# Hypoglycemic, antidyslipidemic and antioxydant effects of *Vitellaria paradoxa* barks extract on high-fat diet and streptozotocin-induced type 2 diabetes rats

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## A R T I C L E   I N F O

## A B S T R A C T

*Background:* Vitellaria paradoxa is a plant belonging to the Sapotaceae family and used in traditional medicine in the treatment of diabetes mellitus. The aim of this work was to evaluate the hypoglycemic, antidyslipidemic and antioxidant effects of *V. paradoxa* on type 2 diabetic rats.
*Methods:* To induce type 2 diabetes mellitus (T2DM), animals were fed a high-fat diet for 4 weeks followed by an intraperitoneal injection of 35 mg/kg of streptozotocin. Diabetic rats were divided into groups and treated for 28 days with *V. paradoxa* extract (AEVP) at doses of 125, 250 and 500 mg/kg. Body weight, urine volume, food and water consumption were assessed at the start and end of treatment. The glucose tolerance test was performed on the last day of treatment. Blood samples were taken for the assay of biochemical parameters, organs (kidneys and liver) for markers of oxidative stress and pancreas for histological sections.
*Results:* AEVP (250 and 500 mg/kg) improved the drop in body weight, polyphagia, polydipsia and polyuria in diabetic rats. AEVP significantly reduced the concentrations of glucose, total cholesterol, triacylglycerol, urea, creatinine, activities of transaminases, and increased the levels of high density lipoprotein cholesterol and serum insulin. AEVP resulted in a decrease in malondialdehyde levels and an increase in catalase and superoxide dismutase activities. An increase in the size and number of islets in the pancreas has also been observed after administration of the extract.
*Conclusion:* AEVP has antidiabetic, antidyslipidemic and antioxidant properties, thus confirming its traditional use for the treatment of diabetes. These effects could be due to the presence of phytoconstituents, phenols and flavonoids presents in the plant extract.

## 1. Introduction

Diabetes is a metabolic disease characterized by abnormally high levels of glucose in the blood. It constitutes a real public health problem in the world. In fact, more than 425 million people suffered from diabetes in 2017 [1]. This number is projected to almost double by 2030 [2]. The insulin resistance and insulin secretion deficiency that characterize type 2 diabetes (T2DM) may be in part linked to the consumption of high-calorie foods, physical inactivity and obesity [3]. Without proper treatment, T2DM can lead to long-term production of reactive oxygen species and damage to organs such as the eyes, nerves, kidneys and blood vessels [4,5].

The treatment of diabetes is mainly based on insulin and/or oral antidiabetic drugs. But, these drugs have harmful side effects and some of them are expensive and contraindicated in pregnant women and some patients [6]. However, around 80% of the world's population uses medicinal plants and their bioactive compounds for effective, less expensive and low-toxicity treatment [7].

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*Vitellaria paradoxa*, a plant belonging to the Sapotaceae family, is traditionally used in Africa for the treatment of gastrointestinal diseases, malaria and diabetes. Rabiat et al. [8] demonstrated the antioxidant effects *in vitro* of methanolic extract from the fruits of *V. paradoxa*. Coulibaly et al. [9] showed the antihyperglycemic effect of hydro-ethanolic extract of the barks of *V. paradoxa* in normal rabbits. The work carried out by Miaffo et al. [10] showed the antidiabetic and antioxidant properties of the bark of *V. paradoxa* in alloxan-induced type 1 diabetes rats. However, no study has been carried out scientifically to prove the antidiabetic effects of the plant on the model of type 2 diabetes. Thus, the objective of the present study was to evaluate the hypoglycemic, antidyslipidemic and antioxidant effects of the aqueous extract. bark of *V. paradoxa* (AEVP) on high-fat diet and streptozotocin-induced type 2 diabetes rats.

## 2. Materials and methods

### 2.1. Plant material

The plant material consisted of the barks of *V. paradoxa*, collected in January 2018 in Ngong, Cameroon. The collected species was authenticated at the National Herbarium of Yaounde (Cameroon) where a sample was kept and registered at No. 47670 HNC. The barks of *V. paradoxa* were cut, washed in tap water and dried in the open air, away from the sun and at room temperature. Then, they were crushed using a grinder until a powder was obtained.

Two hundred grams (200 g) of *V. paradoxa* powder were introduced to 1750 mL of distilled water and the whole was brought to the boil for 30 min. After cooling, the solution was filtered using Wattman No. 1 paper. The filtrate obtained was evaporated in an oven at 45 °C, which allowed us to obtain 33.66 g of crude extract of *V paradoxa*, ie a yield of 16.83%.

### 2.2. Phytochemical assay

#### 2.2.1. Determination of total polyphenols
The total polyphenol content of AEVP was determined according to the protocol described by Lister and Wilson [11]. In fact, 0.5 mL of the AEVP (1 mg/mL) was added to 2.5 mL of the Folin-Ciocalteu reagent. Then, 4 mL of sodium carbonate $Na_2CO_3$ (7.5%, w/v) were added thereto. The mixture was incubated in a 45 °C water bath for 30 min. The intensity of the blue coloration produced was measured using a spectrophotometer at a wavelength of 765 nm against a control prepared according to the same method, except that the AEVP was replaced by the solvent. A calibration curve was drawn with different concentrations of gallic acid (20, 40, 60, 80, 100 μg/mL) under the same conditions as the dosage of the AEVP. The amount of total polyphenols was expressed in milligrams of gallic acid equivalents (mg EAG/g of AEVP), using the linear regression equation of the gallic acid standard curve: $Y = 0.0016x + 0.1285$; R2 = 0.998.

#### 2.2.2. Determination of flavonoids
The flavonoid content of AEVP was determined following the protocol of Dewanto et al. [12]. At room temperature, 1 mL of the AEVP solution was mixed with 0.3 mL of sodium nitrate $NaNO_2$ (5%). Five minutes later, 1 mL of the aluminum chloride solution $AlCl_3$ (2%) was added to the mixture. After 6 min, 2 mL of sodium hydroxide NaOH (1M) were added to the solution. After incubation for 15 min, the absorbance measurement was carried out at 510 nm against a control prepared according to the same method, except that the AEVP was replaced by the solvent. A standard curve was performed with different concentrations of quercetin (25, 50, 75, 100, 125 μg/

mL) under the same conditions as the assay of the sample. The amount of flavonoids was expressed in milligram quercetin equivalents (mg EQ/g of AEVP), using the linear regression equation of the standard curve for quercetin: $Y = 0.004x + 0.082$; $R^2 = 0.9982$.

### 2.3. Animals

Male Wistar albino rats aged 10−12 weeks weighing between 200 and 250 g were used in this study. They were raised in the animal house of the Department of Biological Sciences of the University of Ngaoundere (Cameroon). All the animals were placed in polypropylene cages (n = 6), at room temperature with a 12/12 h cycle (light/dark). They had free access to water and standard diet. Rats were acclimatized to laboratory conditions for 7 days before carrying out the experiments. This study was approved by the Ethic Committee of the Faculty of Sciences of the University of Maroua (Ref. N°14/0261/Uma/D/FS/VD-RC), Cameroon. The animal protocol were accomplished in accordance with the guidelines of Cameroonian bioethics committee (reg N°.FWA-IRB00001954) and NIH-Care and Use of Laboratory Animals Manual (8th Edition).

### 2.4. Induction of T2DM

Animals were divided into two groups: the control group fed with standard laboratory chow (STD) and the experimental group fed with high-fat diet (HFD). Indeed, to induce T2DM, the animals in the experimental group were fed an HFD containing 15% carbohydrate, 20% protein and 75% fat for 4 weeks followed by an intraperitoneal injection of STZ (35 mg/kg suspended in 0.1 mol/L citrate buffer at pH 4.5) [13]. Seventy-two hours (72 h) after the injection of STZ, the blood glucose of the animals was measured and only the rats with a blood glucose greater than or equal to 200 mg/dL were used for the experiment.

### 2.5. Experimental design

Thirty-six (36) rats were randomly divided into 6 groups (n = 6) and treated orally daily for 28 days. Group I (normal control): normal rats received STD and 10 mL/kg of distilled water; Group II (diabetic control): T2DM rats received HFD and 10 mL/kg of distilled water; Group III (positive control): T2DM rats received HFD and metformin (250 mg/kg); Groups IV, V, and VI: T2DM rats received HFD and AEVP at doses of 125, 250 and 500 mg/kg respectively. Fasting blood glucose (FBG) of the rats was measured each week of the experiment using a glucometer (Accu-Chek Active, Roche, Mannheim, Germany). Body weight, urine sample, food and water consumption of animals were evaluated on the 1st and 28th days of the experiment. At the end of study, the oral glucose tolerance test (OGTT) was performed. Immediately, blood and organ (liver and kidneys) samples were collected for the determination of biochemical parameters.

### 2.6. Determination of fasting serum insulin level (FSI), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), Homeostasis Model Assessment of β-cell function (HOMA-β) and Insulin Sensitivity Index (ISI)

FSI was determined according to the enzyme-linked immunosorbent (ELISA) method using a commercial kit (Bexwell, Norfolk PE38 9 GA, UK). HOMA-IR was calculated using the formula: HOMA-IR = insulin (μU/mL) × glycemia (mmol/L)/22.4 [14]. HOMA-β was calculated using the formula: HOMA-β = 20 × insulin (μU/mL)/FBS (mmol/L) - 3.5 [15]. ISI was calculated using the formula: ISI = Ln (1/(FBG × FSI)) [16].

### 2.7. Biochemical analyses

Total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDLc), urea and creatinine (CR) levels, and alanine amino transaminase (ALT) and aspartate aminotransferase (AST) activities were determined in serum using standard kits from Edu-Lab Biology Bexwell, Norfolk PE38 9 GA, UK.

Malondialdehyde (MDA) levels, and superoxide dismutase (SOD) and catalase (CAT) activities were evaluated in kidneys and liver homogenates using enzymatic kits from Sigma-Aldrich, Saint. Louis, USA.

### 2.8. Histopathology

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

### 2.9. Statistical analysis

All results were expressed as the mean $\pm$ SD (Standard Derivation). Data were analyzed using Graph Pad Prism software, version 5.0. Two-way analysis of variance followed by Bonferroni's post-test was used for the treatment of the double-variable data. In contrast, one-way analysis of variance followed by Turkey's post-test was used to analyze the single-variable data. The means were considered significant at the probability threshold of 0.05.

## 3. Results

### 3.1. Total polyphenols and flavonoids content

Fig. 1 shows the amount of total polyphenols (A) and flavonoids (B) in the AEVP. It was found that the contents of total polyphenols and flavonoids were 34.32 $\pm$ 0.29 mg EAG/g of AEVP and 15.95 $\pm$ 0.05 mg EAG/g of AEVP respectively.

### 3.2. Effets of AEVP on body weight, food intake, water intake and urine volume

Table 1 shows the body weight, urine volume, and food and water consumption of diabetic animals. Compared to the normal control group, no significant change in body weight and food and water consumption was noted in animals treated with metformin
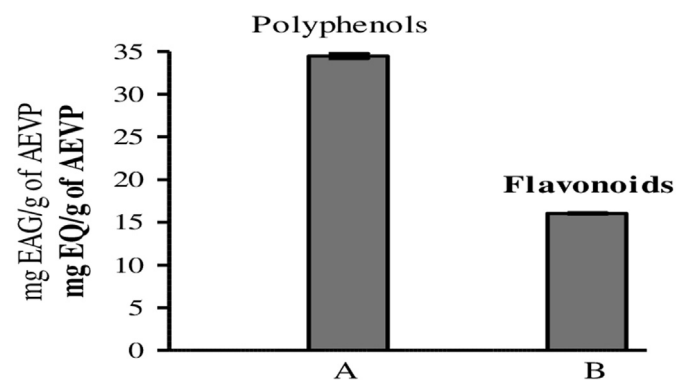


**Fig. 1.** Content of total polyphenols (A) and flavonoids (B) of AEVP. All results are expressed as mean $\pm$ SD (n = 3). Data analysis was performed by one-way ANOVA followed by Turkey's post-hoc test. AEVP: Aqueous extract of *Vitellaria paradoxa*.

and AEVP on the first day of treatment. On the other hand, these parameters were significantly ($p < 0.001$) reduced on the 28th day of treatment in the diabetic control group.

However, compared to the diabetic control group, metformin and doses of 250 and 500 mg/kg of AEVP induced a significant increase ($p < 0.01$) in body weight on day 28. Food consumption was significantly reduced in animals treated with metformin ($p < 0.01$) and AEVP at doses of 250 ($p < 0.05$) and 500 mg/kg ($p < 0.05$). In addition, metformin and doses of 250 and 500 mg/kg of AEVP resulted in a significant decrease ($p < 0.001$) in water consumption in diabetic rats. Urinary volume was significantly reduced with metformin ($p < 0.01$) and doses of 250 ($p < 0.01$) and 500 mg/kg ($p < 0.001$) of AEVP. The lower dose of AEVP (125 mg/kg) induced a significant decrease ($p < 0.05$) in the water consumption of the animals.

### 3.3. Effect of AEVP on fasting blood glucose (FBG)

Fig. 2 shows the FBG values in the rats which received the different treatments during a period of 28 days. At the start of treatment, the FBG level is almost similar in all groups of animals. However there was a significant increase ($p < 0.001$) in FBG in the animals in the diabetic control group on days 7, 14, 21 and 28, compared to the normal control group.

Compared to the diabetic control group, a significant decrease ($p < 0.001$) in FBG levels of the animals treated with metformin and AEVP was noted throughout the treatment.

### 3.4. Effects of AEVP on oral glucose tolerance test (OGTT)

It emerges from Fig. 3 which shows the effects of AEVP during OGTT that the animals in the diabetic control group had significantly ($p < 0.001$) elevated glycaemia and area under the curve (AUC) during the 2 h of observation, compared to the normal control group.

On the other hand, metformin and the doses of 250 and 500 mg/kg of AEVP induced a significant decrease ($p < 0.001$) in glycaemia during the entire observation period, compared to the diabetic control batch. The lowest dose of extract (125 mg/kg) caused a significant drop in blood glucose at the 30th ($p < 0.01$), 60th ($p < 0.05$), 90th ($p < 0.01$) and 120th min ($p < 0.001$). In addition, the AUC of all animals treated with metformin and the different doses of AEVP was significantly reduced, compared to the diabetic control group.

### 3.5. Effects of AEVP on FSI, HOMA-IR, HOMA-$\beta$ and ISI

It emerges from Table 2 which represents the effects of AEVP on FSI level, HOMA-IR, HOMA-$\beta$ and ISI that the rate of FSI and HOMA-$\beta$ has decreased significantly ($p < 0.001$) in the animals of the diabetic control group, compared to the normal control group. On the other hand, we observe a significant increase in HOMA-IR ($p < 0.01$) and ISI ($p < 0.05$).

Furthermore, compared to the diabetic control group, FSI level and HOMA-$\beta$ increased significantly with metformin ($p < 0.001$; $p < 0.001$) and doses of 250 ($p < 0.01$; $p < 0.05$) and 500 mg/kg ($p < 0.001$; $p < 0.001$) of AEVP. In contrast, metformin and the extract at doses of 250 and 500 mg/kg caused a significant ($p < 0.005$) decrease in HOMA-IR. Metformin and AEVP at doses of 250 and 500 mg/kg caused a significant increase ($p < 0.05$) in ISI, compared to the diabetic control group.

### 3.6. Effects of AEVP on the biochemical parameters of rats

The effects of AEVP on the biochemical parameters of diabetic rats are presented in Table 3. It appears from this table that

**Table 1**
Effects of AEVP on body weight, food intake, water intake and urine volume.

| Group | Body weight (g) | | Food intake (g/kg bw) | | Water intake (mL/kg bw) | | Urine volume (mL/mg bw) |
|---|---|---|---|---|---|---|---|
| | 1st day | 28th day | 1st day | 28th day | 1st day | 28th day | 28th day |
| Normal control | 224.00 ±6.68 | 250.83 ± 5.51 | 67.55 ± 10.54 | 98,39 ± 7,21 | 76.87 ± 5.72 | 97.57 ± 10.47 | 50.47 ± 6.50 |
| Diabetic control | 230.50 ± 5.26 | 215.50 ± 2.93*** | 82.06 ± 7.81 | 164.27 ± 15.17*** | 71.29 ± 8.13 | 229.51 ± 20.90*** | 113.51 ± 10.65*** |
| Metformin 250 mg/kg | 220.17 ± 6.18 | 241.50 ± 5.37b | 69.61 ± 11.90 | 116.23 ± 9.72b | 66.42 ± 10.02 | 127.78 ± 11.18c | 70.29 ± 3.15b |
| AEVP 125 mg/kg | 235.17 ± 3.18 | 229.00 ± 7.26 | 77.55 ± 6.45 | 132.06 ± 10.27 | 87.31 ± 8.69 | 179.98 ± 17.35a | 94.90 ± 6.88 |
| AEVP 250 mg/kg | 222.33 ± 6.93 | 237.32 ± 5.80b | 68.76 ± 9.99 | 124.16 ± 11.11a | 75.41 ± 9.14 | 142.36 ± 15.84c | 69.43 ± 8.00b |
| AEVP 500 mg/kg | 230.66 ± 6.54 | 242.00 ± 7.54b | 80.09 ± 5.51 | 121.94 ± 14.30a | 85.03 ± 6.53 | 133.99 ± 10.53c | 63.66 ± 6.69c |

All results are expressed as mean ± SD (n = 6). Data analysis was performed by two-way ANOVA followed by Bonferroni's post-hoc test. ***p < 0.01 versus normal control group. ap< 0.05; bp < 0.01 and cp < 0.001 versus T2D group. AEVP: Aqueous extract of *Vitellaria paradoxa*.
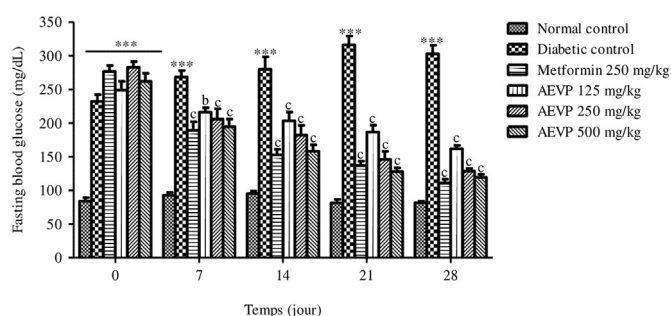


**Fig. 2.** Effects of the AEVP on the blood glucose level. All results are expressed as mean ± SD (n = 6). Data analysis was performed by two-way ANOVA followed by Bonferroni's post-hoc test. ***p < 0.01 versus normal control group. bp < 0.01 and cp < 0.001 versus T2DM group. AEVP: Aqueous extract of *Vitellaria paradoxa*.

compared to the normal control group, there is a significant increase in the rate of TC (p < 0.001), TG (p < 0.001), CR (p < 0.05), urea (p < 0.001), ALT (p < 0.05) and AST activity (p < 0.001), and a

significant decrease (p < 0.001) in HDL-c levels in the rats of the diabetic control group.

However, compared to the diabetic control group, metformin and AEVP at a dose of 500 mg/kg induced a significant drop (p < 0.05 to p < 0.001) in the levels of TC, TG, urea, CR as well as ALT and AST activities, and a significant (p < 0.01; p < 0.001) increase in HDL-c. The dose of 125 mg/kg of AEVP caused a significant (p < 0.05) decrease in TC levels and AST activity. In addition, the dose of 250 mg/kg of AEVP caused a significant decrease (p < 0.01) in the level of TC, urea, and AST activity, and a significant decrease (p < 0.01) in HDL-c level.

### 3.7. Effects of AEVP on oxidative stress markers

The effects of AEVP on the parameters of oxidative stress in the liver and kidneys are shown in Table 4. In fact, compared to animals in the normal control group, there is a significant (p < 0.001) increase in MDA level and a significant (p < 0.001) decrease in SOD and CAT activity in the liver and kidney of animal in the diabetic control group.
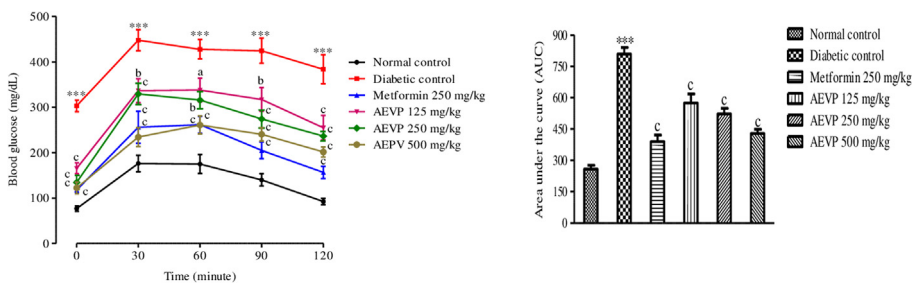


**Fig. 3.** Effects of AEVP on OGTT in diabetic rats. All results are expressed as mean ± SD (n = 6). Data analysis was performed by two-way ANOVA followed by Bonferroni's post-hoc test. ***p < 0.01 versus normal control group. ap < 0.05; bp < 0.01 and cp < 0.001 versus T2DM group. AEVP: Aqueous extract of *Vitellaria paradoxa*. AUC: area under the curve; OGTT: oral glucose tolereance test.

**Table 2**
Effects of AEVP on FSI level, HOMA-IR, HOMA-β and ISI.

| Group | FSI (μU/mL) | HOMA-IR | HOMA-β | ISI |
|---|---|---|---|---|
| Normal control | 38.46 ± 2.45 | 141.85 ± 13.09 | 770.89 ± 56.99 | −5.15 ± 0.09 |
| Diabetic control | 15.67 ± 1.50*** | 209.00 ± 16.12** | 24.28 ± 3.22*** | −5.54 ± 0.07* |
| Metformin 250 mg/kg | 29.83 ± 1.30c | 148.96 ± 12.63a | 239.30 ± 25.45c | −5.20 ± 0.09a |
| AEVP 125 mg/kg | 21.83 ± 1.78 | 156.97 ± 11.19 | 81.34 ± 9.31 | −5.26 ± 0.07 |
| AEVP 250 mg/kg | 26.50 ± 1.65b | 152.80 ± 10.73a | 146.60 ± 10.92a | −5.23 ± 0.08a |
| AEVP 500 mg/kg | 27.71 ± 1.08c | 149.05 ± 10.14a | 181.43 ± 10.88b | −5.21 ± 0.06a |

All results are expressed as mean ± SD (n = 6). Data analysis was performed by one-way ANOVA followed by Turkey's post-hoc test. ***p < 0.01 versus normal control group. ap < 0.05; bp < 0.01 and cp < 0.001 versus T2DM group. AEVP: Aqueous extract of *Vitellaria paradoxa*. FSI: fasting serum insulin level, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, HOMA-β: Homeostasis Model Assessment of β-cell function, ISI: Insulin Sensitivity Index.

**Table 3**
Effects of AEVP on biochemical parameters in diabetic rats.

| Groups | Normal control | Diabetic control | Metformin 250 mg/kg | AEVP 125 mg/kg | AEVP 250 mg/kg | AEVP 500 mg/kg |
|---|---|---|---|---|---|---|
| TC (mg/dL) | 95.88 ± 2.56 | 136.76 ± 5.27*** | 104.81 ± 5.16b | 111.45 ± 5.61a | 107.78 ± 5.13b | 106.45 ± 5.54b |
| TG (mg/dL) | 76.84 ± 5.12 | 116.56 ± 4.45*** | 88.38 ± 4.76a | 97.04 ± 5.21 | 95.6 ± 6.13 | 88.49 ± 8.06a |
| HDL-c (mg/dL) | 36.89 ± 1.33 | 18.63 ± 1.43*** | 27.23 ± 1.42b | 23.69 ± 0.98 | 27.95 ± 1.83b | 29.92 ± 2.02c |
| ALT (U/L) | 79.83 ± 3.77 | 105.33 ± 6.10* | 68.17 ± 5.17b | 98.17 ± 6.82 | 86.50 ± 5.77 | 78.33 ± 7.02a |
| AST (U/L) | 54.50 ± 5.86 | 99.83 ± 3.78*** | 76.66 ± 5.74a | 89.33 ± 4.87a | 71.33 ± 3.32b | 65.83 ± 6.68b |
| Urea (mg/dL) | 23.17 ± 2.12 | 52.33 ± 4.39*** | 29.83 ± 3.47b | 37.17 ± 3.46 | 30.50 ± 4.20b | 28.83 ± 3.97b |
| CR (mg/dL) | 0.47 ± 0.02 | 0.66 ± 0.05* | 0.51 ± 0.05 | 0.54 ± 0.03 | 0.53 ± 0.05 | 0.49 ± 0.03a |

All results are expressed as mean ± SD (n = 6). Data analysis was performed by one-way ANOVA followed by Turkey's post-hoc test. ***$p < 0.01$ versus normal control group. a$p < 0.05$; b$p < 0.01$ and c$p < 0.001$ versus T2DM group. AEVP: aqueous extract of *Vitellaria paradoxa*, TC: total cholesterol, TG: triglycerides, HDL-c: high density lipoprotein cholesterol, ALT: alanine aminotransaminase, AST: aspartate aminotransferase, CR: creatinine.

Compared to the diabetic control group, metformin and the different doses of AEVP resulted a significant decrease ($p < 0.001$) in hepatic and renal MDA levels. In contrast, a significant increase ($p < 0.001$) in SOD and CAT activities was noted in the liver of rats treated with metformin and AEVP at doses of 250 and 500 mg/kg. Likewise, there was a significant increase in SOD ($p < 0.05$) and CAT ($p < 0.01$) activities in the kidneys of animals receiving metformin and AEVP at doses of 250 and 500 mg/kg. The dose of 125 mg/kg of AEVP caused a significant decrease in hepatic SOD ($p < 0.001$) and CAT ($p < 0.001$) activities, and renal CAT activity ($p < 0.05$).

### 3.8. Effects of AEVP on the histology of the pancreas

Histopathology of the pancreas of rats in the normal control group showed islets of normal size (Fig. 4A). However, in the diabetic control group, partial destruction of the pancreas is observed, characterized by reduction in the size and number of islets, and the disappearance of islet borders (Fig. 4B). This damage was considerably reduced after the administration of metformin and the different doses of AEVP (Fig. 4C−F).

## 4. Discussion

T2DM is a metabolic disease characterized by chronic hyperglycemia, dyslipidemia and insulin resistance [17]. Numerous studies have shown that a high fat diet followed by a low dose of STZ leads to hyperglycemia, insulin resistance and insulin deficiency [18]. In the present study, T2DM was induced in rats by a high fat diet for 4 weeks followed by the injection of a low dose of STZ, then we evaluated the antidiabetic, antidyslipidemic and antioxidant effects of AEVP in this model.

In the present study, the results of quantitative phytochemical analyses revealed the presence of secondary metabolites such as polyphenols and flavonoids in the AEVP. These classes of chemical compounds may be responsible for the hypoglycemic, antihyperglycemic, antidyslipidemic and antioxidant effects of the

AEVP. Polyphenols have been shown to have the ability to lower blood lipid levels [19]. In addition, phenolic and flavonoid compounds may exert antidiabetic and antioxidant properties [20].

Weight loss, polyphagia, polyuria and polydipsia are the main features of T2DM [21]. The results obtained from this study showed a significant decrease in body weight and a significant increase in urine volume and food and water consumption in animals fed a HFD, compared to the normal control group. The decrease in body weight is thought to be due to the catabolism of fats and proteins in the tissues caused by an insulin deficiency [22]. The increase in food consumption could be explained either by the decrease in the activity of the leptin receptor in the hypothalamus following an insulin deficiency, or by the decrease in the release of hormones promoting satiety (cholecystokinin, peptide YY and glucagon-like peptide-1) [23]. The increase in water consumption is the cause of hyperglycemia which consequently leads to excessive elimination of urine volume with loss of glucose. However, AEVP at doses of 250 and 500 mg/kg significantly reduced body weight and the signs of polyphagia, polydipsia and polyuria seen in diabetic rats. This could be the result of better control of hyperglycemia in diabetic rats. However, oral administration of the AEVP at doses of 250 and 500 mg/kg significantly reduced body weight and the signs of polyphagia, polydipsia and polyuria seen in diabetic rats. This could be the result of better control of hyperglycemia in diabetic rats.

OGTT and FBG are major indicators in the control of diabetes. In this study, FBG value significantly decreased on days 7, 14, 21 and 28 of treatment after administration of the AEVP and metformin to diabetic animals. Likewise, during OGTT, the blood glucose and AUC of the AEVP treated animals were significantly lower than that of the rats in the diabetic control group. These results are similar to some previous work [24,25]. These effects could be explained by several possible mechanisms: stimulation of the release of insulin, regeneration of β-pancreatic cells and increased sensitivity of target tissues to insulin [26]. Metformin acts mainly on the liver by reducing de novo glucose synthesis (gluconeogenesis), improve hepatic steatosis by inhibiting lipid synthesis and increasing the

**Table 4**
Effects of the AEVP on the parameters of oxidative stress in the liver and kidneys.

| Groups | Liver | | | Kidney | | |
|---|---|---|---|---|---|---|
| | MDA (mmol/mg of tissue) | SOD (U/mg of protein) | CAT (U/mg of protein) | MDA (mmol/mg of tissue) | SOD (U/mg of protein) | CAT (U/mg of protein) |
| Normal control | 3.34 ± 0.29 | 20.24 ± 1.51 | 74.24 ± 2.96 | 3.44 ± 0.43 | 26.70 ± 1.74 | 56.88 ± 2.15 |
| Diabetic control | 9.60 ± 0.76*** | 8.96 ± 0.73*** | 37.44 ± 2.48*** | 10.28 ± 0.70*** | 14.98 ± 0.91*** | 32.88 ± 2.15*** |
| MET 250 mg/kg | 49.00 ± 0.38c | 20.24 ± 1.26c | 71.38 ± 298c | 6.00 ± 0.29c | 18.98 ± 1.41 | 44.66 ± 3.32b |
| AEVP 125 mg/kg | 5.62 ± 0.38c | 15.48 ± 1.16b | 53.26 ± 2.40b | 8.04 ± 0.60a | 20.10 ± 2.71 | 48.22 ± 2.09a |
| AEVP 250 mg/kg | 3.68 ± 0.37c | 21.28 ± 0.67c | 61.88 ± 3.86c | 4.26 ± 0.44c | 24.28 ± 1.56a | 48.70 ± 2.94b |
| AEVP 500 mg/kg | 4.28 ± 0.56c | 23.52 ± 1.24c | 64.68 ± 2.40c | 5.22 ± 0.48c | 23.36 ± 1.88a | 47.80 ± 2.46b |

All results are expressed as mean ± SD (n = 6). Data analysis was performed by one-way ANOVA followed by Turkey's post-hoc test. ***$p < 0.01$ versus normal control group. a$p < 0.05$; b$p < 0.01$ and c$p < 0.001$ versus T2DM group. AEVP: aqueous extract of *Vitellaria paradoxa*, MDA: malondialdehyde, SOD: superoxide dismutase, CAT: catalase, MET: metformin.
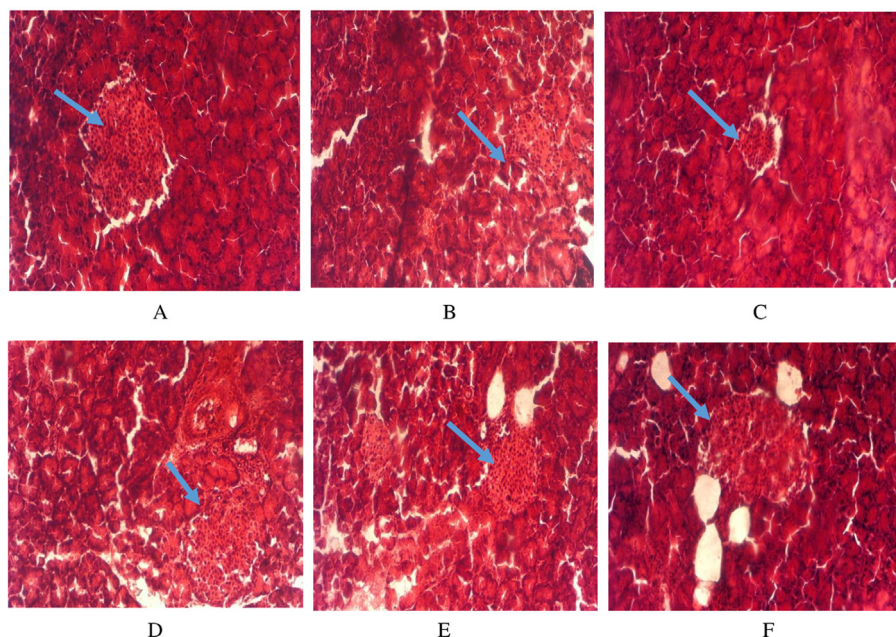
**Fig. 4.** Effects of the AEVP on pancreas histology. (A) Normal control group; (B) Diabetic control group; (C) Metformin group; (D) AEVP 125 mg/kg; (E) AEVP 250 mg/kg; (F) AEVP 500 mg/kg. AEVP: Aqueous extract of *Vitellaria paradoxa*.

oxidation of fatty acids and exerts its beneficial effects on the metabolism by decreasing the intracellular energy load and by activating the AMP-activated protein kinase (AMPK), a key regulator of energy metabolism [27]. AEVP could act via the same mechanisms of action. The phytoconstituents present in the AEVP may be the cause of the hypoglycemic and antihyperglycemic effect observed. Furthermore, we noted in the present study that the serum insulin level significantly increased in diabetic animals treated with the AEVP. In addition, the histopathological study of the pancreas revealed in the same groups of rats, an increase in the size and number of the islets of Langerhans, compared to the group of untreated diabetic animals. These results confirm the effects of the above AEVP elucidated.

One of the treatment approaches for type T2DM is to improve insulin sensitivity. HOMA-IR and HOMA- β values are very important for controlling insulin sensitivity [28]. In this study, administration of the AEVP at doses of 250 and 500 mg/kg significantly resulted in a decrease in HOMA-IR and an increase in HOMA-β index, indicating that the AEVP could improve pancreatic cell function and insulin resistance [29]. This is further confirmed by the increase in ISI observed in the present work in the AEVP treated animals.

Other characteristics of T2DM are marked increases in creatinine, urea and transaminase activity associated with dyslipidemia which can lead to the development of cardiovascular diseases [30]. In this work, rats in the diabetic control group showed a significant increase in TC, TG, urea, creatinine, and AST and ALT activity, and a significant increase in HDL-c. Oral administration of the AEVP at doses of 250 and 500 mg/kg attenuated the increased variation in these different parameters.

The improvement in the lipid profile could probably be due to the ability of the AEVP either to inhibit cholesterol biosynthesis in the liver [31] or to stimulate insulin secretion. Indeed, insulin inhibits lipolysis and increases the absorption of fatty acids in adipose tissue [32]. The observed increase in HDL-c allows us to suspect the preventive effect of the AEVP on the onset of atherosclerosis [32]. The lipid-lowering effect of the AEVP may be due to its richness in

phenolic compounds which impairs intestinal absorption and promotes fat excretion [33].

ALT and AST are major markers of liver function in diabetic rats. It has been reported that increased transaminase activities in diabetics with insulin deficiency is responsible for increased gluconeogenesis [34]. The decrease in ALT and AST activities could be attributed to the ability of the extract either to maintain membrane integrity or to attenuate liver damage caused by chronic hyperglycemia [35]. This beneficial effect can be attributed to the high content of total phenols and flavonoids in the AEVP.

Urea and creatinine are major markers of renal dysfunction in diabetic rats [36]. The decrease in these parameters after administration of the AEVP could be explained by the inhibition of the continuous catabolism of amino acids during the diabetic state, which will result in a decrease in the amount of urea formed [37].

Hyperglycemia can also generate free radicals, which will lead to an increase in lipid peroxidation and a decrease in cellular antioxidants [38]. In our study, diabetic rats developed oxidative stress characterized by increased MDA levels and decreased activities of antioxidant enzymes (SOD and CAT) in the liver and kidney. Administration of the AEVP for 28 days resulted in a decrease in MDA levels and an increase in CAT and SOD activities. These results are in agreement with some previous work carried out on the model of diabetes induced by HFD/STZ [39,40]. The antioxidant effect of the extract could be attributed to its richness in polyphenols and flavonoids which have the capacity to eliminate free radicals and thus prevent oxidative damage by detoxifying reactive oxygen species in the body and/or to trap the superoxide radical by converting them into hydrogen peroxide and molecular oxygen [41].

## 5. Conclusion

AEVP has antidiabetic properties by improving glucose tolerance and insulin sensitivity, improves lipid profile and protects cells against oxidative stress. These effects could be due to the presence of phytoconstituents, phenols and flavonoids presents in the plant

extract. The results obtained at the end of this study confirm the traditional use of the plant against diabetes mellitus and its cardiovascular complications. Future studies will be performed to determine and explain the exact mechanisms of action of AEVP.

## Data availability

We have the data of this research article and can provide it as per the request.

## CRediT authorship contribution statement

**David Miaffo:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources. **Fidèle Ntchapda:** Methodology, Project administration, Resources. **Talba Abba Mahamad:** Conceptualization, Investigation, Methodology, Project administration, Formal analysis, Writing - original draft. **Barthelemy Maidadi:** Conceptualization, Methodology, Investigation, Writing - review & editing. **Albert Kamanyi:** Conceptualization, Methodology, Supervision, Resources.

## Declaration of competing interest

The authors declare no conflict of interest.

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