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Preventive Effects of the Aqueous Extract of *Guiera senegalensis* Roots on Dexamethasone Induced Insulin Resistance in Mice.

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ABSTRACT

Guiera senegalensis is one plant used in traditional medicine to treat diabetes. The present study aimed to evaluate the preventive effects of the aqueous extract of *G. senegalensis* on dexamethasone induced-insulin resistance in mice. In the acute toxicity study, the mice were treated with distilled water and 2000 mg/kg of extract. The signs of toxicity and DL_{50} were assessed. In the glucose tolerance test, animals were treated with distilled water, glibenclamide and 200 and 400 mg/kgof extract. The insulin resistance was induced for 8 days by injection of the dexamethasone (1 mg/kg*s.c*) one hour after pretreatment 200 and 400 mg/kgof extract. Body weight, glucose and insulin levels, insulin resistance index, lipid profile and atherogenic index were evaluated. The extract did not cause any death during the 14 days, the DL_{50}> 2 g/kg. The dose of 400 mg/kg significantly reduced postprandial glyceamia at the 60^{th}, 90^{th} and 120^{th} minute. The extract significantly prevented the reduction in body weight, hyperglycemia and hyperlipidemia, and the increase in insulin level, insulin resistance and atherogenic index. *G. senegalensis* endow with hypoglycemia properties and support its uses in traditional medicine for the treatment of diabetes.
eywords: acute toxicity, *Guiera senegalensis*, insulin resistance, dexamethasone, mice.

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INTRODUCTION

Dexamethasone is a synthetic glucocorticoid used clinically in particular for its anti-inflammatory and immunosuppressive properties. Too high glucocorticoid level is correlated to the development of insulin resistance [1]. Insulin resistance is the inability of the body's cells to absorb blood sugar. It characterizes type 2 diabetes and involves several targets such as the liver, skeletal muscle and adipose tissue. The most common metabolic disorder on our planet is type 2 diabetes. According to the WHO, about 422 million people had the diabetes in 2016 and in 2040, about 642 million people will have the diabetes [2]. Diabetes is due to the many environmental and genetic factors, and can lead over time to degenerative complications that can affect the cardiovascular system, eyes, nerves, limbs and kidney [3]. In addition to a healthy diet and physical activity, the treatment of type 2 diabetes is mainly based on the administration of the oral antidiabetic drug such as metformin [4]. Therapy and limiting complications are the main challenges present in medicine. Despite all the preventive and curative measures, the frequency of type 2 diabetes is on the increase worldwide.

Faced with this dramatic increase in the number of diabetic patients, many studies have evaluated the pharmacological action of traditional plants and their interest in medicine. Indeed, in developing countries, synthetic drugs are still quite expensive for some and herbal medicine is well established in the manners. In developed countries where the treatment of diabetes is easy access, it seemed interesting to use herbal medicine alone or in addition, to reduce the dose of synthetic drugs, but also because some herbal medicines seem to both be able to fight against the diabetes complications.

Guiera senegalensis (Combretaceae) is a plant up to 3 m high and present in the soudano-sahelienne zone [5]. In Cameroon traditional medicine, leaves and roots of *G. senegalensis* are used to treat respiratory, digestive, dermatological and genito-urinary affections, fever, malaria, hypertension, diabetes and epilepsy [6]. His galls are used to treat measles, smallpox, chickenpox, lilies, inguinal hernias, oliguries, malarial fevers and colic, pruritic rash and hiccups [7].

The objective of this study is to evaluate the preventive effect of the aqueous extract of the roots of *Guiera senegalensis* in dexamethasone induced insulin resistance in mice.

MATERIALS AND METHODS

Drugs and chemicals

Dexamethasone, metformine and D-glucose were purchased from Edu-Lab Biology Kit, Bexwell, Norfolk PE38 9GA, UK. The kits for biochemical dosages were purchased from Sigma-Aldrich, Saint. Louis, USA. All chemicals were obtained commercially and were of analytical grade.

Plant material

The plant material was constituted of *Guieras senegalensis*roots, collected in February 2017 to Bagarmiré, village located at approximately 20 km from of Maroua, Far North Region, Cameroon. When harvested, a sample of the plant has been authenticated at the National Herbarium in Yaounde. Thereafter, the collected roots were washed with tap water and then chopped and dried in the shade at room temperature for 6 days. The air-dried plant material was crushed using an electric mill (Binatone, model No: B L G-450) to obtain a fine powder.

Extraction procedure

The powder (300 g) of *G. senegalensis* was dissolved in 2 L of distilled water and the whole was boiled for 45 min. After cooling, the decoction obtained was filtered using a Whatman filter paper No.1and the filtrate was evaporated in an oven set at 45 °C for 3 days, which allowed us to obtain 12.25 g of extract with a yield of 4.08%.

Animals

Male and female mice (Swiss), aged between 8 and 10 weeks and weighing between 20 and 30 g were used. They were provided by the Veterinary Laboratory of Garoua (Northern Cameroon), preserved in plastic cages and maintained in ambient temperature of 24 ± 1^0C, relative humidity of 55-65% and normal light/dark cycle. Food and drinking water were given *ad libutum*during the experimental period. The animals were acclimated under the laboratory conditions for 7 days before the different tests. Prior authorization for the use of laboratory animals was obtained from the Cameroon National Ethics Committee.

Acute toxicity study

Acute toxicity study has been conducted according to the Organization for Economic Co-operation and Development guidelines (OECD) 425 guidelines, where the limit dose of 2000 mg/kg was used [8]. Indeed, 10 female mice were divided into 2 groups of 5 mice each. After fasting for 6 hours, the mice were given by gavage using an esophageal probe, the following treatments :

• Group 1 (control group) received the distilled water to a volume of 10 mL/kg of b.w.• Group 2 (treated group) received the extract at the dose of 2000 mg/kg b.w.

The treated animals were deprived of water and food during the first 4 hours post-feeding, during which they were carefully observed over the following profiles : neurological (sensitivity to the touch, sensitivity to the pain, sensitivity to the noise), behavioral (tremor, aggression, mobility, breathing, convulsion) and autonomic (diarrhea, mortality, state of feces) profiles. After this period, animals have access to drinking water and food. They were kept for 14 days, period during which the same parameters mentioned above were evaluated. At the end of the experimental period, the mean lethal dose (DL_{50}) of the extract was calculated [8].

Glucose tolerance test in normal mice

Twenty (20) male mice were fasted for 16 hours, divided into 4 groups of 5 mice each and treated as follows :

• Group 1 (normal control) received 10 mL/kg of distilled water.
• Group 2 (reference control) received glibenclamide at a dose of 0.3 mg/kg.
• Groups 3 and 4 received the extract at doses of 200 and 400 mg/kg, respectively.

Just after the distribution, the initial blood glucose was taken at time t_0. Immediately, the animals received distilled water, glibenclamide or different doses of extract according to the above groups. After 90 minutes, 3 g/kg D-glucose were administered to all animals. Blood glucose levels were then assessed every 30 minutes for 2 hours.

Induction of insulin resistance and treatment of animals

Twenty-five (25) male mice were divided into 5 groups of 5 mice each and treated daily for 8 days as follows [9]:

• Group 1 (normal control) received distilled water (10 mL/kg) *per os* + 0.9% NaCl (1 mL/kg) *s.c*.
• Group 2 (diabetic control) received distilled water (10 mL/kg) *per os*+ Dexamethasone (1 mg/kg)*s.c*.
• Group 3 (positive control) received metformin (40 mg/kg) *per os*+ Dexamethasone (1 mg/kg) *s.c*.
• Group 4 received the extract (200 mg/kg) *per os*+ Dexamethasone (1 mg/kg) *s.c*.
• Group 5 received the extract (400 mg/kg) *per os*+ Dexamethasone (1 mg/kg) *s.c*.

It is important to note that subcutaneous treatments were administered one hour after oral pretreatment.

Evaluation of relative body weight

The animals were kept at room temperature with free access to water and food. The body weight of animals in different groups was monitored at days1and 8 of treatment. The relative body weight was calculated according the following formula :

$$P = (Pi / P0) \times 100$$

where :
P = relative body weight in g
Pi = weight of the animal each day in g
P0 = weight of the animal at the start of the test in g

Assessing glycemia

Fasting blood glucose (for 6 h) of the animals was taken at the first and last day of the experiment using a glucometer (One Touch Ultra Mini) and strips. Indeed, a small notch was made on the tail, the first drop of blood was removed and the second was deposited on the active zone of the strip. The variation of blood glucose was calculated as follows:

$$G = (Gi / G0) \times 100$$

where :
G = variation of blood glucose in mg/dL
Gi = glycemia of the animal at the end of the test in mg/dL
G0 = glycemia of the animal at the start of the test in mg/dL

Collection of blood samples

One day after the end of treatment, each animal was weighed individually and anesthetized by association kétamine (10 mg/mL)/diazépan (5 mg/mL) then sacrificed. The mice were extended supine, their abdomen was greatly opened and blood was collected by cardiac puncture. The collected blood was placed in dry tubes, left for 30 minutes at 37°C for serum separation, centrifuged at 3000 rpm for 20 minutes, and then sera were carefully aspirated with Pasteur pipette and kept in eppendorf tubes at -20°C for biochemical analysis.

Determination of insulin level and insulin resistance index

Serum insulin level was evaluated by the method with the ELISA kit [10]. The insulin resistance index was calculated by using the relation between the serum rate of insulin and glucose [11].

Insulin resistance index = (fasting insulin x fasting glucose)/22,5

Assessment of lipid parameters

The cholesterol assay was performed following a colorimetric enzymatic method described using Dialab kit [12]. The HDL cholesterol assay was described using Inmesco kit [13]. The triglyceride level was determined by enzymatic colorimetric method using Dialab kit[14]. The LDL cholesterol level was deduced from the other lipids previously obtained[15]:

$$[\text{LDL cholesterol}] = [\text{Total cholesterol}] - \frac{[\text{Triglycerides}]}{5} - [\text{HDL Cholesterol}]$$

Determination of atherogenic index

The atherogenic index (AI) was calculated using the formula :

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IA = (TC-HDL-C) / HDL-c [16]

Statistical analysis

All results were expressed as mean ± ESM (Standard Error of Mean).Statistical analyses were evaluated by one-way ANOVA (Analysis Of the Variance) followed by Turkey posttestusing Graph Pad Prism Software Version 5.0. Statistical significance was accepted atthe < 0.05values.

RESULTS

Acute toxicity study of the aqueous extract of *G. senegalensis* roots

The administration of the dose of 2000 mg/kg in female mice did not cause mortality during the 14 days of observation. The mean lethal dose (DL_{50}) of the extract is higher than 2000 mg/kg. Thirty minutes (30 min) after administration of the extract at a dose of 2000 mg/kg, the animals showed the perceptible intoxication signs characterized by a slight increase in sensitivity to pain and aggressiveness (Table 1). These behavioral disturbances persisted until the 4th hour and disappear as from the 24th hour post treatment. Other behavioral manifestations (sensitivity to the touch, sensitivity to the noise, tremor and mobility) and signs of toxicity (respiratory movements, convulsion, diarrhea, tumors) were not observed during the experimental period.

Table 1: Signs of the toxicity and general behavior of the mice

Time	30 mn		4 h		24 h		48 h		Week 1		Week 2	
Observation	C	D	C	D	C	D	C	D	C	D	C	D
Sensibility to the touch	N	N	N	N	N	N	N	N	N	N	N	N
Sensibility to the pain	N	A+	N	A+	N	N	N	N	N	N	N	N
Sensibility to the noise	N	N	N	N	N	N	N	N	N	N	N	N
Aggressivity	N	A+N	A+N		N	N	N	N	N	N	N	
Mobility	N	N	N	N	N	N	N	N	N	N	N	N
Respiration	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion	A	A	A	A	A	A	A	A	A	A	A	A
Skaking	A	A	A	A	A	A	A	A	A	AA	A	
Diarrheoa	A	A	A	A	A	A	A	A	A	A	A	A
Tumour	A	A	A	A	A	A	A	A	A	A	A	A

C = Normal control ; D = 2000 mg/kg ; N = normal ; A = absent ; A+ = increaseslightly

Effect of the aqueous extract of *G. senegalensis* roots on oral glucose tolerance test

All animals of different groups presented a normal blood sugar regulation except those receiving the dose of 400 mg/kg of extract. Indeed, during the 2 hours of observation, no significant variation in blood glucose level was noted in mice of the reference group and those treated at the dose of 200 mg/kg of extract, compared to the control group animals. On the other hand, there is a significant decrease in postprandial glycemia with the highest dose (400 mg/kg) of extract at the 60th ($p < 0.05$), 90th ($p < 0.01$) and 120th ($p < 0.05$) minute post treatment (Figure 1).

Effect of the aqueous extract of *G. senegalensis* roots on relative body weight

The body weight of the diabetic control group animals was significantly decreased at days 3 ($p < 0.01$), 4 ($p < 0.01$) and 5 ($p < 0.05$), compared to the normal control group. This decrease is more important ($p < 0.001$) at days 6, 7 and 8 of treatment. Compared to diabetic control group, relative body weight in animals treated with metformin and different doses of extract has been no significant change during the 5 days of the experiment. For against, there is a significant increase in the relative body weight of the animals of the reference group at days 6 ($p < 0.05$) and 7 ($p < 0.01$) of the experiment. Similarly, the body weight of the mice

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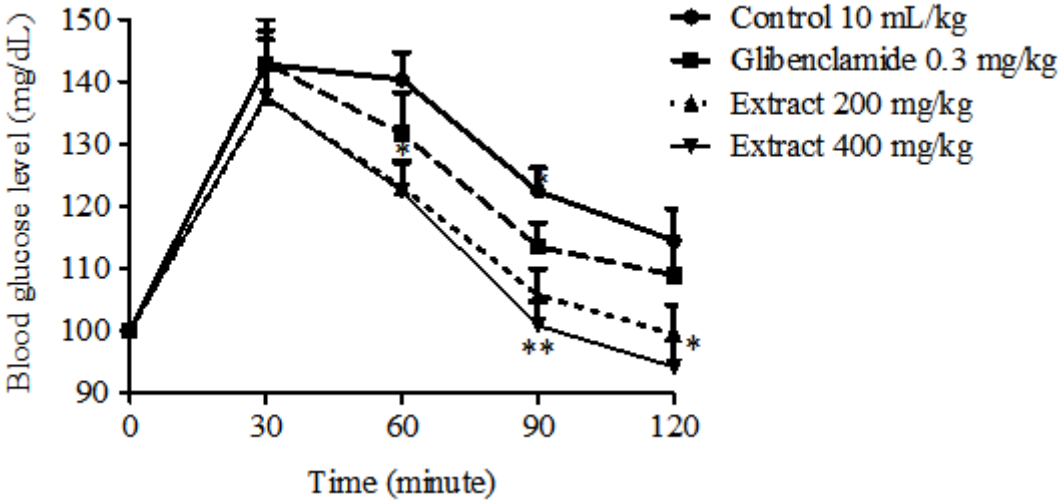
treated at the dose of 200 mg/kg significantly increased at the 6th ($p < 0.01$), 7th ($p < 0.05$) and 8th ($p < 0.01$) day of treatment (Figure 2).



Each curve represents a mean ± SEM of 6 mice in each group. *p<0.05 ; **p<0.01 compared to control group. SEM: Standard error of the mean.

Figure 1: Effect of *G. senegalensis* roots on oral glucose tolerance test in normal mice

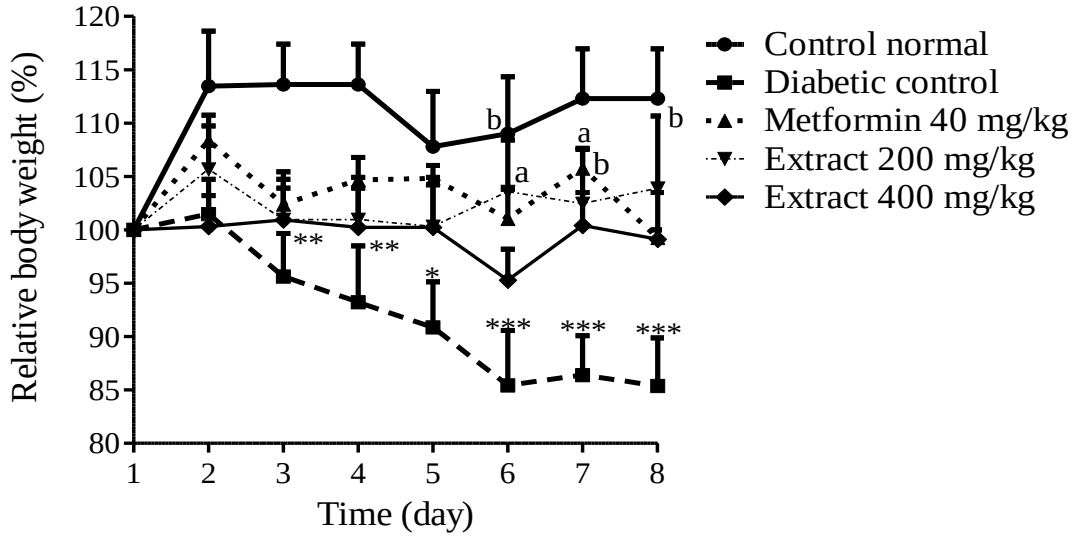


Figure 2: Effect of *G.senegalensis* roots on relative body weight in diabetic mice

Each curve represents a mean ± SEM of 5 mice in each group. *P<0.05; ** P<0.01; ***P<0.001 compared to normal control group. [a]P<0.05 ; [b]P<0.01 compared to diabetic control group. SEM: Standard error of the mean.

Effect of the aqueous extract of *G. senegalensis* roots on blood glucose level

At the 1st day of treatment, the glycemia of all treated animals is similar to that of the mice of the normal control group. However, compared to the normal control group, the blood sugar of the diabetic control group animals significantly increased ($p < 0.001$) at the last day of treatment. Furthermore, at the 8th day,

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metformin and the extract at doses of 200 and 400 mg/kg involved significant drops ($p < 0.01$; $p < 0.05$; $p < 0.01$) of blood glucose level, compared to the diabetic control group (Figure 3).

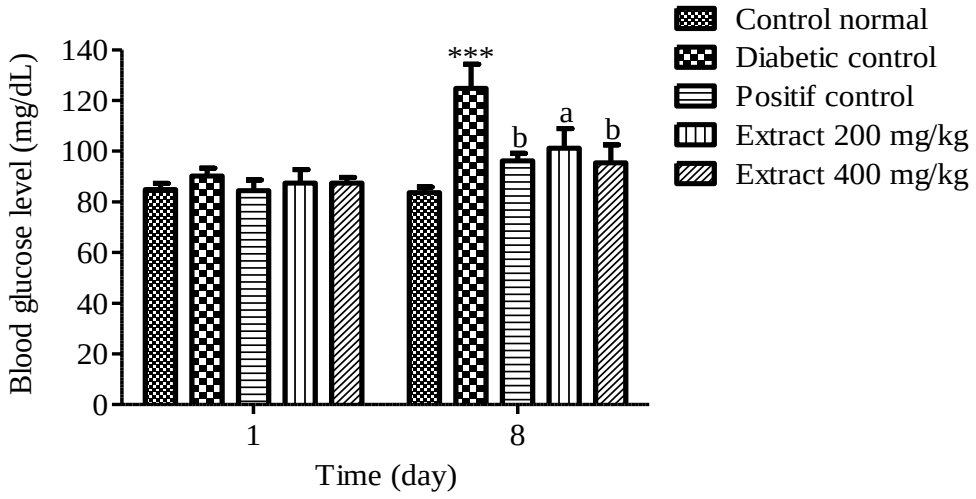

Figure 3: Effect of *G.senegalensis* on blood glucose level in diabetic mice.

Each bar represents a mean ± SEM of 5 mice in each group. ***P<0.001 compared to normal control group. [a]P<0.05 ; [b]P<0.01 compared to diabetic control group. SEM: Standard errorof the mean.

Effect of the aqueous extract of *G. senegalensis* roots on serum insulin level

Compared to the normal control group, the serum insulin level significantly increased in the mice of diabetic control group ($p < 0.001$) and those treated with the extract at doses of 200 ($p < 0.001$) and 400 mg/kg ($p < 0.05$). Compared to the diabetic control group, there was a significant increase ($p < 0.001$) in the serum insulin level of animals receiving the reference product and the different doses of extract (Figure 4).

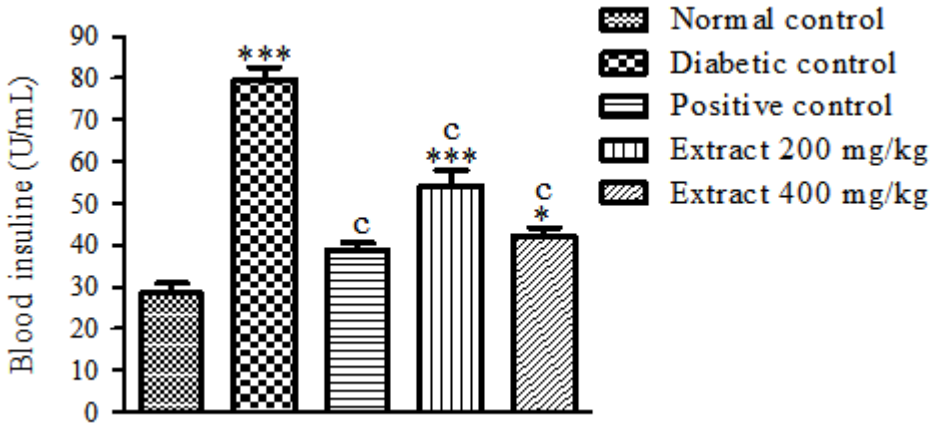

Figure 4: Effect of *G.senegalensis* on blood insuline level in diabetic mice

Each bar represents a mean ± SEM of 5 mice in each group. *P<0.05 ; ***P<0.001 compared to normal control group. [c]P<0.001 compared to diabetic control group. SEM: Standard errorof the mean.

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Effect of the *G. senegalensis* roots on the index of insulin resistance(HOMA)

A significant increase of insulin resistance index was observed with the diabetic control ($p < 0.001$) and dose of 200 mg/kg ($p < 0.05$) of extract, compared to the normal control group. However, compared to the diabetic control, a significant ($p < 0.001$) rise in insulin resistance index was observed in animals treated with metformin and different doses of extract (Figure 5).

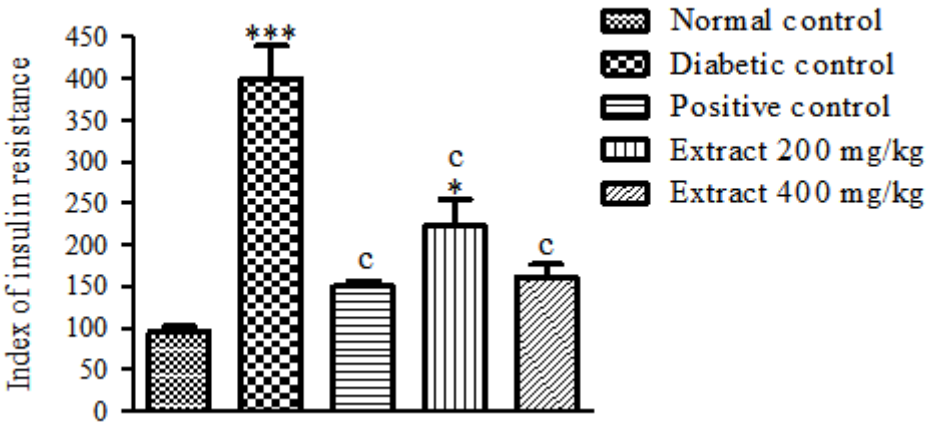

Figure 5: Effect of G. senegalensis on index of insulinoresistance in diabetic mice

Each bar represents a mean ± SEM of 5 mice in each group. *P<0.05 ; ***P<0.001 compared to normal control group. ^{c}P<0.001 compared to diabetic control group. SEM: Standard error of the mean.

Effect of the aqueous extract of *G.senegalensis* roots on serum lipid parameters

Compared to the normal control group,a important increase in triglyceride levels ($p < 0, 01$), total cholesterol ($p < 0.001$) and LDL cholesterol ($p < 0.001$) and a significant ($p < 0.001$) decrease in HDL cholesterol level were recorded. Comparing the results to the diabetic control group, there was a significant and dose-dependent decrease ($p < 0.05$; $p < 0.01$ and $p < 0.001$) in the total cholesterol levels in mice treated with metformin and doses of 200 and 400 mg/kg of extract. Similarly, there was a significant drop in triglyceride levels in animals treated with metformin ($p < 0.05$) and dose of 400 mg/kg ($p < 0.001$) of extract. A significant decrease ($p < 0.001$) in serum LDL cholesterol was also observed with metformin and doses 200 and 400 mg/kg of extract. However, metformin and the dose 400 mg/kg caused a significant increase ($p < 0.01$) in the HDL cholesterol level (Table 2).

Table 2: Effect of *Guierasenegalensis* administration on some lipid parameters of experimental mice

Group	Total cholesterol (mg/dL)	Triglycerides (mg/dL)	HDL-cholesterol (mg/dL)	LDL-cholesterol (mg/dL)
Normal control	101.71 ± 3.78	88.46 ± 3.90	60.08 ± 1.45	24.02 ± 5.26
Diabetic control	128.86 ± 3.77**	110.87 ± 5.70**	34.40 ± 1.77***	72.28 ± 3.16***
Positive control	107.96 ± 6.28a	92.26 ± 1.96a	46.83 ± 1.53***b	42.69 ± 5.41*c
Extract 200 mg/kg	101.65 ± 2.37b	94.97 ± 5.39	42.54 ± 2.39***	40.11 ± 4.42c
Extract 500 mg/kg	95.19 ± 3.30c	84.50 ± 1.45c	47.15 ± 2.42**b	31.14 ± 2.06c

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Values are expressed as mean ± SEM (n = 5). * P < 0.06 ; ** P < 0.01 ; *** P < 0.01 compared to normal control group. [a]P< 0.05; [b]P< 0.01; [c]P< 0.001 compared to diabetic control group. SEM: Standard error of the mean. HDL : High density lipoprotein ; LDL : Lowdensity lipoprotein.

Effect of the aqueous extract of *G.senegalensis* roots on the atherogenic index

Diabetic control group, reference control group and animals treated at the dose of 200 mg/kg of extract showed a significant increase (p < 0.001; p < 0.05; p < 0.01) onthe atherogenic index, compared to the normal control group. Furthermore, compared to the diabetic control group, there was a significant decrease (p < 0.001) of atherogenic index in all groups of animals treated with metformin and different doses of extract (Figure 6).

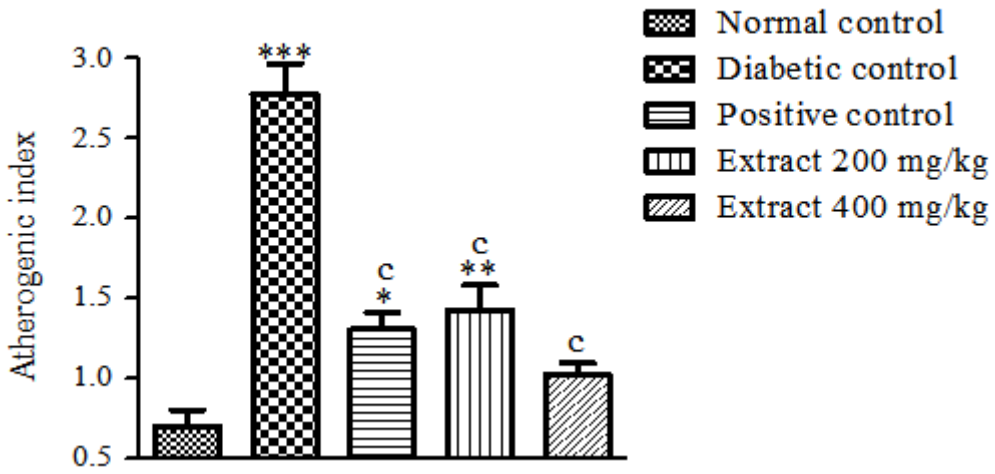

Figure 6: Effect of G. senegalensis on atherogenic index in diabetic mice

Each bar represents a mean ± SEM of 5 mice in each group. *P<0.05 ; **P<0.01 ; ***P<0.001 compared to normal control group. [c]P< 0.001 compared to diabetic control group. SEM: Standard error sof the mean.

DISCUSSION

Dexamethasone has been frequently used to induce insulin resistance in experimental animals [17]. In the present study, dexamethasone caused a decrease in body weight and HDL cholesterol, and increased blood sugar, insulin, insulin resistance index, atherogenic index, total cholesterol, triglycerides and LDL cholesterol levels.

The data obtained after a test of acute oral toxicity in the animal be used to meet the needs of the danger classification through DL_{50} and for the assessment of risks to human health [9]. In the present study, the administration of the extract at a single dose of 2000 mg/kg did not result in any deaths during the 14 days of experience. The DL_{50} is greater than 2000 mg/kg, which permits to classify the aqueous extract of the roots of *G. senegalensis* in the category of low-toxic substances [9]. Changes in behavior characterized by increased aggressiveness and sensitivity to touch and pain, were observed during the first 4 hours, but disappear at 24 hours post treatment. This increase in the sensitivity would be due is with an increase in the rate of algogenic substances (prostaglandins, histamine, etc) which are regulators of the perception of the pinching [18], that is to say with the stimulation of the transmission of the painful message at the central level [19].

During the glucose tolerance test, only the dose of 400 mg/kg induced a significant decrease in postprandial blood glucose at the 60th, 90th and 120th minute post treatment. It is known that the hypoglycemic substances lower the glyceamia by different action mechanisms: either by stimulating the secretion of insulin by the beta cells of the Langerhans islets either by miming the effects of insulin at the peripheral tissues [20]either by inhibiting the intestinal absorption of glucose [21]. Moreover, oral

administration of the extract at doses of 200 and 400 mg/kg for insulin-resistant mice resulted in significantly lower blood glucose level, insulin level and insulin resistance index, similarly to the product reference (metformin). These results corroborate those obtained by Dzeufiet *et al*. [22], which showed a significantly lower blood glucose level, insulin level and insulin resistance index after administration of the aqueous extract of the bark of *Milicia excelsa* in insulin resistant rats. Indeed, the extract would act through several action mechanisms : reduction of the hepatic production of glucose due to inhibition of gluconeogenesis and glycogenolysis, increase in peripheral sensitivity to insulin, leading to a better uptake and use of glucose by skeletal muscle and delayed-action and/or reduction in the intestinal absorption of glucose [23,24].

One of the main symptoms of diabetes is weight loss. In this study, the administration of dexamethasone significantly lowered the relative body weight to the normal control mice. Dexamethasone has lipolytic and proteolytic properties. In fact, it decreases the uptake of amino acids and protein synthesis in the muscles and increases lipolysis in fat cells [25]. The fall of relative body weight would be on the use of tissue protein and fat reserves due to lack of carbohydrates as the main energy substrates [26]. Compared to the animals of the diabetic control group, the extract and metformin involved an increase in body weight of animals at the 6th day of treatment. Our results are similar to those of Das et al. [27] which showed that the aqueous extract of *Azadirachta indica* stimulates the increase in the body weight of the diabetic animals after 21 days of treatment. It has been shown that the rise of the body weight observed in subjects receiving of the substances with antidiabetic activity can be due either to an insulinomimetic activity or with an insulin secreting activity [28]. Consequently, the extract of *G. senegalensis* would cause body weight gain in diabetic rats by similar mechanisms.

Insulin resistance is often associated with dyslipidemia characterized by an increase in total cholesterol, triglycerides, LDL cholesterol and a low of HDL cholesterol [29]. In the present study, the administration of dexamethasone in mice induced hyperlipidemia. On the other hand, the metformine and the doses of 200 and 400 mg/kg prevented this increase in the mice. This effect is beneficial in the sense that it prevents the formation of atherosclerosis and thus reduces cardiovascular risk in diabetic patients. This is supported by the significant decrease of atherogenic index in diabetic subjects receiving different doses of extract of *G. senegalensis*. These results are similar to those obtained by Maiffo et al. [30]which showed the hypolipidemic effect of the extracts of the twigs of *Combretum molle* in insulin resistant rats. In adipose tissue, insulin has an anti-lipolytic action by inhibiting the hormone-sensitive lipase. The extract of *G. senegalensis* would have imitated the insulin action in adipose tissue. It probably acts by decreasing the biosynthesis of cholesterol specifically by reduction in the activity of the 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase enzyme. Moreover, the extract would have reduced the rate of serum triglycerides by reduction in the synthesis of the fatty-acids, increase in the catabolism of the LDL and reduction of the production of the precursors of triglycerides such as the acétyl-CoA and the glycerol phosphates [31]. The effects of metformin observed in this present study correspond to those described by Severino et al. [32]which showed that metformin was able to improve the lipid profile of diabetic patients by reducing the total cholesterol, triglycerides and LDL cholesterol and increasing HDL cholesterol. The extract *G. senegalensis* would have improved the lipid profile by the mechanisms of action similar to those of metormin.

CONCLUSION

The aqueous extract of *G. senegalensis* possess remarkable antidiabetic properties in insulin resistance mice, thereby validating the merits of ethnopharmacological use of this extract as preventive medication for type 2 diabetes.

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