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Antihyperglycemic and antihyperlipidemic effects of *Cymbopogon citratus* leaves in dexamethasone-induced diabetic rats

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Abstract

Background: In sub-Saharan Africa, especially in Cameroon, different parts of *Cymbopogon citrarus* (*C. citratus*) are prescribed as remedies for diabetes mellitus and dyslipidemia. This study was designed to investigate the effects of hydroalcoholic extract of *C. citratus* (HACC) leaves in dexamethasone-induced-diabetic (Dex-db) rats.

Materials and Methods: The HACC was obtained by decoction for 15 min by mixing 250 g of dry powder of the leaves of *C. citratus* by completing the total volume to 1L with a hydroalcoholic solution (water-ethanol, 30:70). After cooling to room temperature and filtration using Whatman No. 4 filter paper, the extract was concentrated using a rotary evaporator at 45 °C. Moderate diabetes was induced by daily subcutaneous injection of dexamethasone (5 mg/kg) once daily for 7 days. On the 8th day, the animals which have a blood glucose level greater than 120 mg/dL were selected and randomized into 5 groups of 5 animals each who received the different treatments for two weeks as follows: two negative control groups, negative normal control (NNC) and negative dexamethasone control (NDC) received only vehicle (distilled water); one positive control group received glibenclamide (5 mg/kg) and two groups received HACC at doses of 50 and 100 mg/kg respectively. On the other hand, compared to the NDC group, we observed a significant ($P<0.001$) dose-response after 14 days of treatment a decrease in serum concentrations of TC, LDLc, and AI, and an increase in HDLc. A highly significant decrease ($P<0.001$) was also observed in serum TG concentration but with a more pronounced action at the lowest dose of HACC (50 mg/kg).

Results: After two weeks of administration of the HACC, we observed during the oral glucose tolerance test (OGTT) a highly significant rate of reduction in glycemia (%) at the two doses tested (50 and 100 mg/kg) compared to the NNC group ($P<0.001$) 2 hours after glucose load, no significant difference was observed ($P>0.05$). With regard to the serum lipid profile (total cholesterol (TC), HDL cholesterol (HDLc), triglycerides (TG), LDL cholesterol (LDLc) and atherogenicity index (AI)), after 14 days of administration of the various treatments, with the exception of the TC which decreased significantly ($P<0.001$), no significant difference ($P>0.05$) was observed on the other parameters in the animals having received the HACC only at the dose of 100 mg/kg compared to the NNC group.

Conclusion: This finding suggests that the leaves of *C. citratus* have a highly significant antihyperglycemic and antihyperlipidemic activity in diabetic rats by preventing the postprandial glycemia peak and by readjusting the lipid profile, in particular by lowering serum LDL-cholesterol, triglycerides and the atherogenicity index.

Keywords: *Cymbopogon citratus*; Type 2 Diabetes mellitus; Dexamethasone; Antihyperglycemic; Antihyperlipidemic; Rat

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1 Introduction

Diabetes is one of the five leading causes of death in the world, of all forms of diabetes, type 2 diabetes mellitus is the most common and accounts for about 80 % of most diagnosed diabetes. Diabetes mellitus is a global public health problem as it affects 5 % of the world's population and accounts for approximately 10 % of total health expenditure in many countries [1]. Hyperglycemia in diabetic patients is mostly associated with alterations in glucose and lipid metabolism and modification in liver enzyme levels [2]. Physiological glucocorticoids (cortisone and hydrocortisone) are essential metabolic hormones. Synthetic corticosteroids, including dexamethasone, are used primarily for their anti-inflammatory effect. In high doses, they reduce the immune response. Furthermore, glucocorticoids can elevate plasma lipid levels in humans and induce dyslipidemia in laboratory animals, they have also been recognized as secondary causative agents of dyslipidemia [3], [4]. Administration of glucocorticoids can cause hyperlipidemia both in man and other animal species, including Wistar rats [5]. The pattern and extent of hyperlipidemia varies depending on the dosage of glucocorticoids and on the animal species [3].

2 Material and methods

2.1 Chemical and drugs

All chemicals used where from analytical grade: Dexamethasone (RYAN PHARMA®-UK, D-(+)-Glucose (Sigma Aldrich, Germany), Glibenclamide (Daonil®, Sanofi, Paris-France), Lipid Profile Kit (BIOLABO®, Maizy-France; Cholesterol CHOD-PAP Ref. 80106, Cholesterol-HDL PTA Precipitant Ref. 86516, Triglycerides GPO Method, Ref. 80019).

2.2 Collection and preparation of plant materials

The leaves of *C. citratus* were harvested in a private garden in the city of Yaoundé, Cameroon in May 2019. The aerial portion of the plant was sampled approximately 7 cm from the base of the plant where the roots began. Once harvested, the leaves were thoroughly washed using tap water and drained in a colander. After being drained, the leaves were cut to a length of about 1 cm and then placed on newspaper so that they could dry for two weeks at room temperature in the laboratory and away from sunlight. After drying, the leaves were crushed using an electric grinder and then sieved using a sieve whose mesh diameter was less than 0.5 mm. The powder thus obtained was stored in a dark bottle in order to prepare the hydroalcoholic extract later.

The HACC was obtained by decoction for 15 min by mixing 250 g of dry powder of the leaves of *C. citratus* by completing the total volume to 1L with a hydroalcoholic solution (water-ethanol, 30:70). After cooling to room temperature and filtration using Whatman No. 4 filter paper, the extract was concentrated using a rotary evaporator at 45 °C.

The concentrated extract thus obtained was stored in a dark glass container sealed and then stored in the refrigerator at 4°C for later use.

2.3 Study design and population

2.3.1 Animals

The animals used during this experiment were male albino rats of the Wistar strain, reared in polypropylene cages where the litter was replaced every two days. The rats were eight weeks old at the beginning of the experiment, including the two weeks when they were acclimatized with a day-night cycle in hours of 12:12 and an ambient laboratory temperature of 24 ± 2 °C during this period of the year (March - May). The animals had ad libitum access to water and food whose energy intake was composed of 55 % carbohydrates, 25 % proteins and 20 % lipids.

2.3.2 Induction of type 2 diabetes mellitus

Moderate type 2 diabetes mellitus was induced as previously described [6], by a daily subcutaneous (*sc*) injection of dexamethasone at a dose of 5 mg/kg for seven consecutive days between 7 am and 8 am. On the seventh day of injection, the animals were fasted on food and not on water from 6 p.m. for a period of at least 12 h (6 p.m. to 7 a.m. on the eighth day). Animals that had a fasting blood glucose level above 120 mg/dL were considered diabetic and selected for the experiments.

2.3.3 Grouping of experimental animals

For carrying out the experiments, five batches of six animals each were carried out and randomized from animals whose glycaemia after 12 hours of fasting was greater than 120 mg/dL. The sixth animal of each batch was used for making histological sections. As a result, the sixth animal in each group was not sampled throughout the experiment. Thus, five animals from each batch were the subject of blood samples respectively on days 1, 7 and 14 for the determination of blood glucose level and lipid profile parameters. The animals were divided into groups as follows:

- **Group 1:** normoglycemic negative control group (NNC) having received no treatment except for the vehicle during the fourteen days of experimentation, distilled water orally (10 mL/kg, *po*);
- **Group 2:** Negative diabetic control group (NDC) who received exclusively distilled water (10 mL/kg, *po*);
- **Group 3:** positive control group, having received glibenclamide (5 mg/kg, *po*) during the fourteen days of the experiment;
- **Group 4 and 5:** experimental groups having received HACC at respective doses of 50 and 100 mg/kg (*po*) for fourteen days.

2.3.4 Animal sacrifice and collection of samples

After fourteen days of administration of the various substances, the animals were subjected to a food and non-water fast of 12 hours after which the blood samples were collected by the retro-orbital method after anesthesia of the animals with ether respectively on the first, seventh and fourteenth day of the experiment.

For the determination of the lipid parameters, the blood was centrifuged at a speed of 2500 revolutions per minute for 15 minutes in order to obtain the serum. Serum from each experimental group was collected using a micropipette and aliquoted into 2 mL Eppendorf tubes and then stored in the refrigerator at -20 °C for subsequent determination of lipid parameters.

2.4 Experimentation

The experiments were carried out over a period of fourteen days. During this period, distilled water (10 mL/kg, *po*), glibenclamide (5 mg/kg, *po*) and hydroalcoholic extract of *C. citratus* (50 and 100 mg/kg, *po*) were respectively administered to the different groups.

2.5 Oral Glucose Tolerance Test (OGTT)

The OGTT was performed as previously described [7], [8]. The diabetics animals were fasted for 12 h and treated with distilled water (vehicle, 10 ml/kg), glibenclamide (5 mg/kg), and HACC (50 and 100 mg/kg). A group of normoglycemic control animals was also formed and received as treatment distilled water (10 mL/kg).

The OGTT was carried out on days 1, 7 and 14. Before the administration of the different treatments, the blood glucose level of each animal was taken 30 min (t = -30 min) before the administration of the different substances using d a *Vivachek™Ino* glucometer and the different substances were immediately administered to the different groups of animals. For an immediate blood glucose reading, a drop of blood was taken from the distal end of each rat's tail and placed on the strip, allowing the blood glucose value to be read 5 seconds after the drop was placed blood on the test strip. 30 min after the administration of the different substances (t= 0 min) the blood glucose level of each animal was taken, a solution of glucose (0.3 g/mL) was immediately administered to all the groups at a dose of 3 g/kg. The blood glucose levels were then taken respectively at times (min) 30, 60, 90 and 120 after the oral glucose overload.

2.6 Evaluation of lipid profile

The evaluation of the serum lipid profile consisted in determining, using the BIOLABO® kit, the TC (equation N_o 1), the HDLc (equation N_o 2), and the TG (equation N_o 3). LDLc was determined by Friedwal's formula (equation N_o 4), and AI was also determined by calculation using equation N_o 5.

$$\text{TC}\ (g/L) = \frac{sample\ optical\ density}{standard\ optical\ density}\ x\ standard\ concentration\ (2\ g/L) \text{..... Equation No 1}$$

$$\text{HDLc}\ (g/L) = \frac{sample\ optical\ density}{standard\ optical\ density}\ x\ standard\ concentration\ (1\ g/L) \text{ ..... Equation No 2}$$

$$\text{TG}\ (g/L) = \frac{sample\ optical\ density}{standard\ optical\ density}\ x\ standard\ concentration\ (2\ g/L) \text{..... Equation No 3}$$

$$\text{LDLc } (g/L) = \text{TC} - \frac{TG}{5} - HDLc \text{ ..... Equation No 4}$$

$$\text{LDLc } (g/L) = \frac{\text{TC}}{HDLc} \text{ ..... Equation No 5}$$

2.7 Statistical analysis

All the tests were performed as individual quintuple experiment and analyses were performed using GraphPad Prism 5.0.3. all the data are expressed as mean ± standard error mean (S.E.M. n = number of experiments). Analysis of variance (ANOVA, Bonferroni post-test) and pair t-test were done as the test of significance. The confidence interval was set at 95 % with a significance threshold of less than 5 % ($P<0.05$).

3 Results

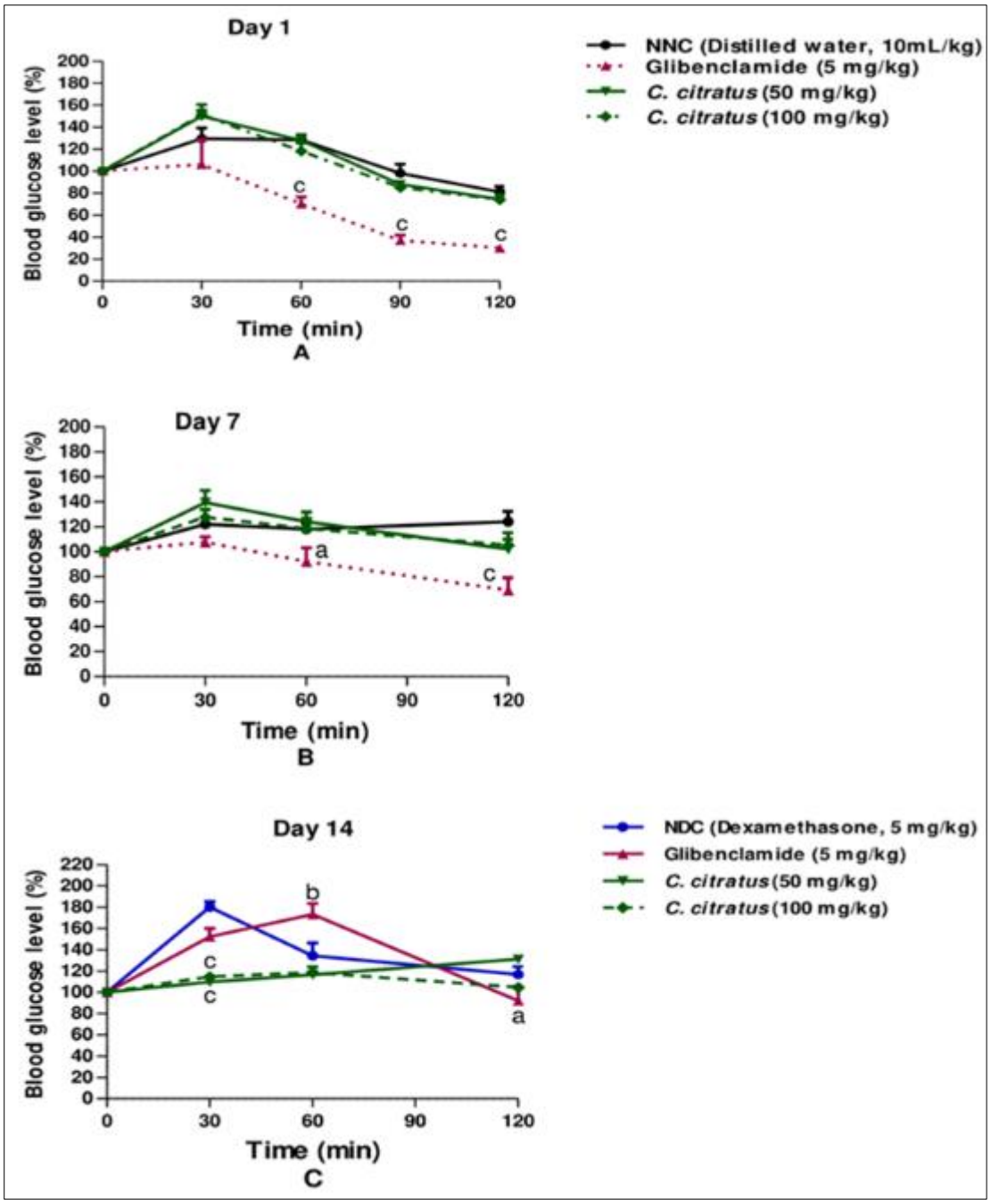
3.1 Effect of glibenclamide and *Cymbopogon citratus* on OGTT on the 1st, 7th and 14th day

Figure 1 shows the effect of glibenclamide and HACC in diabetic rats following oral glucose overload (3 g/kg) after a single administration of the different treatments on day 1 (Figure 1A) and repeated subacute administration of the different treatments respectively on days 7 and 14 (Figure 1B and 1C respectively). On days 1 and 7, the variation in the glycemia level (%) of the various diabetic animals was compared with that of the animals of the normoglycemic control group having received no treatment except the vehicle (distilled water, 10 mL/ kg) while on day 14, which marks the end of treatment, the variation in the blood glucose level of the different groups of diabetic animals treated with an insulin-secreting agent, the reference oral antidiabetic product (glibenclamide 5 mg/kg) and plant extract (HACC, 50 and 100 mg/kg) was compared with the dexamethasone-induced diabetic rats (Dex-db) control group which had not undergone any treatment other than the vehicle.

Figure 1A shows that the single administration of glibenclamide prevented the postprandial glycaemia peak in a non-significant manner ($P>0.05$) compared to the group of normoglycemic animals. On the other hand, the plant extract at the two doses tested (50 and 100 mg/kg) did not prevent the postprandial glycaemia peak although this was not significant ($P>0.05$) and this until 120 min after the oral glucose overload, where values of the glycemic levels of the plant extract were observed to be lower than those of the normoglycemic control group. In addition, 60, 90 and 120 min after oral glucose overload, a significant reduction ($P<0.001$) in the value of glycemia is observed in the group of animals having been treated with glibenclamide compared to the normoglycemic control group at the point where the average glycemia value after 120 min after oral glucose overload represents less than 40 % of the initial glycemia.

Figure 1B shows an effect similar to that of Figure 1A after the oral glucose overload test on day 7 of the treatment with glibenclamide and the plant extract at the two doses tested compared to the normoglycemic control group. 30 min after the oral glucose overload, the plant extract had a dose-dependent effect with the dose of 100 mg/kg which exhibits an anti-hyperglycemic effect similar to that of the normo-glycemic control group ($P>0.05$) and after 120 min after oral glucose overload, a rate of reduction in glycaemia of approximately 20 % compared to the normoglycemic control group is observed. Moreover, compared to the normoglycemic control group, glibenclamide, a reference hypoglycemic antidiabetic, prevented the postprandial glycemia peak 30 min after the oral glucose overload ($P>0.05$), and also significantly reduced the postprandial glycemic levels after 60 ($P<0.05$) and 120 min ($P<0.001$) respectively after oral glucose overload.

After fourteen days of treatment of diabetic rats with glibenclamide and the plant extract (Figure 1C), it appears that the plant extract prevented the postprandial glycemia peak at the two doses tested in a highly significant manner ($P<0.001$) 30 min after oral glucose overload compared to the control group of untreated Dex-db animals. On the other hand, in diabetic rats treated with the reference insulin secretor (glibenclamide, 5 mg/kg), although 30 min after oral glucose overload the blood glucose rate was lower than that of the Dex-db control group, it did not significant ($P>0.05$) and the peak in the postprandial glycemia level is rather observed at 60 min after oral glucose overload and proves to be higher than that of the Dex-db control group ($P<0.01$) having undergone no treatment and it was only after 120 min that the postprandial glycemia level of the group of Dex-db animals having received glibenclamide was significantly reduced ($P<0.05$) compared to the Dex-db control group of animals.



The results are expressed as mean ± SEM (n=5). a (P<0.05); b (P<0.01); c (P<0.001): significant difference compared to the NNC/NDC group. A: Day 1; B: Day 7; C: Day 14.

Figure 1 Effect of the hydroalcoholic extract of *Cymbopogon citratus* on the variation of postprandial glycaemia

3.2 Effect of glibenclamide and *Cymbopogon citratus* on lipid profile on the 7th and 14th day

The effects of glibenclamide and HACC on the lipid profile of dexamethasone-induced diabetic animals are shown in Figure 2.

3.3 Effect of *Cymbopogon citratus* on Serum Total cholesterol (TC)

Concerning the serum TC concentration in the Dex-db animals (Figure 2A), it appears on the seventh day of treatment with glibenclamide that there is no significant difference (P>0.05) compared to the group of normoglycemic animals control and a significant difference (P<0.05) compared to the animals of Dex-db control group. On the other hand, on the fourteenth day of treatment with glibenclamide in diabetic animals, a highly significant reduction in the serum concentration of TC is observed (P<0.001) compared with the normoglycemic and diabetic control animals. On the

seventh day of treatment of Dex-db animals with HACC, only the 100 mg/kg dose had a significant difference ($P<0.001$) in serum TC level compared to the group of normoglycemic animals. No significant difference ($P>0.05$) was observed in serum TC concentration compared to the control group of Dex-db animals at the respective doses of 50 and 100mg/kg of HACC. On the fourteenth day of treatment of Dex-db animals with the plant extract, we observed a highly significant ($P<0.001$) dose-dependent reduction in serum TC concentration compared to the control group of Dex-db animals. On the other hand, when we made the comparison with the group of normoglycemic animals, only the dose of 100 mg/kg of the plant extract also proved to be highly significant ($P<0.001$) in the reduction of serum TC concentration.

3.4 Effect of glibenclamide and *Cymbopogon citratus* on Serum High Density Lipoprotein Cholesterol (HDLc)

After seven days of treatment of Dex-db animals with glibenclamide and the plant extract at doses of 50 and 100 mg/kg, we observed a non-significant reduction ($P>0.05$) in the serum HDLc concentration of the different groups of treated animals compared to the group of normoglycemic control animals (Figure 2B). On the other hand, compared to the Dex-db control group, the serum reduction of HDLc after seven days of treatment decreased significantly in the groups treated with glibenclamide ($P<0.01$), and with HACC at doses of 50 ($P< 0.001$) and 100 mg/kg ($P<0.01$). On the other hand, after fourteen days of treatment of Dex-db animals, a highly significant ($P<0.001$) increase in serum HDLc concentration was observed compared to the Dex-db group of animals and the normoglycemic control group only at the dose of 50 mg/kg ($P<0.001$) while we observed in Dex-db animals treated with glibenclamide a non-significant ($P>0.05$) and highly significant ($P<0.001$) serum HDLc decrease compared to the normoglycemic control and Dex-db groups respectively.

3.5 Effect of glibenclamide and *Cymbopogon citratus* on Serum Low Density Lipoprotein Cholesterol (LDLc)

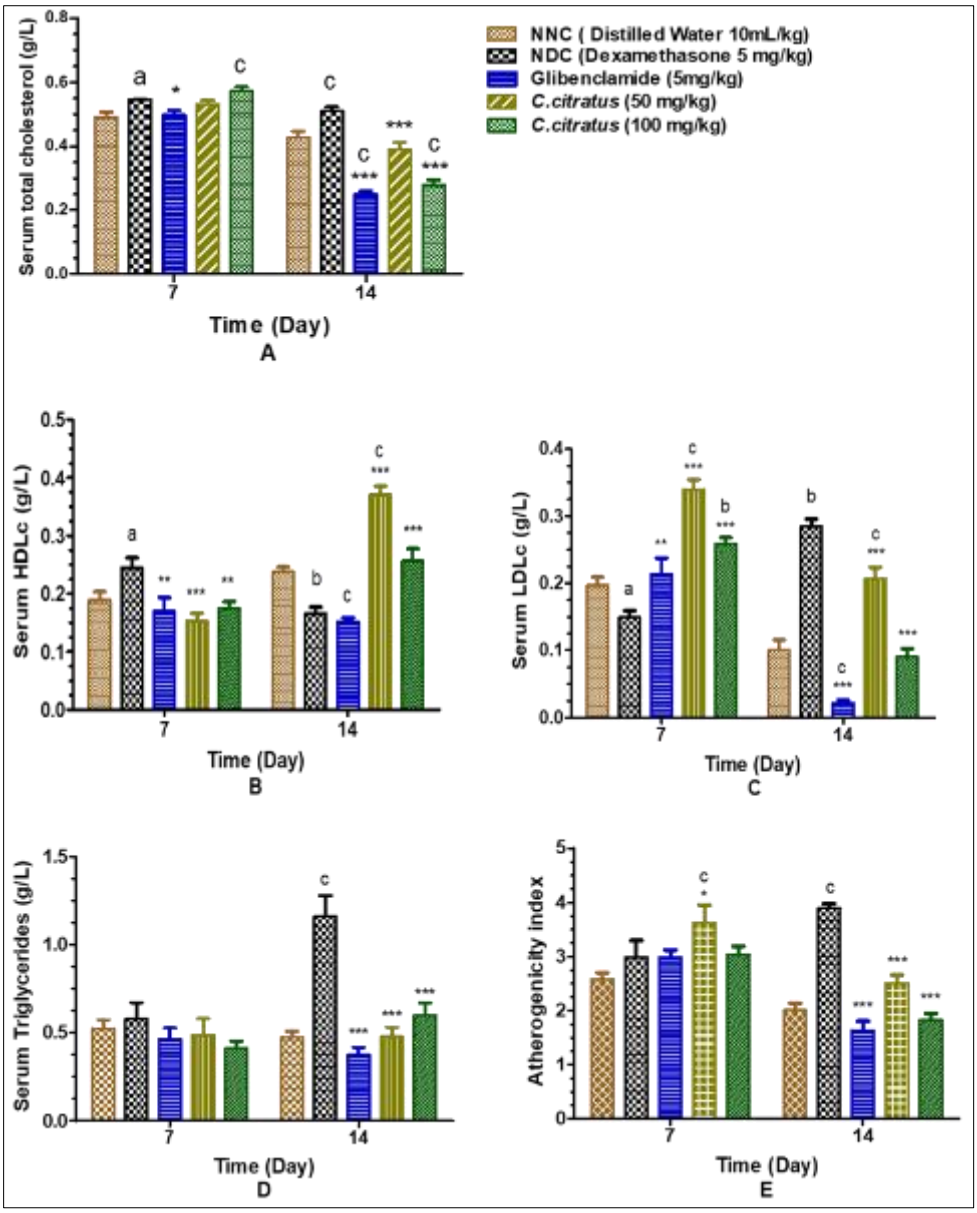
Figure 2C shows the serum LDLc change of the animals treated with glibenclamide and HACC for fourteen days. Glibenclamide and the plant extract at the two doses tested show similar results after seven and fourteen days of treatment where, compared to the Dex-db control group of animals, a very significant increase in serum LDLc concentration was respectively observed ($P<0.01$ for glibenclamide and $P<0.001$ for the plant extract at the two doses tested) and a highly significant reduction in serum LDLc concentration both in the group of Dex-db animals treated with glibenclamide and those treated with HACC at the two doses tested. Furthermore, compared to the normoglycemic control group, we also noted an increase in serum LDLc concentration on the seventh day of treatment in the groups of Dex-db animals treated with glibenclamide ($P>0.05$) and plant extract at doses of 50 ($P<0.001$) and 100 mg/kg ($P<0.01$). After fourteen days of treatment, compared to the normoglycemic control group, we observed a drop in serum LDLc in the groups of Dex-db animals treated respectively with glibenclamide ($P<0.001$) and HACC at a dose of 100 mg/kg ($P>0.05$) and an increase to the dose of 50 mg/kg ($P<0.001$) which gives the plant extract a dose-dependent effect in reducing serum LDLc concentration.

3.6 Effect of glibenclamide and *Cymbopogon citratus* on Serum Triglycerides (TG)

Figure 2D shows the change in serum TG concentration of Dex-db animals that underwent fourteen days of treatment with glibenclamide and HACC. After seven days of treatment, compared to the different groups of control animals (normoglycemic and Dex-db), a non-significant reduction ($P>0.05$) of the serum TG of the different groups of Dex-db animals treated respectively is observed in the reference molecule and in the plant extract at the two doses tested. On the fourteenth day of treatment, no significant difference ($P>0.05$) was also observed in the serum TG concentration both in the group of animals treated with glibenclamide and in the group treated with plant extract compared to the group of normoglycemic control animals. On the other hand, at the same period (fourteenth day), compared to the group of Dex-db control animals, a highly significant decrease in plasma TG ($P<0.001$) is observed in the different groups of Dex-db animals treated with glibenclamide and HACC.

3.7 Effect of glibenclamide and *Cymbopogon citratus* on Atherogenicity Index (AI)

The variation in AI of Dex-db animals treated with glibenclamide and HACC is shown in Figure 2E. After seven days of treatment, we observed a significant increase in AI only in the group of animals having received HACC at a dose of 50 mg/kg compared to the control groups of normoglycemic animals ($P<0.001$) and Dex-db ($P<0.05$). Moreover, compared to the control group of Dex-db animals, on the fourteenth day of treatment, a highly significant reduction ($P<0.001$) of the AI is observed in the groups of animals treated with glibenclamide and with the extract of the plant at the two doses tested. No significant variation in AI was observed in the groups of animals treated with glibenclamide and HACC at the respective doses of 50 and 100 mg/kg when compared to the AI of the normoglycemic control group.

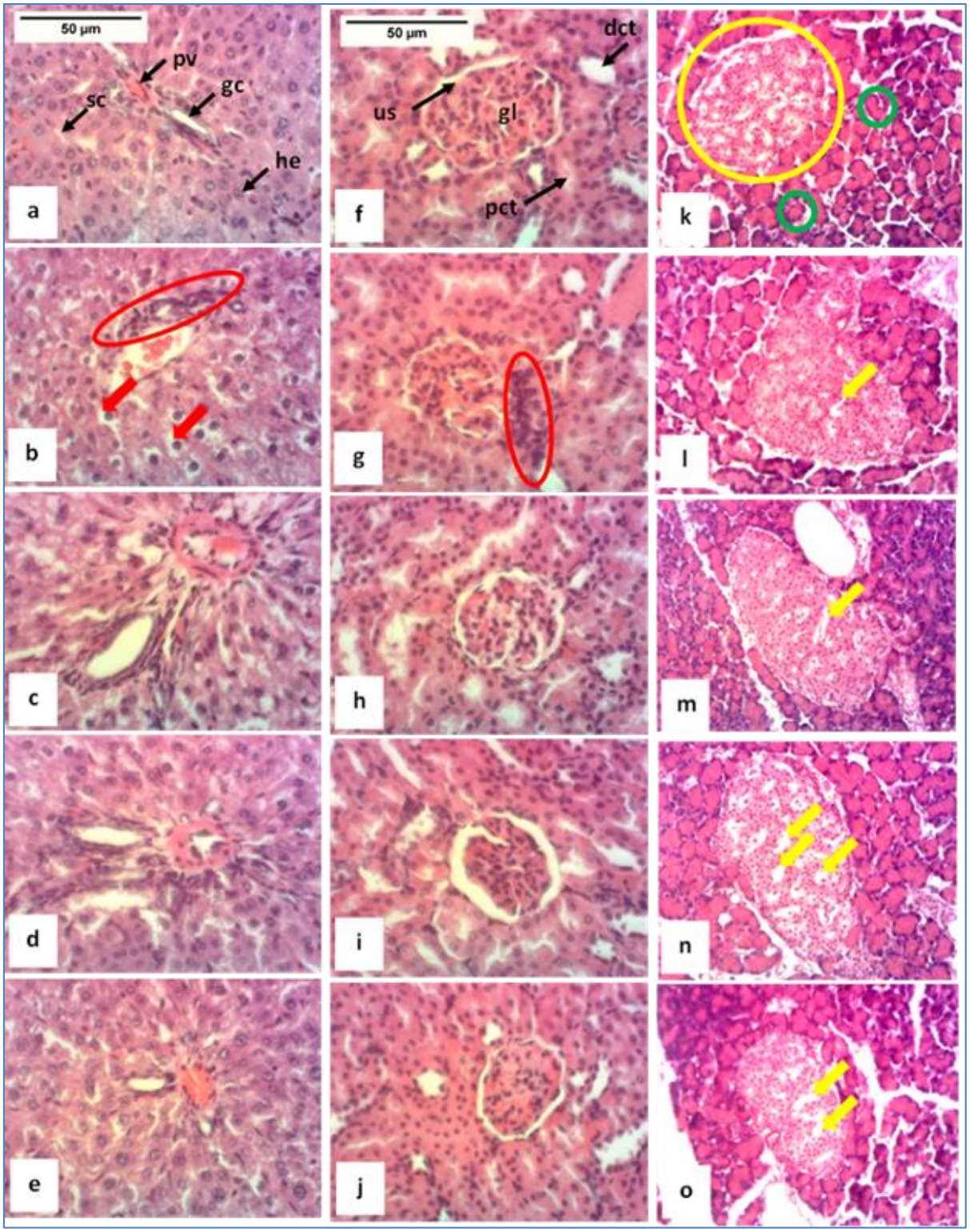


The results are expressed as mean ± SEM (n=5). a (P<0.05); b (P<0.01) c (P<0.001): significant difference compared to the NNC group. * (P<0.05); ** (P<0.01); *** (P<0.001): significant difference compared to the NDC group. A: serum total cholesterol; B: serum HDL cholesterol; C: serum LDL cholesterol; D: serum triglyceride; E: atherogenicity index.

Figure 2 Effects of the hydroalcoholic extract of *Cymbopogon citratus* on the variation of the lipid profile in the dexamethasone-induced-hyperglycemic rat

3.8 Histopathological examination of the liver, kidney and pancreatic tissues

Figure 3 shows mmicrophotography of liver, kidney and pancreatic tissues. The histological analysis showed in the untreated normoglycemic rats (NNC), a normal structuring of the hepatic, renal and pancreatic parenchyma. Compared to normoglycemic group, diabetic animals from the untreated dexamethasone-induced diabetic rats (NDC) presented several histopathological alterations such as cytolysis in the liver, marked by a halo around the nuclei of hepatocytes (red arrows), leukocyte infiltrations in the liver and kidney (red circles) and hypertrophy of the islets of Langerhans (yellow cercle) in the endocrine pancreas, characterized by a reduction in the interglandular spaces (yellow arrows). The groups of animals treated with the reference substance (glibenclamide, 5 mg/kg) as well as with the hydroalcoholic extract of *Cymbopogon citratus* at the respective doses of 50 and 100 mg/kg presented a restructuring of these organs, close to that of the normoglycemic group.



NNC = Negative Normoglycemic Control; NDC = Negative Diabetic Control; dct = distal convoluted tube; gc =galic canalicus; gl = glomerula; ha = hepatic artery; he = hepatocyte; pct = proximal convoluted tube; pv = portal vein; sc = sinusoidal capillary; us = urinary space; green circle = acini (exocrine pancreas); red arrows = hepatic cytolysis; red cycles = leukocyte infiltration; yellow arrows = interglandular spaces; yellow circle = islet of Langerhans.

Figure 3 Microphotograph of liver tissue H&E, stain, X200 (a, b, c, d, e), kidney tissue H&E, stain, X200 (f, g, h, i, j) and pancreatic tissue H&E, stain, X100 (k, l, m, n, o) of normoglycemic rats (NNC: a, f, k), untreated dexamethasone-induced diabetic rats (NDC: b, g, l) and dexamethasone-induced diabetic rats treated with glibenclamide 5 mg/kg (b, g, l) and hydroalcoholic extract of *Cymbopogon citratus* at doses of 50 mg/kg (d, i, n) and 100 mg/kg (e, j, o) respectively

4 Discussion

Diabetes mellitus is a metabolic disease characterized by chronic hyperglycemia resulting from insufficient production of insulin by pancreatic ß-cells (type 1 diabetes mellitus) or from tissue resistance to the action of insulin (type 2 diabetes mellitus) [9]. Effective glycemic control accompanied by a healthy lifestyle is the essential first step in preventing diabetes complications in type 1 and type 2 diabetic patients. In this study, type 2 diabetes mellitus was induced by repeated administration of a high dose of dexamethasone (5 mg/kg) once daily for seven days to eight-week-old male rats. Dexamethasone is a synthetic glucocorticoid with anti-inflammatory and anti-allergic activity. Administered in high doses and repeatedly, dexamethasone can induce diabetes mellitus with hepatic steatosis following chronic hyperglycemia and accumulation of fat in the hepatic parenchyma [10]–[12].

Diabetes mellitus is mainly treated with oral antidiabetics for type 2 diabetes or a combination of oral antidiabetics with insulin (type 1 diabetes mellitus). Glibenclamide is an oral antidiabetic belonging to the class of sulfonylureas, which are insulin secretors that can cause hypoglycemia both in humans and in experimental mouse models. Thereafter, glibenclamide has been used widely in the type 2 diabetes mellitus [13].

In this study, glibenclamide was used as a positive control in the treatment of type 2 dexamethasone-induced diabetic rats (Dex-db). The hydroalcoholic extract of *C. citratus* was also used in the treatment of Dex-db rats at the respective doses of 50 and 100 mg/kg, in order to compare its effects on the regulation of glycemia and the lipid profile with those of glibenclamide. OGTT performed after fourteen days of administration of the various treatments to Dex-db rats showed that the plant extract at the two doses tested prevented the postprandial glycemia peak ($P<0.001$) 30 min after the oral glucose overload compared to the group Dex-db control animals that received only the vehicle. Compared to the Dex-db control group, the antihyperglycemic effect of HACC was more pronounced ($P<0.001$) than that of glibenclamide ($P>0.05$) 30 min after oral glucose overload, the postprandial glycemia peak of the group who received glibenclamide occurred after 60 min after oral glucose overload and was superior ($P<0.01$) to that of the Dex-db control group at 60 min. However, 120 min after oral glucose overload, only the group of Dex-db animals having been treated with glibenclamide had a significant reduction ($P<0.05$) in glycemia compared to the group of Dex-db control animals. HACC at a dose of 100 mg/kg had a non-significant ($P>0.05$) reduction in blood glucose compared to the Dex-db control group. However, it should be noted that the plant extract at the two doses tested brought the postprandial glycemia values close to those of the initial glycemia 120 min after the oral glucose overload. On the other hand, after oral glucose overload in the group having received glibenclamide, postprandial glycaemia (120 min after oral glucose overload) was reduced by more than 20 % compared to the initial glycemia.

These results suggest that HACC potentiated insulin sensitivity in Dex-db rats while insulin resistance was still observed in the group of animals having received glibenclamide treatment with a late postprandial glycemia peak which was observed 60 min after oral glucose overload instead of 30 min. The insulin sensitivity as well as the antihyperglycemic effect obtained after the treatment of Dex-db rats with the plant extract could have a mode of action combined with that of glibenclamide and metformin to regulate and bring blood glucose level to normal values in diabetic rats [7]. It should be noted that glibenclamide acts exclusively at the level of ß-pancreatic cells to stimulate only insulin secretion and make insulin available for the cells but has no effect on insulin sensitivity [14]. On the other hand, metformin is an oral antidiabetic belonging to the family of normoglycemic biguanides (antihyperglycemic agents) specially used in the treatment of type 2 diabetes [7], [15]. The role of metformin is to reduce the insulin resistance of the organism intolerant to carbohydrates and to reduce hepatic gluconeogenesis. The mechanism of action of metformin includes direct stimulation of glycolysis in the tissues with an increase in glucose from the blood, a reduction in hepatic and renal gluconeogenesis, a reduction in intestinal absorption from the gastrointestinal tract with the conversion of glucose to lactate by enterocytes, and reduction in plasma glucagon levels [16].

Insulin resistance and hyperinsulinemia are often associated with a group risk factors including dyslipidemia, impaired glucose tolerance, hypertension and obesity [17]. In this study, type 2 diabetes mellitus and dyslipidemia were induced for seven consecutive days by a single daily administration of dexamethasone at a dose of 5 mg/kg. In untreated dexamethasone-induced diabetic rats, an increase in serum TC, TG, LDLc and AI was observed. On the other hand, a serum reduction of HDLc was also observed. Atherosclerosis is the primary cause of ischemic heart diseases, and macrophage play a critical role in the pathogenesis of atherosclerosis and formation of vulnerable plaque [13]. In this study, we observed between the seventh and fourteenth day of treatment that HACC significantly increased serum HDLc concentrations and considerably reduced TC, TG, LDLc and AI concentrations. It has been demonstrated in vitro that, glibenclamide (10 µM) directly inhibited the lipopolysaccharide-induced TNF-α production by RAW264 cells [18]. In a mouse model of atherosclerosis, intragastric administration of glibenclamide at 2.5 mg/kg inhibited the formation or development of vulnerable plaque, diminished the vulnerability index (VI) and decreased the macrophage content in the plaque [18]. Glibenclamide is an oral hypoglycemic antidiabetic used in the therapiy of type 2 diabetes. A drug that

is found to be active in type 2 diabetes models may have some role in decreasing cholesterol and TG levels [6], [19]. This is similar to the present study which also revealed that the administration of HACC to the Dex-db rats allowed a significant normalization of the effects induced by dexamethasone in particular on the increase in serum TC, TG, LDLc and AI.

Histological analysis of the liver, kidneys, and pancreas showed normal structuring of the hepatic, renal, and pancreatic parenchyma in the normoglycemic control. Compared to the normoglycemic group of animals, the animals in the control group of Dex-db animals showed several histopathological alterations such as hepatic cytolysis, leukocyte infiltration in the liver and kidneys, as well as hypertrophy of the islets of Langerhans. The groups treated with the reference drug (glibenclamide), like those having received the plant extract at the respective doses of 50 and 100 mg/kg, presented a restructuring of these organs, close to that of the normal control.

5 Conclusion

Overall, the results obtained in this study confirmed the traditional use of *Cymbopogon citratus* by showing its therapeutic potential in the management of metabolic diseases, in particular type 2 diabetes mellitus and obesity, while reducing the cytotoxic effects induced by dexamethasone in diabetic rats in the liver, kidney and pancreas. However, for the use of the hydroalcoholic extract of this plant in the treatment of metabolic diseases in humans, it will be necessary in the near future to carry out clinical studies of this plant extract on human subjects.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors declare that there is no conflict of interest.

Statement of ethical approval

All animal experiment were in accordance with Arrive guidelines and were performed in accordance with the scientific procedures of UK Animals [20].

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