.

RESULTS

Initial body weight, body weight gain and organ relative weight: The results presented in Table 1 showed a significant decrease ($p<0.05$) in weight gain in diabetic rats compared to the control and a significant increase ($p<0.05$)in the treated group compared to diabetic rats. The obtained results show also a highly significant increase ($p<0.01$) in the relative weight of the liver, kidneys, and heart in the diabetic groups compared to the control. On the other hand, the treatment with the aqueous extract of *Oudneya africana* has a benefic effect ($p<0.05$) on the relative weight of liver, kidney, and heart compared to diabetic rats (Table 1).

Blood hematological parameters: Concerning the hematological parameters, results obtained illustrated in Table 2 show that there is a very highly significant decrease ($p<0.001$) in the number of lymphocytes in diabetic rats in comparison with the control. On the other hand, the results show no significant variation in the

Table 1: Weight of control and experimental rats

			Relative weight		
Parameters	Initial Body weight (g)	Body weight gain (g/j/rat)	Liver	Kidney	Heart
Control	182.00±4.52	0.944±0.050	3.001±0.069	0.297±0.003	0.316±0.003
Diabetic	173.25±3.78	0.736±0.123*	3.350±0.0927**	0.365±0.018**	0.373±0.012**
Diabetic+AEOa	163.75±7.56	0.835±0.236[a]	3.042±0.256[a]	0.320±0.033**[a]	0.340±0.03**[a]

*p<0.05, **p<0.01: significantly different from control group, [a]p<0.05 significantly different from Pb group.Data are expressed as Mean±SD (n = 4), AEOa: Aqueous Extract of Oudneya africana

Table 2: Leukocyte and Erythrocyte line markers in control and experimental animals

Parameters	White blood cell (10^3/µL)	Lymphocyte (10^3/µL)	Red blood cell (10^6/µL)	Hemoglobin (g dL^{-1})	Platelet (10^3/µL)
Control	3.40±0.26	2.200±0.22	7.65±0.21	13.22±0.35	499.8±60.7
Diabetic	3.70±0.312	1.950±0.02***	7.59±0.18	13.22±0.293	493.3±43.3
Diabetic+EAOa	5.02±0.61*[a]	3.033±0.52[b]	8.41±0.15**[c]	14.15±0.22**[b]	541.8±31.5[a]

*p<0.05, **p<0.01, ***p<0.001: Significantly different from control, [a]p<0.05, [b]p<0.01, [c]p<0.001: Significantly different from diabetic, Data are expressed as Mean±SD (n = 4), AEOa: Aqueous Extract of Oudneya africana

Table 3: Mean blood glucose and biochemical markers of control and experimental animals

Parameters	Glucose (mmol L^{-1})	Glycosylated hemoglobin (%)	Urea (g L^{-1})	Creatinin (mg dL^{-1})	Uric acid (mg dL^{-1})	GOT (U L^{-1})	GPT (U L^{-1})
Control	5.71±0.11	5.3±0.5	0.39±0.07	12.88±3.16	19.25±0.86	38.40±13.4	39.92±4.84
Diabetic	9.20±0.31***	6.6±0.22*	0.70±0.11*	14.16±2.94*	30.50±2.12**	69.25±5.11**	52.81±1.66***
Diabetic+EAOa	7.37±0.11**[c]	5.2±0.17[a]	0.59±0.09[a]	12.88±2.71[a]	14.50±2.45[b]	45.23±2.89*[c]	26.20±0.88***[c]

*p<0.05, **p<0.01, ***p<0.001: Significantly different from control, [a]p<0.05, [b]p<0.01, [c]p<0.001: Significantly different from diabetic, Data are expressed as Mean±SD (n = 4), AEOa: Aqueous Extract of *Oudneya africana*, GOT: Glutamate oxaloacetate transaminase, GPT: Glutamate pyruvate transaminase

Table 4: Tissue lipid peroxidation level in control and experimental animals

Parameters	Liver MDA	Kidney MDA	Heart MDA	Pancreas MDA	Aorta MDA
Control	1.41±0.26	1.83±0.44	1.42±0.31	1.46±0.23	1.47±0.10
Diabetic	2.44±0.45**	1.96±0.11	1.69±0.43	2.33±0.61*	1.66±0.04
Diabetic+EAOa	2.04±0.37*[a]	3.27±0.09***[c]	2.06±0.09	1.43±0.21[b]	1.96±0.38

*p<0.05, **p<0.01, ***p<0.001: Significantly different from control, [a]p<0.05, [b]p<0.01, [c]p<0.001: Significantly different from diabetic, Data are expressed as Mean±SD (n = 4), AEOa: Aqueous Extract of Oudneya africana, MDA: Malondialdehyde

Table 5: Tissue Reduced Glutathione (GSH) level in control and experimental animals

Parameters	Liver GSH	Kidney GSH	Heart GSH	Pancreas GSH	AortaGSH
Control	0.554±0.058	0.458±0.051	0.619±0.062	0.743±0.142	0.463±0.101
Diabetic	0.458±0.040*	0.465±0.072	0.624±0.076	0.326±0.028***	0.347±0.041*
Diabetic+EAOa	0.935±0.151*[a]	0.734±0.031	0.874±0.150	0.390±0.051**[a]	0.433±0.157[a]

*p<0.05, **p<0.01, ***p<0.001: Significantly different from control, [a]p<0.05, [b]p<0.01, [c]p<0.001: Significantly different from diabetic, Data are expressed as Mean±SD (n = 4), AEOa: Aqueous Extract of Oudneya africana, GSH: Reduced Glutathion

number of white blood cells, red blood cells, platelets and the hemoglobin level in the diabetic group compared to the control. However, treatment with the aqueous extract of *O. africana* for 21 days significantly increases the number of red blood cells (GR) ($p<0.001$) and the hemoglobin level ($p<0.01$) in diabetic rats and increase significantly ($p>0.05$) the number of lymphocytes, white blood cells and the number of blood platelets (PLT) in diabetic rats.

Blood biochemical values: For the biochemical markers, the results obtained (Table 3) show a significant increase in the concentration of blood glucose ($p<0.001$), glycosylated hemoglobin, urea, Creatinine ($p<0.05$) and uric acid ($p<0.01$) levels and a very highly significant increase in GOT ($p<0.001$) and GPT ($p<0.001$) activities in diabetic rats compared to control rats. Treatment with the aqueous extract of *O. africana* significantly reduced the level of all of these parameters in diabetic rats.

Tissues oxidative stress marker

Lipid peroxidation level: The results of oxidative stress presented in Table 4 show a significant increase in lipid peroxidation in the liver ($p<0.01$) and pancreas ($p<0.05$) but no variation in the concentration of MDA in the heart and aorta in diabetic rats compared to control. Treatment with aqueous extract of *O. africana* for 21 days decreases the lipid peroxidation in these tissues.

Reduced glutathione (GSH) level: Regarding the results of reduced glutathione our results (Table 5) shows a significant decrease in the level of GSH in the liver ($p<0.05$), the pancreas ($p<0.001$) and the Aorta ($p<0.05$) but no variation in the concentration of GSH at the heart level in diabetic rats compared to the control.

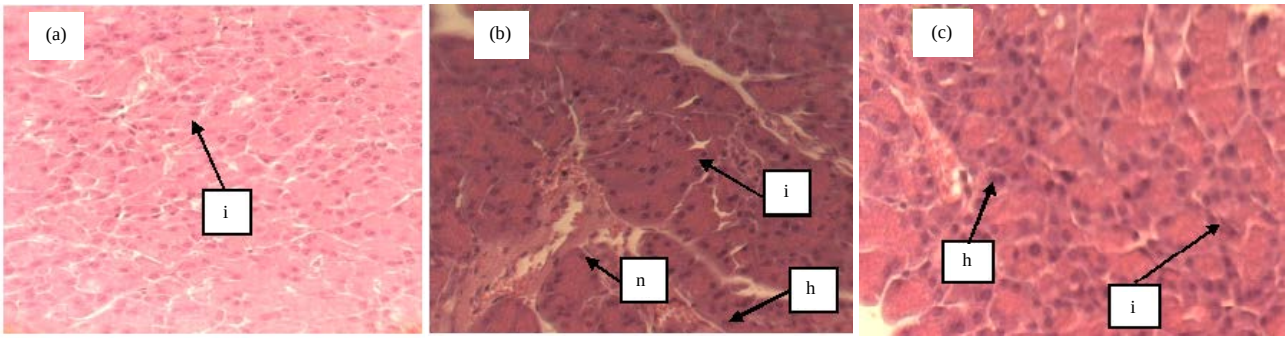

Fig. 1(a-c): Histology of the pancreas following induction of diabetes mellitus and treatment with *O. africana*leave extract in rats, (a) normal controls with normal Islet (i), (b) untreated diabetic group with congestion of vessels, hemorrhage (h) and necrosis (n) and (c) diabetic treated with 200 mg kg^{-1} *O. africana* with moderate, Histologic slides were stained with hematoxylin and eosin (×400)

Adding the aqueous extract of *O. africana* for 21 days significantly increased the level of GSH in liver, pancreas and Aorta but not significantly ($p<0.05$) in the heart in diabetic rats.

Histopathology: Microscopic observation of the rat's pancreas treated with Alloxan reveals a visible cell change, which results in cell atrophy, hemorrhage, and cell necrosis. While the histological study of the pancreas of rats treated with the aqueous extract of *Oudneya africana*. R.Br. shows a slight improvement at the cellular level (Fig. 1a-c).

DISCUSSION

Diabetes mellitus (DM) is a group of metabolic disorders characterized by chronic hypoglycemic disease resulting from defects in insulin secretion, insulin action, or both[12]. The study of the effect of treatment with the aqueous extract of *Oudneya africana*, for 21 days on the bodyweight of the rats shown a significant difference between the weight gain of the diabetic rats treated with the aqueous extract *Oudneya africana*, and untreated diabetic rats. The aqueous extract of *Oudneya africana* has a role in improving the weight gain of diabetic rats, therefore it can be said that this plant protects the rats against the associated weight loss to diabetes disease and ensure their normal growth. This moderation in the loss of body weight is due to the control of hyperglycemia and the activation of structural protein synthesis[13]. The aqueous extract of *Oudneya africana* may stimulate the pancreatic secretion of insulin which promotes the storage of lipids and triglycerides[14]. The ability of *Oudneya africana* aqueous extract to protect bodyweight loss appears to be the result of its ability to reduce hyperglycemia[15]. The significant hypoglycemic effect of the aqueous extract of *Oudneya africana* may well be linked to the presence of flavonoid compounds probably acting synergistically[16]. Results obtained from another study [17]revealed that the flavonoid compounds have significant hypoglycaemic activity in Swiss albino rats. Other studies have reported that tannins, in general, can act on glucose by various mechanisms including better absorption of glucose in peripheral tissue, stimulation of insulin secretion from β cells of the pancreas, decrease in glycation circulating proteins, in particular glycated hemoglobin, a marker of the long-term glycemic state of type 2 diabetes[18]. The antihyperglycemic mechanism of the actions, of the

aqueous extract of *Oudneya Africana* process of regeneration, or increase of pancreatic secretion of insulin from existing β cells and/or inhibition of the α-glucosidase enzymes of the intestine transforms disaccharides into monosaccharides for absorption purposes[19]. Current results showed that the aqueous extract of *Oudneya africana* can reduce the level of urea, creatinine, and uric acid in the blood and activate the renal function. This reduction in uric acid levels may be due to the reduction in lipid peroxidation, triglycerides and cholesterol, while the elevation of these metabolites may increase the synthesis of uric acid[20]. The results showed a very highly significant increase ($p<0.001$) in the serum activity of TGO and TGP in the diabetic group compared to the control group. This is explained by the destruction of liver cells (hepatic cytolysis) by toxic substances (hepatotoxic effect of alloxan)[21]. So the results of this study showed that the treatment of diabetic rats with the aqueous extract of *Oudneya africana* decreased the enzymatic activity of transaminases compared to untreated diabetic rats which mean that the aqueous extract of *Oudneya africana* inhibits liver damage caused by alloxan.On the other hand, in diabetic rats treated with the aqueous extract of *Oudneya africana*, lipid peroxidation is reduced in the liver and pancreas. These results coincide with other studies[22]. The inhibitory effect of lipid peroxidation translated by the aqueous extract of *Oudneya africana* and its richness in polyphenols play a very important role in the neutralization of free radicals. Treatment of rats with the aqueous extract of *Oudneya africana*. significantly increased the level of tissue glutathione compared to untreated diabetic rats. The increased levels of reduced glutathione (GSH) in the various organs studied in diabetic rats treated with the extract clearly show the antioxidant properties of the aqueous extract of *Oudneya africana*. This result can be explained by the presence of compounds "such as flavonoids" which are endowed with antioxidant activity[23].Current results showed that the aqueous extract of *Oudneya africana*.R.Br has a protective effect on the structure and function of Langerhans β cells, and improved the histological architecture of the islets of Langerhans. This protective effect of the islands observed could be due to the improvement of the activity of the pancreatic antioxidant enzymes, which play a key role in the defense mechanism against the damage of the pancreas caused by free radicals[24].

CONCLUSION

The present study concluded that aqueous extract of leaves of *O. africana* possesses the ability to control blood glucose in diabetes, its antioxidant and protective action on pancreatic β-cells, which in turn improve glucose metabolism and diabetic complications.

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SIGNIFICANCE STATEMENT

This study discovered the effect of aqueous extract of *Oudneya africana* that can be beneficial for diabetes mellitus. This study will help the researchers to uncover the critical areas of the cellular and molecular mechanism of hypoglycemic activity of plant that many researchers were not able to explore. Thus a new theory on new drugs against diabetes may be arrived at.

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